Tunnel Vision

Treatment of Carpal Tunnel Syndrome and the role of Ultrasound

Stefanie Evers

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Part of the research described in this thesis was financially supported by the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases Grant RO1 AR62613.

Printing of this thesis was financially supported by (in no particular order):
Chipsoft, Equipe Zorgbedrijven Nederland, Maatschap Plastische Chirurgie Erasmus MC, Nederlandse Vereniging voor Plastische Chirurgie, van Wijngaarden Medical

Lay-out: Nikki Vermeulen - Ridderprint BV
Printing: Ridderprint BV - www.ridderprint.nl
Cover design: Mariëtte Scholtens-de Jongh - Art Studio Jet

ISBN: 978-94-6375-344-9

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Tunnelvisie:
behandeling van carpaletunnelsyndroom
en de rol van echografie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 29 mei 2019 om 13:30 uur

door

Stefanie Evers
geboren te Zwolle

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor: Prof.dr. S.E.R. Hovius

Overige leden: Prof.dr. J.H. Coert
Prof.dr. B.W. Koes
Dr.ir. J.G. Bosch

Copromotor: Dr. R.W. Selles

Paranimfen: Dr. M.W.M. Braakhekke
Drs. E.S. Rezaie

Voor mijn ouders

CONTENTS

1

GENERAL INTRODUCTION

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1. Prevalence and risk factors

With approximately 600.000 carpal tunnel releases (CTRs) performed annually in the United States, Carpal Tunnel Syndrome (CTS) is the most common surgically-treated condition of the hand[1]. Although epidemiological studies report widely ranging incidences of CTS across countries, most likely due to a combination of factors including different diagnostic criteria, it is clear that it is a common disorder[2]. Generally it is believed to be the most common peripheral neuropathy with a prevalence of 1-4% of the population[3,4].

The characteristic symptoms of CTS include (nocturnal) pain and paresthesias in the median nerve distribution, loss of manual dexterity, and loss of sensation in the hand (Figure 1). Although CTS is a mononeuropathy that only affects a small part of the nerve, it is a serious health problem that can result in decreased quality of life due to sleep disturbance and interferes with one's ability to work[5,6]. Consequently, CTS can lead to economic burden as a result of direct costs of surgery and work absence[7,8].

Several risk factors for the presence of CTS have been identified. For example, a higher prevalence of CTS has been found in high-force repetitive jobs[9]. In addition, non-occupational risk factors such as genetic predisposition, female gender and increasing age[10,11] have been identified as independent risk factors for CTS. The cut-off point in which age becomes a risk factor varies between studies from 40 to 55 years[10,12,13]. In addition, higher BMI, pregnancy, rheumatoid arthritis and systemic diseases such as diabetes mellitus and hypothyroidism have found to be associated with CTS[10,14-16].

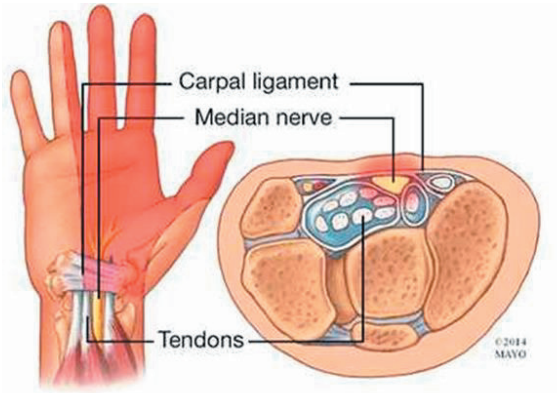

Figure 1. Cross-section of the wrist with the carpal tunnel structures illustrated (right). Area supplied by median nerve highlighted in red (left).

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2. Aims of the thesis

This thesis consists of 3 different parts including three aims:

1) Firstly, since it remains difficult to predict treatment outcome for a patient with CTS, our aim was to explore factors that influence treatment outcome of CTS.
2) Dynamic ultrasonographic examination may contribute to prediction of treatment outcome and would ultimately allow individualization of treatment for patients with CTS. Therefore, our second aim was to assess the role of ultrasound in CTS.
3) In addition, ultrasound may also be valuable to guide interventions in CTS. Therefore, the third aim was to assess the role of ultrasound guidance in the treatment of CTS.

In this introduction we will first describe the background necessary for understanding the current literature on these three topics. Lastly the outline of the thesis will be described.

3. Treatment options and outcomes

In the following paragraph the background leading to three different studies on treatment outcomes in CTS is described. Firstly, we focused on the long term-follow up of steroid injections in the treatment of CTS. In addition, we evaluated predictors for symptom relief after a CTR. Furthermore, we assessed whether surgical-outcome improved when CTR was performed by more experienced surgeons.

Splinting, local steroid injection and CTR are recommended treatment options for CTS. Most guidelines recommend splinting or a local steroid injection before considering surgery[17]. Clinical trials have shown that both injection and CTR are generally effective in reducing symptoms[18-20]. Nevertheless, although local steroid injections are effective in providing symptom-relief, there is only strong evidence for benefits of steroid injections in the short-term. Reported rates of subsequent treatment, either reinjection or surgery, vary from 10% -81% at one year following initial injection[20-25]. Consequently, we evaluated long-term results of corticosteroid injections in CTS in a population-based cohort. To date, although some prognostic factors for treatment outcome have been identified, it has been difficult to identify those patients who might benefit from an injection. A more severe electrodiagnostic study, higher symptom severity score (SSS) on the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), larger ultrasonographic cross-sectional area of the median nerve, the presence of fibromyalgia, diabetes mellitus, and female gender have all been found to be associated with less symptom improvement or higher risk of symptom recurrence after an injection for CTS[23-28]. Nevertheless, study results have been inconsistent since some of these variables have not been significant predictors for treatment outcome in other studies. Our aim in this study was to identify prognostic factors for treatment outcome following a steroid

injection for CTS. In addition, since the optimal volume for a corticosteroid injection in CTS has not yet been established, we also assessed the influence of injection volume on the rate of subsequent intervention over 1 year follow-up.

In regard to outcome of CTR a previous review on long-term outcome of CTR described that 10-25% of surgically-treated patients with CTS did not reach the desired effect[29]. Moreover, it has been challenging to predict treatment outcome after CTR. The following prognostic factors for poor treatment outcome after a CTR have been identified: higher age, male gender, diabetes mellitus, poor health status, thoracic outlet syndrome, double crush, alcohol use, smoking, muscular atrophy in the thenar area and both a normal electrodiagnostic study (EDS) as well as very severe EDS results have been associated with worse outcome after a CTR[30-35]. Nonetheless, these results have not been consistent. Predictability of outcomes after an intervention in individual patients is desirable in order to be able to manage patient expectations (preoperative counseling) and to provide careful case selection for a specific type of treatment. We therefore assessed predictors for symptom relief following a CTR and determined their contribution to symptom relief at six months after surgery. Furthermore, for many high-risk procedures it has been shown that surgeons who performed the procedure more often achieved better patient outcomes[36-39]. In hand surgery and carpal tunnel release specifically it is unknown if such a volume-outcome relationship exists. Therefore, we assessed whether hand surgeons performing more open carpal tunnel releases show better patient outcomes.

4.1 Ultrasound of structures within the carpal tunnel

The exact pathophysiology of CTS remains unknown and the syndrome is therefore most often listed as idiopathic. Although CTS has consistently been related to an increased pressure within the carpal tunnel[40,41], a precise model of causation has not been developed yet. It is known that an elevated pressure within the carpal tunnel can result in ischemia once the pressure exceeds the arterial pressure, leading to the neuropathy[42]. Nevertheless, the cause of the pressure elevation is mostly unknown.

Another consistent finding in CTS is fibrosis of the subsynovial connective tissue (SSCT) surrounding the tendons within the carpal tunnel[43-46]. The multilayered SSCT consists of collagen and elastin fibers and is an unique characteristic of the carpal tunnel. It serves as an interface and carrier of vasculature to the tendons and the median nerve. Previous studies have shown that the SSCT in CTS patients is thickened, stiffer and fibrotic compared to healthy controls[43,46]. Changes in SSCT in CTS patients may result in altered dynamics of the structures within the carpal tunnel. Accordingly, quantification of these dynamics might support management of CTS in terms of prevention and treatment.

Ultrasound imaging has the potential to quantify the dynamics of carpal tunnel structures. Ultrasound of the musculoskeletal system has gained interest, as it is a non-invasive, safe, and easily accessible imaging modality that is relatively inexpensive compared to, for example, magnetic resonance imaging (MRI)[47]. Ultrasound also enables visualization of structures within the carpal tunnel[48]. The most commonly used form of ultrasound is based on Brightness-mode (B-mode) images, in which the amplitude of the reflected soundwave is linearly encoded in shades of gray as a function of distance from the source, providing a two-dimensional view (see Figure 2).

To date, the focus of ultrasound research in CTS has predominantly been on static measurements of the median nerve within the carpal tunnel in the transverse plane. Cross-sectional area of the median nerve, for example, has been extensively studied, as it can contribute to diagnosing CTS[49-51]. However, since ultrasound provides high resolution, high-frame rate imaging, it also allows for dynamic imaging of the carpal tunnel. It has been shown that dynamic ultrasound imaging, whereby alterations of shape and excursion of structures within the carpal tunnel can be measured during motion, has the ability to detect biomechanical alterations in patients with CTS[52,53]. Excursions of the median nerve, tendons and SSCT in both the transverse and longitudinal plane have been studied[52].

Analysis of transverse ultrasound clips is relatively straightforward, since the border of the median nerve and tendons are clearly visible and therefore the displacement can be easily tracked either manually or using automated algorithms (Figure 2). Longitudinal image analysis requires a more custom approach, since there is no anatomical landmark, such as the musculo-tendinous junction (mostly used in analysis of tendon movement) visible to manually track the motion (Figure 3).
Speckle tracking, a method in which ultrasound speckles generated by the reflected ultrasound beam are tracked from frame to frame to assess the motion of speckles, can be used to study longitudinal motion of tissue. Speckle tracking provides a two-dimensional displacement estimate. The use of speckle tracking is attractive, as anatomical landmarks are not required due to utilizing inherent speckles and it is independent of the angle of the ultrasound transducer. Yoshii et al. were the first to assess the relative motion of the flexor tendon and surrounding SSCT in the carpal tunnel of healthy subjects using speckle tracking[54]. For the analysis, they used Velocity Vector Imaging (VVI) Syngo software, a speckle tracking algorithm, originally developed for the quantitation of myocardial function[55,56]. Korstanje et al. introduced a different technique,[57] developing and validating a speckle tracking algorithm optimized for quantification of tendon motion. The novelties of the algorithm included a manually

selected stationary region of interest (ROI) divided into a number of multiple overlapping kernels to estimate frame-to-frame displacement. Normalized cross-correlation was used to calculate the average correlation-weighted kernel displacement. Korstanje et al. demonstrated that this speckle tracking algorithm accurately quantifies tendon displacement at different physiological velocities. This algorithm has been applied in several clinical studies assessing longitudinal displacement of structures within the carpal tunnel[52,58].

The Mayo Clinic, Rochester, MN, USA, is conducting a clinical trial on ultrasound in CTS: '*Dynamic Ultrasound to Enhance Understanding in Carpal Tunnel Syndrome*'. One of the aims of this clinical trial is to assess whether there is a correlation between dynamic ultrasound parameters and treatment outcome. The ultimate goal is to build a prediction model for treatment outcome in order to be able to provide more tailored treatment for specific patients. We proposed to use the speckle-tracking algorithm developed by Korstanje et al. to analyze longitudinal ultrasound data of this clinical trial. Although Korstanje et al. found relatively small errors in their validation study of the customized speckle-tracking algorithm[57], the algorithm tended to underestimate the motion due to noise and semi-static artifacts (stationary background, clutter, and shadowing) in the images, which limits the performance of the tracking algorithm. In our study we therefore wanted to optimize the speckle-tracking algorithm and test its validity and reliability.

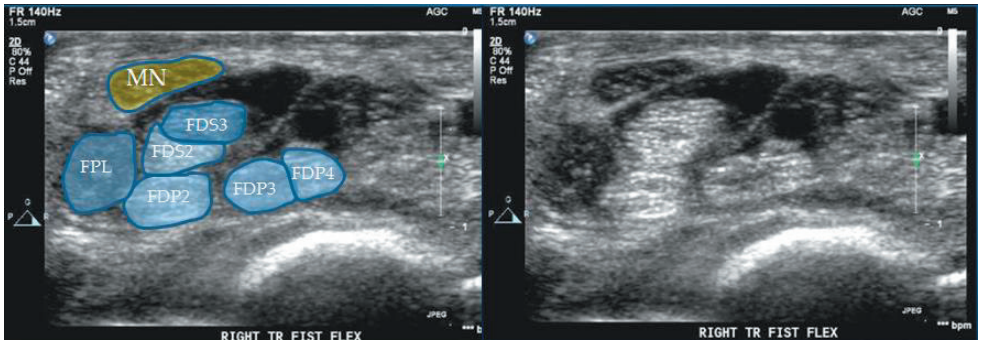

Figure 2. Cross-sectional ultrasound image of the carpal tunnel at the wrist crease. Left: polygons on the outside borders of the median nerve (MN), tendon of the flexor digitorum superficialis (FDS) 2 and 3, flexor digitorum profundus (FDP) 2, 3 and 4 and flexor pollicis longus (FPL). The FDS 4 and 5 and FDP 5 are not distinguishable in this figure.

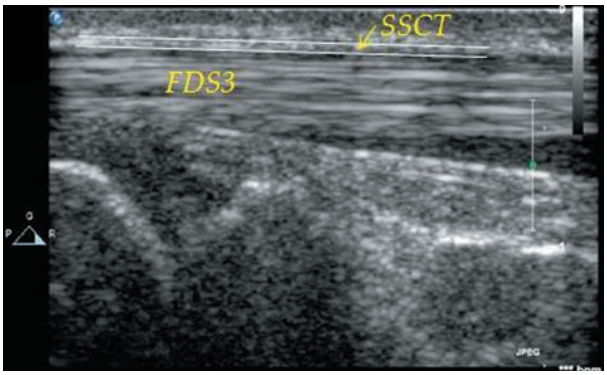

Figure 3. Longitudinal ultrasound image, including the tendon of the flexor digitorum superficialis 3 (FDS 3), with the subsynovial connective tissue (SSCT) on top. The left bony landmark indicates the os lunatum, the right bony landmark indicates the radius.

4.2 Ultrasonographic assessment of CTS

After testing and optimizing the methods for ultrasound analysis we wanted to conduct a clinical study, since there is expanding support for the added value of ultrasound in the management of CTS[50,51,59].

Cross-sectional area of the median nerve has been most extensively studied and this parameter has been proven to contribute to the diagnosis of CTS[50,51]. The Dutch Guideline for CTS recommends performing diagnostic testing in absence of a classic presentation of CTS[60]. Since ultrasound examination has a similar sensitivity and specificity to EDS[61,62], which can be painful, ultrasound (if available) is the preferred diagnostic tool, while in the past there was a preference to use EDS. Increased cross-sectional area of the median nerve at the level of the os pisiforme supports the diagnosis of CTS, however, due to the large variation in the normal physiological cross-sectional area of the median nerve, thus far no consensus has been reached on the cut-off value between healthy and pathological subjects[63,64]. It has been suggested to use center-specific references or reference values from the literature from a similar population[60,63]. In addition, it should be taken into account that the image quality and consequently, interpretation of the ultrasound clips can vary between raters[65]. Furthermore, a disadvantage of ultrasound compared to EDS is lack of information on nerve function. On the other hand, ultrasound does not only provide information on the median nerve, but also on the presence of other abnormalities at the wrist, such as a ganglion cyst[66].

Although the most common ultrasound variable for CTS involves the cross-sectional area of the median nerve, other variables might be diagnostically relevant as well. In patients with CTS, the motion patterns of the median nerve as well as the tendon and

SSCT within the carpal tunnel is different compared to normal subjects[52]. For example, it has been shown that median nerve displacement in patients with CTS is inhibited[53,67]. In addition, an altered relative motion between SSCT and tendon in patients with CTS has been described[68]. This observation is twofold; 1) the SSCT can be either completely adhered to the tendon, or 2) there is a complete disconnection/dissociation between SSCT and the tendon, whereas normally the tendons and SSCT move in synchrony. Analyzing these differences may help predict which treatment, injection or surgery, may be more beneficial for specific patients. Therefore we assessed the association between pre-surgical ultrasound parameters and clinical outcome.

4.3 Ultrasound guidance in the treatment of CTS

Recently, novel interventions in the treatment of CTS have been proposed. Besides serving as a diagnostic imaging tool, ultrasound can also serve to guide interventions, such as injections in the upper extremity[69]. The development of high-frequency ultrasound probes allows us to accurately visualize structures within the carpal tunnel (epineurium, perineurium and fascicles of the nerve) in real time, as described above. This visualization may also help to guide a carpal tunnel injection. Consequently, ultrasound-guidance may improve the accuracy and consequently the efficacy of the injection. Previous studies on ultrasound-guided injections for CTS generally indicate that ultrasound-guided injections result in better symptom relief and increased therapeutic duration compared to blind injections[70-72].

Several techniques to perform an ultrasound-guided injection within the carpal tunnel have been described. Smith et al. described the ulnar approach and additionally performed hydrodissection of the median nerve within the carpal tunnel[73], which is a proposed new technique to treat nerve entrapment[70,74], based on the theory that entrapment is exacerbated by median nerve fixation to surrounding tissues such as the transverse carpal ligament. Although the exact relationship between fibrosis and nerve abnormalities is unknown, freeing the median nerve from fibrosis by a volume of saline creating a perineural fluid plane, might free the entrapped nerve. While hydrodissection is clinically used, there is very limited data available that support its effectiveness[75]. Therefore we wanted to: 1) assess the effectiveness of ultrasound-guided compared to blind injections in the treatment of CTS and 2) explore the underlying mechanism of action of hydrodissection.

5. Thesis outline

To summarize, this thesis contains three parts following the three main aims.

Part I: Treatment outcomes of CTS

In **chapter 2**, we describe the long-term follow-up of corticosteroid injections for CTS in a population-based cohort. In addition, we identify prognostic factors for subsequent treatment following a corticosteroid injection for CTS.
Chapter 3 focuses on injection volume**.** Since the optimal volume for a corticosteroid injection in CTS has not yet been established, we assess the influence of injection volume on rate of subsequent intervention over 1 year follow-up.
Chapters 4 and 5 focus on surgical treatment for CTS. Since prediction of treatment outcome of carpal tunnel release has been challenging, we aim to predict clinical outcome after surgical treatment in patients with CTS in a large surgical cohort (**chapter 4**). In addition, we assess whether hand surgeons performing more open carpal tunnel releases show better patient outcomes (**chapter 5**).

Part II: Ultrasonographic assessment of CTS

In **chapter 6**, we propose a novel technique: Singular Value Decomposition (SVD), to mitigate the effects of clutter and noise to increase the robustness of the tracking algorithm presented by Korstanje et al. and assess its validity.
In **chapter 7**, we optimize the algorithm using a human cadaver study, since pilot studies have shown that the performance of the algorithm is highly sensitive to different settings of parameters such as frame difference.
In **chapter 8**, the reliability of the ultrasound speckle tracking algorithm including SVD is assessed.
In **chapter 9**, the changes in median nerve morphology and its mobility in CTS patients are assessed before and after CTR and we explore the prognostic potential of static and dynamic ultrasound assessments using patient reported outcomes.

Part III: Ultrasound guidance in the treatment of CTS

In **chapter 10**, the effectiveness of ultrasound-guided compared to blind steroid injections in the treatment of CTS is assessed.
In **chapter 11**, we perform a cadaver study in which we assess gliding resistance of the median nerve within the carpal tunnel pre- and post ultrasound-guided hydrodissection, because it has not been formally investigated whether hydrodissection mobilizes the median nerve within the carpal tunnel.

Finally, **chapter 12** provides a general discussion including future research perspectives.

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PART I

TREATMENT OUTCOMES OF CTS

2

CORTICOSTEROID INJECTIONS FOR CARPAL TUNNEL SYNDROME: LONG-TERM FOLLOW-UP IN A POPULATION-BASED COHORT

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Plast Reconstr Surg. 2017 Aug;140(2):338-347.

ABSTRACT

Background

Corticosteroid injection is a recommended treatment option for carpal tunnel syndrome, before considering surgery. Nevertheless, injections remain controversial because there is strong evidence of only short-term benefits. This study aimed to determine the reintervention rate and to identify prognostic indicators for subsequent treatment after a corticosteroid injection for carpal tunnel syndrome.

Methods

This study evaluated residents of Olmsted County treated with a corticosteroid injection for CTS between 2001 and 2010. Treatment failure was the primary outcome of interest. Two definitions for failure were examined: (1) the patient receiving subsequent procedural intervention and (2) the patient undergoing carpal tunnel release. Survival was estimated using Kaplan-Meier methods, and association of covariates with increased failure was modeled using Cox proportional hazards regression.

Results

The study included 774 affected hands in 595 patients. The median follow-up period was 7.4 years. Reintervention was performed in 68 percent of cases, of which 63 percent resulted in eventual surgery. Injectate volume was significant for the outcome of any retreatment [hazard ratio, 0.879 (95% CI, 0.804 to 0.96]) and surgery (hazard ratio, 0.906 (95 percent CI, 0.827 to 0.99]). Rheumatoid arthritis was also significant in both models, with a hazard ratio of 0.627 (95 percent CI, 0.404-0.97) for any retreatment and 0.493 (95 percent CI, 0.292 to 0.83] for surgery.

Conclusions

In this cohort, 32 percent of the patients did not receive subsequent treatment after a single injection, which indicates that there is a therapeutic role for corticosteroid injections in the treatment of CTS. Further research is necessary to identify those patients who will benefit from an injection, to provide more individually tailored treatment.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a common yet disabling condition, with an annual incidence of 2 to 5 percent for women and 1 to 3 percent for men[1-3]. Splinting, local steroid injection and carpal tunnel release are all recommended treatment options for this condition[4,5]. Most guidelines suggest trying local steroid injection or splinting before considering surgery, and several studies have shown that local steroid injections are effective in providing at least short-term symptom relief[4,5]. However, the role of steroid injections in the treatment of CTS remains controversial, because there is strong evidence for benefits of steroid injections only in the short term[6,7].

Two recent systematic reviews on the effectiveness of steroid injections concluded that the effects appear to be time limited, and there is limited evidence on the long-term effectiveness[6,7]. Reported rates of subsequent treatment, either reinjection or surgery, vary from 10% -81% at 1 year after initial injection[8-13]. Jenkins et al. reported that 272 of the 824 (33 percent) with mild to moderate CTS who underwent a local corticosteroid injection required surgery at-5 year follow-up[13]. This indicates that there is a subgroup of patients who will achieve lasting symptom improvement from an injection.

It would be important to identify the likelihood of long-term benefit from a local steroid injection. For those unlikely to have long-term benefit, surgery would be a more appropriate option, as it would hasten the resolution of symptoms, and avoid the discomfort or potential complications of an injection. For those likely to have long-term benefit, injection therapy would prevent unnecessary surgery and reduce health care costs. Previous studies have investigated predictors for subsequent treatment of CTS after initial injection. A diagnosis of diabetes mellitus, higher preinjection score on the Boston Carpal Tunnel Questionnaire (BCTQ), longer duration of symptoms and a more severe electrodiagnostic study (EDS) result have all been suggested as risk factors for poor clinical outcome following a local corticosteroid injection[11-15]. However, these results are not consistent across different studies.

The purpose of this study was to determine the long-term rate of reintervention (additional injection or surgery) after a single corticosteroid injection in the management of CTS and to identify prognostic indicators for subsequent treatment in a population-based cohort.

METHODS

Data collection

This retrospective study is based on data from residents of Olmsted County, MN, USA, treated with a corticosteroid injection for CTS between 2001 and 2010. Patients were identified using the resources of the Rochester Epidemiology Project (REP) medical

records linkage-system[16]. The REP organizes demographic data, diagnostic codes and surgical procedure codes in electronic indexes that can be searched. Patients' residency status is also checked. Multiple medical records for the same individual are linked within and across institutions to create a comprehensive record, regardless of where a county resident is seen[17]. Participating institutions and providers include not only those within Olmsted County but also those in the surrounding region. Studies have shown that the database includes nearly all care provided to nearly all (i.e., >90 percent) Olmsted County residents. Our selection was based on a *Current Procedural Terminology* code for diagnosis of carpal tunnel syndrome (*International Classification of Diseases, Ninth Revision,* code 354.0) and carpal tunnel injection (*Current Procedural Terminology* code 20526). The REP list of patients with diagnosis of CTS and a procedure of carpal tunnel injection within the specified time frame was retrieved using the computerized indexes, and the consolidated records of these patients were reviewed by three physicians (SE, AB, TS) to verify the diagnosis. Information on the diagnosis was abstracted from the medical charts and cases of possible or unlikely CTS (based on previously described criteria[18]) were excluded from this study. In addition, detailed record abstraction was used to collect data on comorbidities, EDS severity and volume and dose of injectate. Patients were followed through their medical record until 2014. The last day of follow-up was defined as the most recent day the patient had visited a REP health care provider, or December 31, 2014 if the patient visited a REP health care provider after 2014.

Patients were included if they had a diagnosis of primary CTS, no previous injection for CTS or carpal tunnel release in that hand, received a therapeutic corticosteroid injection for CTS, were at least 18 years old, had at least one day of follow-up, and had provided research authorization. Patients diagnosed with pregnancy-related CTS and observations missing injectate volume or steroid dose were excluded from the analysis. Ultrasound-guided injections were excluded from analysis, because they were the subject of a different report and also because literature suggests that they have a different failure rate compared to blind injections[19,20]. Study data were managed using Research Electronic Data Capture (REDCap).

The risk factors examined were age, sex, total injectate volume (combined steroid and anesthetic volume), effective dose of steroid, history of diabetes mellitus, diagnosis of peripheral neuropathy or cervical radiculopathy, diagnosis of rheumatoid arthritis and EDS severity at time of injection. Dose of steroid was standardized to equivalent effective dose of triamcinolone, which had the highest use in the cohort and was converted using Table 3 in Leversee et al.[21]. The severity of CTS was assessed using available EDS data. EDS severity was classified in the following categories: normal, mild, moderate and severe based on the classification of Stevens[22]. Subjects without information, which allowed EDS severity to be assessed, were assigned to a fifth EDS category: untested.

Outcome measurements

Failure of treatment was the primary outcome of interest. Two definitions for failure of treatment were examined: (1) failure defined as any subsequent procedural intervention (i.e. corticosteroid injection or CTR) and (2) failure defined as patient receiving eventual CTR on the injected hand regardless of the number of injections.

Statistical analysis

Summary statistics for demographics and clinical characteristics are shown as N (%), mean ± standard deviation (SD) or median [interquartile range (IQR)]. Subjects without events were censored at the earlier of the date of last follow-up present in the medical record or Dec. 31, 2014. The Kaplan-Meier method was used to estimate median failure time for both definitions of failure. Cox proportional hazard models with robust variance estimators were fit to test for covariates' associations with increased risk of treatment failure. Robust variance estimators were used to adjust for correlated outcomes between hands of the same patient. Model assumptions, such as proportional hazards, were assessed. Stratification was performed to adjust for variables failing the proportional hazard assumptions. Hazard ratios (HR) and 95% confidence intervals (CI) are reported. Values of $p<0.05$ were considered significant. Statistical analyses were performed using R (version 3.1.2; Vienna, Austria); survival analyses used the survival package (version 2.39-4)[23-25].

Comparison to surgery without previous injection cohort

To give an overview of the characteristics of the full cohort of patients treated for CTS, the group of patients who went directly to surgery was also examined. This allowed us to compare the patient and disease specific characteristics of the patients who received an injection to patients who proceeded directly to surgery within the specified time window and within the same population.

Patients that proceeded directly to surgery were selected using the same resource as the injection cohort, with selection based on a *Current Procedural Terminology* code for diagnosis of carpal tunnel syndrome (*International Classification of Diseases, Ninth Revision,* code 354.0) and open carpal tunnel release (64721) or endoscopic carpal tunnel release (29848).

The following were criteria for the inclusion: diagnosis of primary CTS, no previous injection or surgery for CTS in that hand, no acute CTS, at least 18 years old and provision of research authorization. Patients who received a therapeutic injection on either hand, including bilateral cases where only one hand was treated with injection, were excluded from this subset. Characteristics of interest were age, sex, EDS severity, history

of diabetes mellitus, diagnosis of peripheral neuropathy or cervical radiculopathy, and diagnosis of rheumatoid arthritis. Under the assumption that distributions would be similar to the injection cohort, this group was randomly sampled to allow estimation of EDS severity proportions with a precision of ± 5%. Chi-Square or Wilcoxon rank sum tests were used to compare baseline characteristics between groups.

RESULTS

Patient selection and baseline characteristics

A total of 1144 observations within the specified time window were identified. Of these, a total of 988 subjects had a primary diagnosis of CTS. Subjects who had pregnancy-related CTS (N=20), had US-guided procedures (N=93), were missing injectate volume or dose of steroid (N=88), and subjects who did not have at least 1 day of follow-up or had another indication for exclusion (N=13) were also removed. After exclusions, there were a total of 774 affected hands in 595 distinct individuals (Figure 1).

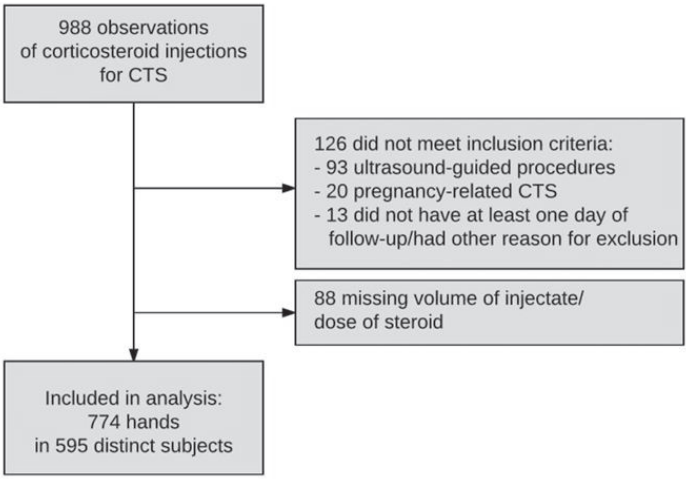

Figure 1. Subject selection flowchart.

Descriptive statistics are displayed in Table 1, and whether they are reported at the subject or hand level is indicated. The cohort was 30.4% men, with 8.74% having a diagnosis of diabetes mellitus, 7.73% having peripheral neuropathy or cervical radiculopathy, and 5.38% having rheumatoid arthritis. The mean (SD) age at injection was 51 years (13.5). The injections used an average injectate volume of 3.7 mL (1.16) and an average steroid dose of 39.9 mg (22.3). For EDS severity, 14.5% were not tested, 8.3% were classified as normal, 29.6% were classified as mild, 41.2% were classified as moderate, and 6.5%

were classified as severe. The median follow-up period was 7.3 years (minimum 7 days, maximum 12.6 years).

Table 1. Demographics and clinical characteristics of the injection cohort.

	Subject level (n=595) Hand level* (n=774)
Age at injection* Mean (SD)	50.6 (13.5)
Gender (Male) (n/%)	181 (30.4%)
Diabetes mellitus (n/%)	52 (8.74%)
Peripheral neuropathy or cervical radiculopathy (n/%)	46 (7.73%)
Rheumatoid arthritis (n/%)	32 (5.38%)
EDS severity*	
Normal	64 (8.27%)
Untested	112 (14.5%)
Mild	229 (29.6%)
Moderate	319 (41.2%)
Severe	50 (6.46%)
Injectate volume (mL)* Mean (SD)	3.66 (1.16)
Effective steroid dose (mg)* Mean (SD)	39.9 (22.3)

**Hand-level characteristics*

Overall, reintervention (injection or CTR) was performed in 525 of 774 cases (67.8%), with eventual CTR in 485 cases (62.7%). Median (IQR) time to failure was 259 days (121 to not applicable) for any retreatment and 446 days (147 to not applicable) for CTR (Figure 2). Estimates of the 75th percentile for time to failure are not available, as that proportion of failure was not observed. There were 131 subjects (N=159 hands) who received a second injection for treatment of CTS. Of these, 85 subjects [N=100 hands (62.9%)] eventually were treated with CTR.

Prognostic factors

Results for Cox proportional hazard models are displayed in Tables 2 and 3 for the outcomes of any reintervention and carpal tunnel release, respectively. EDS severity failed proportional hazard assumptions and was used as a stratifying variable. Figures 3 and 4 show the survival curves stratified by EDS severity. Although we are not able to formally test within the context of the model between strata, these curves indicate that patients with more severe EDS results were more likely to experience injection failure. Higher injectate volume was found to be significantly associated with a decreased likelihood of injection failure for the outcome of any retreatment (HR 0.879 [0.804-

0.96], p=0.004) and carpal tunnel release (HR 0.906 [0.827-0.99], p=0.034). Rheumatoid arthritis was found to be significantly associated with a decreased likelihood of injection failure in both models, with HR 0.627 [0.404-0.97] (p=0.037) for any retreatment and HR 0.493 [0.292-0.83] (p=0.008) for carpal tunnel release. The effective dose of steroid was not significantly associated with either outcome measurement (any subsequent treatment: HR 0.998 [0.994, 1.00], p=0.510 and carpal tunnel release: HR 0.996 [0.991, 1.00], p=0.105).

Table 2. Demographics and clinical characteristics and their association with re-intervention (either second corticosteroid injection or carpal tunnel release) in patients with carpal tunnel syndrome after initial treatment with corticosteroid injection in a Cox proportional hazards model. Risk factors, model parameter estimates (Beta) and standard errors (SE), hazard ratios, 95% confidence intervals (CI), and model p-values are presented. Electrodiagnostic study (EDS) severity was used as a stratifying variable.

Risk factor	Beta (SE)	Hazard Ratio (95% CI)	*p*
Age(/10 years)	-0.026 (0.036)	0.975 [0.909, 1.05]	0.471
Gender (male)	-0.155 (0.111)	0.856 [0.689, 1.06]	0.162
Diabetes mellitus	-0.127 (0.191)	0.881 [0.606, 1.28]	0.508
Rheumatoid arthritis	-0.467 (0.224)	0.627 [0.404, 0.972]	0.037
Peripheral neuropathy or Cervical radiculopathy	-0.082 (0.179)	0.921 [0.649, 1.31]	0.647
Injectate volume	-0.129 (0.045)	0.879 [0.804, 0.960]	0.004
Effective dose of steroid	-0.002 (0.002)	0.998 [0.994, 1.00]	0.510

Table 3. Demographics and clinical characteristics and their association with subsequent carpal tunnel release in patients with carpal tunnel syndrome after initial treatment with corticosteroid injection in a Cox proportional hazards model. Risk factors, model parameter estimates (Beta) and standard errors (SE), hazard ratios, 95% confidence intervals (CI), and model p-values are presented. Electrodiagnostic study (EDS) severity was used as a stratifying variable.

Risk factor	Beta (SE)	Hazard Ratio (95% CI)	*p*
Age(/10 years)	-0.036 (0.037)	0.965 [0.897, 1.04]	0.336
Gender (male)	-0.177 (0.115)	0.837 [0.668, 1.05]	0.124
Diabetes mellitus	-0.078 (0.194)	0.925 [0.632, 1.35]	0.687
Rheumatoid arthritis	-0.708 (0.266)	0.493 [0.292, 0.830]	0.008
Peripheral neuropathy or Cervical radiculopathy	-0.011 (0.190)	0.989 [0.682, 1.44]	0.955
Injectate volume	-0.098 (0.046)	0.906 [0.827, 0.993]	0.034
Effective dose of steroid	-0.004 (0.002)	0.996 [0.991, 1.00]	0.105

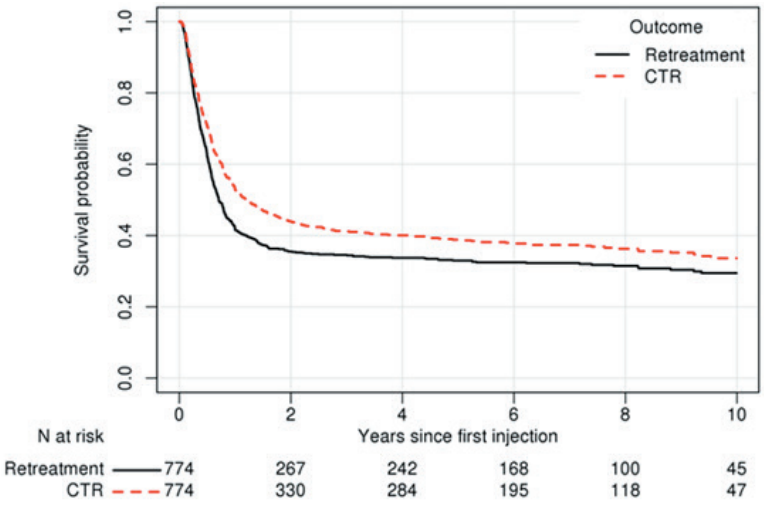

Figure 2. Kaplan-Meier curve for survival (i.e. no subsequent intervention received) in the injection cohort. Subsequent interventions were classified as 1) retreatment (i.e. either a second corticosteroid injection or carpal tunnel release (CTR)) or 2) CTR only. The table underneath the figure represents the number remaining at risk (i.e. who are still being followed and have not yet experienced the event of interest) at baseline, 2, 4, 6, 8, and 10 years after the initial injection for both the outcome of any retreatment and for CTR.

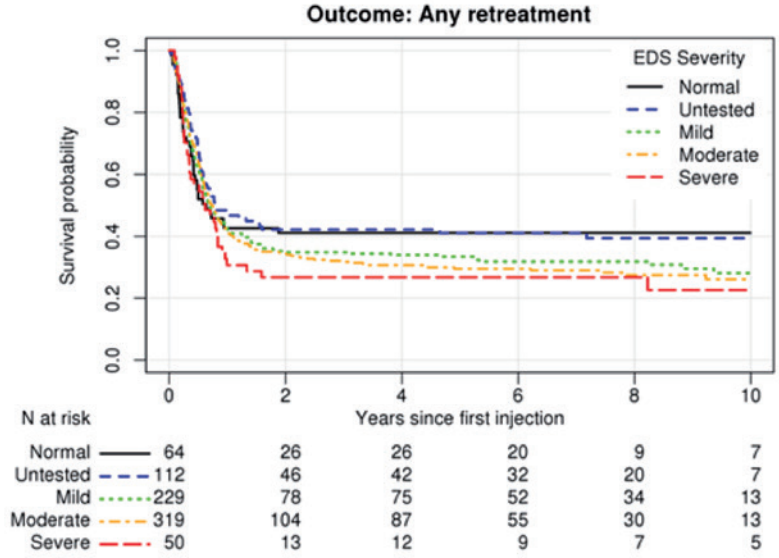

Figure 3. Survival curve for injection cohort stratified by electrodiagnostic study (EDS) severity based on estimates from a Cox proportional hazards model. The table underneath the figure represents the number remaining at risk (i.e. who are still being followed and have not yet experienced the event of interest) at baseline, 2, 4, 6, 8, and 10 years after the initial injection for the outcome of any retreatment (re-injection or carpal tunnel release).

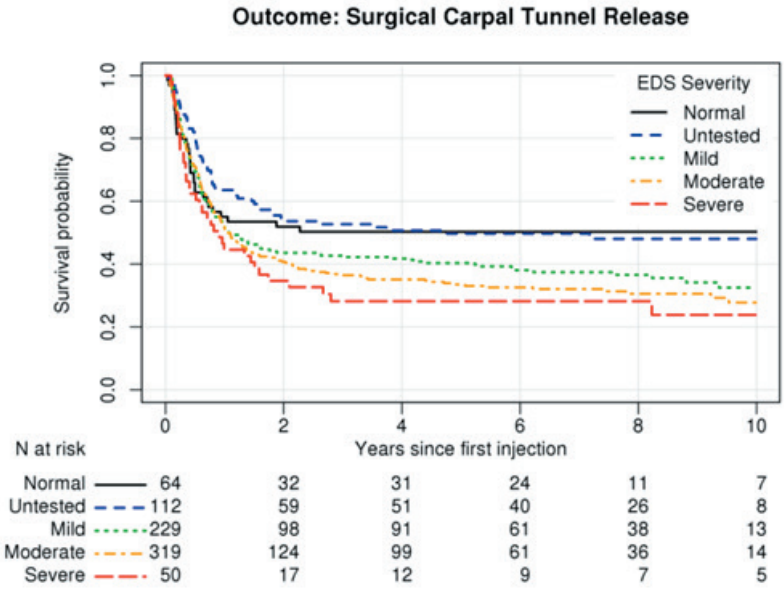

Figure 4. Survival curve for injection cohort stratified by electrodiagnostic study (EDS) severity based on estimates from a Cox proportional hazards model. The table underneath the figure represents the number remaining at risk (i.e. who are still being followed and have not yet experienced the event of interest (carpal tunnel release)) at baseline, 2, 4, 6, 8, and 10 years after the initial injection within each stratum.

Injection versus Surgical cohort

There were 931 unique subjects who received carpal tunnel surgery without previously receiving an injection in 2001-2010; 300 were randomly selected to represent this group. Of the 300 subjects in the direct to surgery sample, 104 had surgery on both hands (total, N=404 hands), 35.3% were male, 15.7% had diabetes mellitus, 2.0% had rheumatoid arthritis, and 8.33% had peripheral neuropathy or cervical radiculopathy. They were on average 55.0 (SD 14) years of age and 9.65%, 3.47%, 16.3%, 44.8%, 25.7% had EDS severities of untested, normal, mild, moderate, and severe, respectively. Compared to the injection cohort, they were older (p<0.001) and had a lower proportion of patients with rheumatoid arthritis (p=0.028), a higher proportion of diabetics (p=0.003), and more severe EDS results (p<0.001). Table 4 shows the demographics and clinical characteristics of the surgical sample and comparison to characteristics of the injection cohort.

Table 4. Demographics and clinical characteristics comparing subjects who went directly to surgery (i.e. carpal tunnel release without previous corticosteroid injection: surgical sample) and the injection cohort. *Hand-level characteristics

Characteristic	Surgical sample Subject level n= 300 Hand level n= 404*	Injection Cohort Subject level n=595 Hand level n= 774*	*p*
Demographics			
Age at intervention, year, mean (SD)*	55 (14)	50.6 (13.5)	<0.001
Gender (Male) (n/%)	106 (35.3%)	181 (30.4%)	0.158
EDS severity (n/%)*			<0.001
Normal	14 (3.47%)	64 (8.27%)	
Mild	66 (16.3%)	229 (29.6%)	
Moderate	181 (44.8%)	319 (41.2%)	
Severe	104 (25.7%)	50 (6.46%)	
Unknown	39 (9.65%)	112 (14.5%)	
Comorbidity (n/%)			
Diabetes mellitus	47 (15.7%)	52 (8.74%)	0.003
Rheumatoid arthritis	6 (2%)	32 (5.38%)	0.028
Peripheral neuropathy/ Cervical radiculopathy	25 (8.33%)	46 (7.73%)	0.854

DISCUSSION

In this population-based cohort, with median follow-up of 7.4 years, 32% of the subjects did not receive subsequent treatment after a single steroid injection. The presence of rheumatoid arthritis and a higher volume of injectate were associated with decreased likelihood of subsequent treatment.

Most guidelines suggest a course of non-operative treatment in patients diagnosed with CTS, however there remains controversy about the role of steroid injections. Some physicians consider corticosteroid injections to be a diagnostic tool only[4,5]. It has been suggested that regional variation in the use of surgery for many conditions is mainly a result of physician beliefs about the indications for surgery[18,26]. This may explain the regional variation in rates of carpal tunnel release[27]. Our result, that approximately a third of patients did not receive subsequent treatment in the long term, suggests a role for corticosteroid injections in the treatment of CTS. A local corticosteroid injection is less invasive and less expensive compared with surgery and does not require time off from work. Although corticosteroids injections do come with risks and potential adverse events, as median nerve injury or infection may occur[28], the low morbidity and low cost of a steroid injection make it an excellent form of initial treatment in some CTS patients[29-31]. We believe that this approach is especially relevant since the natural history of CTS

remains unknown, and some patients experience spontaneous improvement in their symptoms, with reported rates of 33% to 40% experiencing some improvement, depending on EDS severity[32-35].

The rate of subsequent treatment found in this study correlates with previous studies, which mostly looked at shorter term follow-up. Meys et al. followed 113 patients who received an injection for CTS and found that 67% had surgery within one year[12]. Jenkins et al. found that 33% of the patients receiving a local corticosteroid injection underwent carpal tunnel release within 5 years post initial treatment[13]. The proportion is lower than in our study, but their result was based on patients with mild to moderately severe CTS only. Berger et al. found that 75% underwent surgery after a single injection, a slightly higher proportion than our result[10]. In that prospective study, patients were offered a reinjection or surgery when there was minor or no relief of symptoms at follow-up, which might have resulted in a higher proportion of injection failure. A randomized placebo-controlled trial on the effect of steroid dose showed a surgery rate of 73% to 81% at one year follow-up[8]. The choice to proceed to surgery was solely made by the patient; however, the study design might make it challenging to extrapolate the failure rate to a clinical setting, because the participation in a randomized controlled trial and chance of receiving a placebo injection may heighten vigilance of patients, thereby increasing the chance of residual symptoms[36]. Our retrospective study was free from this type of bias.

The proportion of patients undergoing surgery after the second injection was similar to the proportion proceeding to surgery after one injection. Ashworth and Bland assessed the effectiveness of second corticosteroid injections for carpal tunnel syndrome in 229 patients[37]. They found that the change in Boston Symptom Severity Scale and Functional Status Scale was not significantly different between first and second injections and concluded that second injections appear to be at least as effective as first injections. To the best of our knowledge, the maximum number of injections that an individual might benefit from is unknown[10].

Several risk factors for recurrence after a single steroid injection have previously been identified.

However, the negative association between a diagnosis of rheumatoid arthritis and subsequent treatment found in this study has not been previously described. Rheumatoid arthritis-associated CTS might respond better to an injection due to the underlying pathophysiology: an inflammatory condition versus non-inflammatory fibrosis in idiopathic CTS[38]. However, we cannot rule out that rheumatoid arthritis was a confounder in our cohort. Rheumatologists might be less likely to refer patients to a hand surgeon for a carpal tunnel release. The effect of volume of injection has not been studied in depth. A Cochrane review by Marshall et al. stated that no particular

dosage or type of medication provided a superior outcome for the treatment of CTS[6]. Our results that a larger volume of injection is associated with lower risk of injection failure could be related to greater fluid distribution or greater contact area with the soft tissues within the carpal tunnel[39]. The finding that patients with more severe EDS results are more likely to experience injection failure has already been documented[14].

In contrast to previous studies, we did not find a diagnosis of diabetes mellitus to be a predictor for subsequent treatment[11,13,15]. However, there was a significantly smaller proportion of patients with diabetes mellitus in the injection cohort compared to the surgical sample. Thus, patients with diabetes mellitus might have had more severe CTS and were therefore more likely to proceed to surgery directly or their physicians may have been more likely to operate on CTS patients with diabetes because it has already been well-described that they are less likely to benefit from an injection.

Our study has some limitations. First, this study was retrospective in design and lacked a control group. Ideally, there should have been a control group of patients without treatment, since some patients improve spontaneously[34,35]. Second, our outcome measure where failure of injection is defined as receiving subsequent treatment may not adequately capture clinically relevant failures, where patients have ongoing symptoms of CTS but elect for some other reason not to receive subsequent treatment. Third, there was variability in techniques of corticosteroid injection that were used. Literature suggests that some techniques are more effective than others and this might have affected the results[39,40]. Fourth, although the study is based on a large number of patients, we have to take into account an exclusion of about 7% of potential cases because the patients had not authorized the use of their medical records for research[16]. Finally, despite the comprehensive nature of the REP medical record linkage system, it is possible that some patients received treatment from non-REP providers (e.g., while traveling. Despite these limitations, the strength of this study is the comparison with patients who proceeded directly to surgery, which describes the characteristics of the full population-based cohort of patients treated for CTS.

In conclusion, this study shows that a substantial proportion of the patients undergoing a steroid injection for CTS did not receive subsequent treatment, even after a lengthy follow up, ranging up to 12 years. Further research is necessary to identify those patients who will benefit in the long term from a corticosteroid injection, to provide more individualized treatment for patients with CTS.

ACKNOWLEDGEMENTS

This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes

of Health under Award Number R01AG034676. The project was additionally supported by NIH/NCRR Colorado CTSI Grant Number UL1 RR025780, NIH/NIAMS Grant Number R01AR62613 and Mayo Foundation.

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3

INFLUENCE OF INJECTION VOLUME ON RATE OF SUBSEQUENT INTERVENTION IN CARPAL TUNNEL SYNDROME OVER 1 YEAR FOLLOW-UP

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J Hand Surg Am. 2018 Jun;43(6):537-544.

ABSTRACT

Background

The optimal volume and dose of corticosteroid injections for treatment of carpal tunnel syndrome (CTS) has not yet been established. It is unknown whether volume of injectate influences the outcome of carpal tunnel injection. The purpose of our study was to assess whether there is an association between volume of injectate and subsequent intervention in the treatment of CTS.

Methods

This study evaluated residents of Olmsted County, MN, who were treated with a corticosteroid injection for CTS between 2001 and 2010. Failure of treatment was the primary outcome, defined as a subsequent intervention: either a second injection or carpal tunnel release within 1 year of initial injection. General estimating equations logistic regression was used to assess the association between injectate volume and rate of treatment failure, adjusting for age, sex, effective dose of steroid, type of steroid injected, electrodiagnostic severity, and the presence of comorbidities such as rheumatoid arthritis, diabetes mellitus, peripheral neuropathy, and radiculopathy.

Results

There were 856 affected wrists in 651 patients. A total of 56% (n = 484) of treated hands received subsequent treatment within 1 year. Multivariable analysis showed that a larger injectate volume was significantly associated with reduced rate of treatment failure within 1 year. Rheumatoid arthritis and ultrasound-guided procedures were also associated with a reduced rate of failure, whereas severe electrodiagnostic results were associated with an increased rate of failure.

Conclusions

This study showed that a larger volume of corticosteroid injection is associated with reduced odds of subsequent intervention after a single corticosteroid injection in CTS. Further research is needed to determine the optimal volume for steroid injections in the treatment of CTS.

INTRODUCTION

For patients with carpal tunnel syndrome (CTS), local corticosteroid injection provides greater clinical improvement in symptom relief 1 month after the injection compared with a placebo injection[1]. An injection for CTS commonly involves a combination of steroid and local anesthetic[2,3].

A systematic review reported that the site of injection, dose of steroid, type of steroid and/or local anesthetic, and concomitant use of an orthosis after injection do not alter the underlying efficacy of a steroid injection for CTS[4]. However, most recorded interventions involved injections of relatively low volumes of total injectate, most commonly 1 to 3 mL.

Although corticosteroid injection provides short-term benefit to many patients with CTS, and longer-term benefit to some, the optimal volume of corticosteroid injections for CTS has not yet been determined, and it is unknown whether the volume of injectate influences the outcome of carpal tunnel injection. It is the opinion of some practitioners that larger volumes may be associated with a reduced risk of symptom relapse, owing to the effects of the added volume to hydrodissect and mobilize the nerve[5,6]. In addition, higher-volume injections could be related to a larger area of fluid dispersion or distribution, greater contact area with soft tissues, or extravasation of fluid outside the canal[7-9]. Therefore, the aim of this retrospective study was to assess whether an association exists between volume of injection and subsequent intervention after a single corticosteroid injection in patients with CTS.

MATERIALS AND METHODS

Data collection

The cohort of patients receiving an injection for CTS was identified from residents of Olmsted County, MN, using the medical records-linkage system of the Rochester Epidemiology Project (REP)[10]. The Institutional Review Board approved the study. The REP is a research infrastructure system that links together nearly all of the medical records (1966 to the present) of the residents of Olmsted County. The REP consists of demographic data, diagnostic codes and surgical procedure codes organized in electronic indexes that can be searched. Multiple medical records for the same patient are linked within and across institutions to create a comprehensive record, irrespective of where a county resident is seen. Participating health care providers include not only those within Olmsted County as well as those in the surrounding region. Studies have shown that the database includes nearly all care provided to nearly all (i.e., greater than 90%) county residents[11]. Thus, there is a high degree of confidence that treatment

failures will be captured, even if subsequent treatment is provided at a different facility. The study subjects were selected based on an International Classification of Disease diagnosis code of CTS (ICD-9 354.0) and a Current Procedural Terminology (CPT) code for carpal tunnel injection (CPT 20526) between 2001 and 2010**.**

Failure of treatment, defined as any subsequent corticosteroid injection or carpal tunnel release (CTR) surgery performed on the injected hand within 1 year of initial injection, was the primary outcome of interest. Inclusion criteria included a diagnosis of primary CTS, no previous invasive intervention (injection or CTR) for CTS in that hand, a therapeutic corticosteroid treatment for CTS, age at least 18 years, and affirmative research authorization (over 90% of county residents have provided such authorization for record review research). Subjects who had less than 1 year of follow-up in their medical record were excluded from the analysis. If a patient did not have at least one visit to any REP health care provider of any specialty by at least 1 year past their date of injection, we considered the patient as having less than one year of follow-up. All steroids were standardized to be able to compare the relative anti-inflammatory potency. The dose of steroid was standardized to an equivalent effective dose of triamcinolone, which had the highest use in the cohort and was converted according to Leversee[12]. For example, the equipotent dose of 0.6 mg betamethasone was 4.0 mg triamcinolone. Subsequently, the standardized dose (milligrams per milliliter) was multiplied by the volume of the steroid in milliliter. The volume of the steroid was documented in milliliter in the medical charts, ranging from 0.5 – 3.0 with an interval of 0.5 mL. The amount of anesthetic was separately documented.

Study data were collected and managed by 3 physicians (S.E., A.J.B., and T.L.S.) using Research Electronic Data Capture software. Age, sex, laterality, comorbidities including diabetes, rheumatoid arthritis, peripheral neuropathy/cervical radiculopathy, and other relevant comorbidities such as previous trauma to the affected hand or wrist, Kienbock's disease, or ganglion cyst were recorded. In addition, information on the diagnosis for CTS was abstracted from the medical charts. We required a clinical diagnosis of CTS to be entered in the medical record, based on the clinical impression of treating physician. We also collected the type and dose of steroid injected, type and volume of anesthetic injected, number of injections, and surgical intervention (CPT code for surgical cases 29848 and 64721). Furthermore, the severity of CTS was assessed by documenting available electrodiagnostic (EDX) data, with severity graded as recommended by Stevens[13]. Our study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies[14].

Statistical analysis

For the purposes of power calculations, we assumed that the injectate volume would follow a normal distribution (n[3,1]) and that the proportion of treatment failure would be 50%. For a logistic regression model, we would have 80% power at α = .05 to detect an odds ratio (OR) of 1.3 for a 1-mL unit change in injectate volume with n = 600 patients. Summary statistics for demographics and clinical characteristics are shown as n (%) or means (±SD) and are divided into characteristics at the patient and hand levels. Patient-level covariates include sex and previous history of comorbidities. Hand-level covariates include type and volume of anesthetic, type and dose of steroid, total injectate volume, age at treatment, use of US guidance and EDX severity at the time of injection. Confidence intervals for failure proportions by volume use degrees of freedom-adjusted effective sample sizes to account for clustered observations.

We used general estimating equations logistic regression to model the suspected association of risk factors with treatment failure[15,16]. General estimating equations are a type of generalized linear model that account for correlated repeated measurements within individuals. To calculate variance appropriately for repeated-measures analyses, the general estimating equations method requires a correlation structure to be specified. Model fit and choice of correlation structure were assessed using the quasi-likelihood under the independence model information criterion[17]. General estimating equations methods are typically robust to misspecification of correlation structure; nevertheless, several possible correlation structures were fit for each model and the best selected by quasi-likelihood under the independence model information criterion. Ultimately, an exchangeable correlation structure was sued, i.e., one in which any pair of observations for a subject will have the same correlation.

Before inclusion in the model, the dose of steroid was converted to the effective dose of triamcinolone, as previously specified. Factors that were assessed included age, sex, total injectate volume (combined steroid and anesthetic volume), effective dose of steroid, type of steroid injected, type of anesthetic injected, volume of anesthetic injected, ultrasound guidance, history of diabetes, diagnosis of peripheral neuropathy or cervical radiculopathy, diagnosis of rheumatoid arthritis, diagnosis of other relevant comorbidities, and EDX severity at the time of injection. Four categories of EDX severity were originally assigned: normal, mild, moderate, and severe[13]. Subjects on whom EDX study was not performed or EDX severity was not known were assigned to a fifth category. Variables were reviewed for evidence of collinearity by means of variance inflation factors and principal component analysis prior to model inclusion.

Sensitivity analyses for different parameterizations of variables (e.g., groupings of EDX severity) and other model diagnostics were performed. First-order interactions among all variables were assessed during model fitting but were excluded from the final

model if they were nonsignificant. Odds ratios and 95% Wald confidence intervals were reported. *P* values less than .05 were considered significant.

RESULTS

We identified a total of 988 eligible patients. Patients without at least 1 year of follow-up (N = 21), those who were diagnosed with pregnancy-related CTS (N = 20), and observations made with a missing injectate volume or steroid dose (N = 91) were excluded from the analysis (Figure 1). After exclusions, the cohort consisted of 856 observations in 651 distinct patients. Patients were treated by plastic surgeons, orthopedic surgeons, physical medicine and rehabilitation physicians, family physicians, rheumatologists, radiologists, and internists.

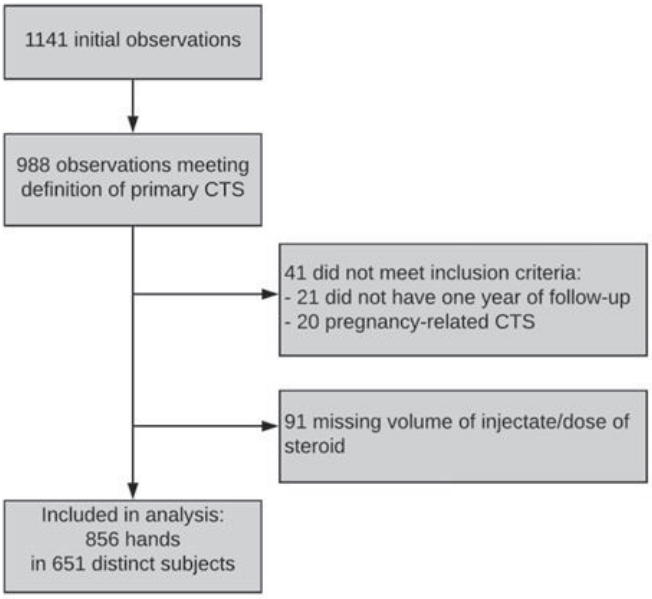


Figure 1. Subject selection flow chart.

Table 1 lists demographic, clinical, and procedural characteristics. Patients were 30% male, mean (SD) age at treatment of 51 (13.7) years. Injections had a mean total injectate volume of 3.54 (1.17) mL and effective steroid dose of 41 (21.9) mg. Over 96% of injections used 1% lidocaine as the anesthetic, with an additional 2% having an undocumented type. Given this distribution, type of anesthetic was not included as a predictor in the final model. At the hand level, 57% (N = 484) received subsequent treatment within 1 year. Of those, 30% were treated with a second injection (N = 143) and 70% (N = 341)

underwent CTR. Of the patients who experienced failure of treatment within 1 year, median time to a second injection was 161 days and median time to surgery was 128 days.

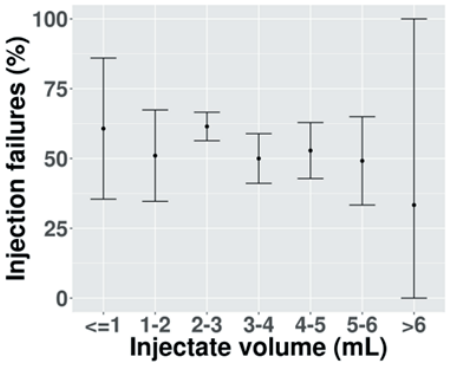
Table 1. Demographic, clinical, and procedural characteristics of corticosteroid injection for treatment of carpal tunnel syndrome cohort. Electrodiagnostic (EDX) severity. *Indicates hand-level characteristics.

	Subject-level (N=651) **Hand-level* (N=856)**
Age (years)* Mean (SD)	51 (13.7)
Sex (Male)	194 (30%)
EDX severity*	
Untested	129 (15%)
Normal	81 (9%)
Mild	244 (29%)
Moderate	346 (40%)
Severe	56 (7%)
Injectate volume (mL)* Mean (SD)	3.54 (1.17)
Type of anesthetic	
1% Lidocaine	824 (96%)
2% Lidocaine	3 (<1%)
0.25% Bupivacaine	6 (1%)
0.5% Bupivacaine	5 (1%)
None/Other/Unknown	18 (2%)
Effective steroid dose (mg)* Mean (SD)	41 (21.9)
Type of steroid	
Triamcinolone	488 (57%)
Betamethasone	304 (36%)
Methylprednisolone	62 (7%)
Rheumatoid arthritis	44 (7%)
Diabetes mellitus	56 (9%)
Peripheral neuropathy or Cervical radiculopathy	48 (7%)
Other comorbidity	18 (3%)

Figure 2A shows the number and proportion of failure of injections grouped by volume of injectate in the cohort unadjusted for other covariates. Overall, a downward trend was observed for proportion of failures with higher injectate volumes (Figure 2B). Given data sparsity at high and low levels of injectate volume, models were also fit excluding extreme values of injectate volume (less than 1mL and more than 6mL) to test model

sensitivity. Because we found no change in sign or significance of injectate volume, results presented are from the model fit on the full set of data (i.e. with no exclusions owing to injectate volume). A model using injectate as a binary variable (3 mL or less, or more than 3 mL) was also assessed. Although this model showed poorer overall model fit, we include the results from the binary representation of volume in addition to the one based on a numeric representation of volume. Based on model fit criteria, EDX severity was collapsed into e categories (severe vs. not severe, which included untested, normal, mild, and moderate). Sensitivity analyses were performed and changes in how the levels of EDX severity were grouped did not affect the sign or significance of other variables included in the model. No first-order interactions were significant.

A.



B.

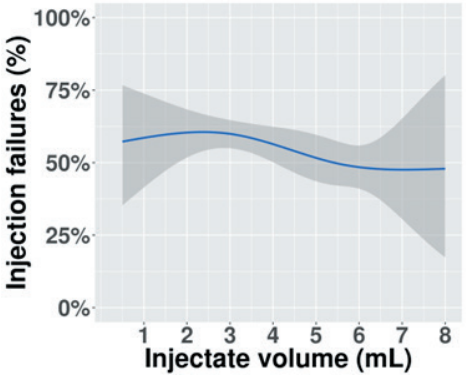


Figure 2 A. Proportion of failure of injections subdivided by volume of injectate into categories by 1-mL volumes, adjusted to account for subjects with multiple observations. Error bars represent 95% confidence intervals. **B.** Percentage of corticosteroid injections failures by injectate volume, with observations treated as independent. Solid line represents a natural cubic spline fit with 3 knots; shaded area is the 95% confidence interval for the estimate.

Table 2 shows ORs (95% Wald confidence intervals) from the final multivariable model fit. Higher injectate volume was significantly associated with reduced treatment failure within 1 year (adjusted OR = 0.777 [0.671-0.901], *P* <0.001). Rheumatoid arthritis and ultrasound-guided procedures were also associated with reduced treatment failure (rheumatoid arthritis-adjusted OR = 0.432 [0.22-0.846], *P* = 0.01; ultrasound guided-adjusted OR = 0.447 [0.247-0.806], *P* = 0.01) and severe EDX result was associated with increased failure within one year (adjusted OR = 1.82 [1.07-3.07], *P* = 0.03). Effective dose of steroid was not significant (adjusted OR = 0.998 [0.990-1.01], *P* = 0.38), nor was type of steroid injected (*P* = 0.65). Table 3 shows the estimates from the binary representation of volume (3 mL or less and greater than 3 mL).

Table 2. Demographics, clinical characteristics and procedural characteristics and their association with re-intervention (either second corticosteroid injection or carpal tunnel release) within one year using a General estimating equations (GEE) logistic regression model. Odds ratios (OR), 95% confidence intervals (CI), and model p-values are presented.

Variable	OR	Lower CI	Upper CI	P-value
Sex (Male)	0.761	0.543	1.07	.11
Age (/10 years)	0.984	0.877	1.10	.78
Diabetes	0.947	0.545	1.64	.85
Peripheral Neuropathy or Cervical Radiculopathy	0.811	0.448	1.47	.49
Rheumatoid Arthritis	0.432	0.221	0.846	.01
Other Comorbidity	1.40	0.569	3.44	.46
EDX severity (Severe vs. all other severities)	1.82	1.07	3.07	.03
Injectate volume	0.777	0.671	0.901	<.001
Effective steroid dose	0.998	0.990	1.01	.68
US-Guided	0.447	0.247	0.806	.01
Type of steroid injected (compared to Triamcinolone)				0.65
Betamethasone	0.855	0.594	1.23	
Methylprednisolone	0.817	0.387	1.73	

Table 3. Results from model with binary volumes (<=3, >3), showing significant results only

	OR	95% low	95% high	p-value
Rheumatoid Arthritis	0.465	0.237	0.913	.026
Severe EMG	1.80	1.06	3.05	.029
US-guided	0.435	0.241	0.785	.006
High volume (>3mL)	0.509	0.35	0.741	<.001

DISCUSSION

This retrospective population-based study showed that larger volume of injection is associated with reduced odds of subsequent intervention within 1 year after a single corticosteroid injection in patients with CTS. There is currently no consensus regarding the optimal volume of injection for CTS. The effectiveness of corticosteroid injections has been studied and there is strong evidence for the benefits in short term compared with placebo[18]. Armstrong et al. evaluated 43 patients given 1 mL of 6 mg betamethasone and 1mL lidocaine and compared them with 38 patients who received 1 mL of saline placebo combined with 1 mL lidocaine[1]. Primary outcome measures were satisfaction and symptom relief. Thirty patients in the steroid-treated group (70%) were satisfied or highly satisfied compared with 13 of placebo-treated patients (34%). Reported rates of subsequent treatment vary from 10% to 81% within 1 year[18-23]. However, most studies were based on only relatively low injectate volumes (1 to 3 mL). As opposed to dose-response, the volume-response relationship in corticosteroid injections for CTS has not been studied. A placebo controlled trial comparing injection of 40mg methylprednisolone, 80mg methylprednisolone, and placebo in patients with idiopathic CTS found no difference between 40mg and 80mg methylprednisolone injections (both 3-mL mixtures) at 10 weeks, but compared with patients who received placebo, those who received 80 mg methylprednisolone were less likely to have surgery at 1-year follow-up[18]. In the current study, we found no association between an effective dose of steroid and the proportion of subsequent intervention. Karadas et al. compared local injection of 40 mg triamcinolone with procaine (4 mL) in a randomized, placebo-controlled trial[24]. At 6-months follow-up, the steroid and procaine both had a significant improvement in clinical outcome and electrophysiological findings, with no difference between groups. The groups with 1-mL saline (placebo) did not improve. This result indicates that the mechanism of action of an injection in CTS might not depend solely on the effect of a corticosteroid drug.

Our finding that large-volume injections lead to a reduced rate of subsequent intervention might be the result of a greater distribution of the injectate. Cadaveric studies showed that there is a wide variability in the distribution of injectate in the carpal tunnel[7-9]. Jariwala et al. investigated the diffusion pattern of a 3.2-mL injectate of local anesthetic, steroid, and dye into the carpal tunnel in a cadaveric model using a commonly used technique described by Green in 1984[7,25]. Their study showed 3 dye distribution patterns: free distribution within the carpal tunnel (60%), distribution in the tendon sheath, and a mixed distribution (40%). The variability in the distribution suggests that, especially with smaller injectate volumes, the injectate might have had little or no contact with the median nerve and little distribution within the carpal tunnel

synovium. This may be important because recent studies suggested that fibrosis of the carpal tunnel subsynovial connective tissue is an important part of the pathophysiology of CTS[26,27]. Larger-volume injectates might lead to greater distribution within the synovium and consequently have a greater effect on this tissue.

Increased pressure within the carpal tunnel is a characteristic finding of CTS[28]. Therefore, it might be argued that there should be concern regarding using a large-volume injectate, considering that the average carpal tunnel volume is approximately 5-6 mL[29,30], and injecting a large-volume solution might further increase pressure within the carpal tunnel. However, there is no anatomical evidence that the carpal tunnel is a closed compartment[31]; thus, extravasation of the injectate outside the tunnel will likely occur. Moreover, to the extent that subsynovial connective tissue fibrosis may create a closed compartment where none existed normally, the fluid volume might serve to disrupt this mechanically through the mechanism of hydrodissection[5,6].

This study has several important limitations. First, the review was retrospective in nature. This introduced the potential for errors in documentation of inclusion and exclusion criteria, relevant comorbidities and other risk factors, as well as missing outcomes. For example, we excluded over 9% of potential subjects because of the lack of data on volume and steroid dose, and 2% owing to a lack of follow-up, and it is unknown what effect inclusion of these subjects might have had. The lack of randomization makes it more likely that unmeasured confounders might have had an effect. For example, injectate volume and type of steroid were physician-dependent and so individual variations in injection technique, or even patient selection, might be confounders[8]. Although we have accounted for ultrasound-guided procedures, we could not rule out that injection technique influenced the outcome.

The review was powered to assess for the effect of a change in injectate volume on retreatment. Although we included other risk factors as adjustors in the multivariable model and tested first-order interactions, the study was not powered to assess potential interactions. This may have led to nonsignificance of risk factors previously shown to be associated with increased failure in CTS patients or exclusion of relevant interactions from the model. In addition, although this study showed an association between increased volume of injectate and a lower risk for subsequent treatment, it is difficult to state what the optimal volume of injectate might be. The relationship between injectate volume and outcome might change at volumes outside the reported range.

As defined, our outcome (seeking retreatment with a second injection or carpal tunnel surgery within 1 year) is only a proxy for overall clinical outcome. Whereas a relatively small percentage of observations were excluded owing to insufficient follow-up (2.1%), the outcome likely underestimates the true rate of treatment failure both for patients who still have clinically relevant symptoms but choose not to seek reinjection or surgery for other reasons and for subjects who receive treatment that is not captured in the available medical record. Gelfman et al. stated in their study on long-terms trends in CTS using data from the REP that approximately 80% of the administrative diagnostic data met symptom criteria for CTS[32]. Because the original data for this study were derived from administrative diagnostic codes of the REP, we confirmed the diagnosis of CTS through chart review.

This cohort showed an association between larger injectate volumes and reduced rates of subsequent intervention after a single corticosteroid injection in the treatment of CTS. Further research is necessary to define an optimal volume, as well as the mechanism for this effect. A prospective study with a low- and high-volume injection group and to reassess outcomes would be ideal.

ACKNOWLEDGEMENTS

This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award R01 AG034676. The project was additionally supported by NIH/NCRR Colorado CTSI Grant UL1 RR025780, NIH/NIAMS Grant RO1 AR62613 and the Mayo Foundation.

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4

PREDICTING CLINICAL OUTCOME AFTER SURGICAL TREATMENT IN PATIENTS WITH CARPAL TUNNEL SYNDROME

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J Hand Surg Am. 2018 Dec;43(12):1098-1106.

ABSTRACT

Background

Carpal tunnel release (CTR) is typically offered to symptomatic patients with electrophysiological abnormalities when night orthoses no longer prevent waking with numbness and preferably before there is any static numbness, weakness, or atrophy. The ability to predict the amount of symptom relief after CTR could be beneficial for managing patient expectations and, therefore, improve treatment satisfaction. Therefore, the aim of this study was to identify predictors for symptom relief after CTR and to determine their contribution to symptom relief at 6 months after surgery.

Methods

A total of 1049 patients who underwent CTR between 2011 and 2015 at 1 of 11 Xpert Clinics in the Netherlands were asked to complete online questionnaires at intake and 3 and 6 months after surgery. Patient demographics, comorbidities, and baseline scores were considered potential predictors for the amount of symptom relief on the Boston Carpal Tunnel Questionnaire (BCTQ) score, which was the primary outcome measure.

Results

A low score on the BCTQ at intake, a codiagnosis of a trigger finger, ulnar nerve neuropathy, trapeziometacarpal joint arthrosis, and instability or arthrosis of the wrist were associated with a smaller improvement in the BCTQ domains after a CTR at 6 months after surgery and accounted for 35% to 42% of the variance on the BCTQ domains in our multivariable regression models.

Conclusions

In this study, we showed that clinical severity of carpal tunnel syndrome at intake is the most important factor in estimating symptom relief after surgical treatment. Furthermore, this study contributes to a more precise understanding of the capabilities of CTR in relieving symptoms for different subgroups of patients. Results of our study can be used to manage patient expectation on symptom relief from CTR.

INTRODUCTION

It has already been shown that surgical treatment for carpal tunnel syndrome (CTS) is generally more effective than non-operative treatment (such as splinting or corticosteroid injections) in terms of recurrence rate, improvement of symptoms, and hand function[1,2]. Although the main goals of carpal tunnel release (CTR) are to resolve symptoms of a sensory disturbance and prevent further progression of disease, some patients continue to have symptoms after surgery[3,4]. Although clinical trials can establish whether a treatment is effective on average, further research is needed to improve the predictability of outcomes after surgical treatment for CTS in individual patients.

The ability to predict symptom relief after CTR is desirable because it could help manage patient expectation of the treatment and, therefore, improve self-reported postoperative well-being[5,6]. Because patients present with different symptoms and levels of median nerve conduction abnormalities as measured by electrodiagnostic testing[7], it is at present difficult to predict the outcome after CTR for individual patients with CTS.

Therefore, the aim of this study was to identify those factors that can predict the amount of symptom relief after surgical treatment and to determine the contribution of these factors in predicting the amount of symptom relief for individual patients. By identifying these predictive factors, our goal is to create a risk model to quantify the amount of symptom relief when patients are treated surgically for CTS.

MATERIALS AND METHODS

Study sample

All patients with CTS who were offered surgical treatment between November 2011 and November 2015 in a hand clinic (Xpert Clinic, the Netherlands) were asked to complete online questionnaires in our Web-based outcome registration system at intake and at three months and six months after surgery. Xpert Clinic is a group of specialized clinics in 11 locations throughout the Netherlands with, at the time of the study, twelve European board-certified hand surgeons performing procedures.

We included patients who received a CTR and had filled-in the Boston Carpal Tunnel Questionnaire[8] (BCTQ) as part of routine clinical care at intake and six months after surgery. We excluded patients with previous surgical treatment for CTS on the ipsilateral hand. In patients who underwent bilateral CTR, only the first treated hand was included. For this study, we decided not to exclude patients with specific comorbidities or concomitant surgeries because these factors could be potential predictors of symptom relief after CTR. We adhered to the STrengthening the Reporting of OBservational

studies in Epidemiology (STROBE) guidelines. Furthermore, the study was approved by the local institutional review board and written informed consent was obtained from all patients.

Treatment

All patients underwent an open CTR. Subsequently, all patients received standard postoperative care, which consisted of three to five days of bandages and a sling around the operated hand. After this, standardized hand therapy, consisting of nerve and tendon gliding exercises, was started by a hand therapist. Patients were seen at our outpatient clinic within fourteen days after surgery to monitor progress and to remove sutures.

Measurements

Baseline characteristics

We collected sociodemographic data preoperatively from all patients including age, sex, hand dominance, duration of symptoms, body mass index, occupation, and smoking and alcohol usage. Patients were diagnosed with CTS by a physician based on a combination of symptoms, physical examination findings and electrodiagnostic testing. In addition, information on the presence of comorbidities was retrieved from the medical record. Comorbidities were diagnosed by a physician, based on the medical history, physical examination, radiographic imaging, or electrodiagnostic testing. We defined that comorbidities and concomitant procedures needed a minimum of ten cases, within the sample, to be included in the analyses. Moreover, the comorbidities ulnocarpal impingement, scaphoid nonunion collapse wrist, pisotriquetral arthrosis, distal radioulnar arthrosis, and scapholunate dissociation were grouped under the variable "instability and/or arthrosis of the wrist". Cubital tunnel syndrome, Guyon canal syndrome, and unspecified ulnar nerve neuropathy were also grouped under a separate "ulnar nerve neuropathy" variable.

Primary outcome measurement: BCTQ

To assess the symptom intensity of CTS, patients filled out the BCTQ (Dutch Language Version[9]: 1, no complaints; 5, maximum complaints possible) at baseline and 3 months and 6 months after surgery. The BCTQ covers two domains; the symptom severity scale (SSS) and the functional status scale (FSS), including eleven and eight items, respectively.

Complications

Complications were registered during a 6-months' period after surgery. These included infections treated with antibiotics, wound dehiscence, iatrogenic median nerve injury, and postoperative bleeding.

Statistical analysis

A proportion of the data from the included patients had missing values owing to nonresponse. At baseline, there was a proportion of nonresponse for the following variables: body mass index (33% missing), duration of symptoms (18% missing), smoking status (33% missing), and alcohol intake (33% missing). Nonresponse for all other baseline characteristics was 0% to 3%. Regarding the outcome measurements, there was a nonresponse of 0%, 8%, and 0% for the BCTQ at baseline, 3 months and 6 months, respectively. Because information on the presence of comorbidities and concomitant surgery was retrieved from the medical record for every patient, we had no missing data for these variables. However, it should be noted that some information might not have been well documented within the medical records.

Because of the proportion of missing values and to check for selection bias in our inclusion criteria, a nonresponder analysis for baseline variables was performed (Supplementary Table 1). This analysis was done by conducting analyses of variance, chi-square statistics and unpaired *t* tests. After Bonferroni correction for multiple testing, we concluded that the missing data were independent of both observable and unobservable variables and could, therefore, be classified as missing completely at random[10]. Therefore, Multiple Imputation[11] was used to impute the missing values at baseline and follow-up 10 times. The collected data was used as auxiliary variables in our imputation model. Auxiliary variables are variables that are not imputed during the imputation process but are used to impute the missing values.

Bivariable analyses were done to identify potential predictive baseline factors for clinical outcome defined as the difference between scores at baseline and 6 months after surgery on the SSS score, the FSS score and the total BCTQ score. From these bivariable analyses, all associated variables with a significance of p less than .20 were considered for a backwards multivariable regression analysis. Subsequently, variables with a pooled significance level of less than .05 were used in the final multivariable models.

Because the convergent pattern of the postoperative courses of the different subgroups of patients presented in Figure 1 might be partly explained by regression to the mean, a correction for regression to the mean was done to adjust the postoperative scores of the SSS, FSS and BCTQ-total by using the method suggested by Kelly et al[12].

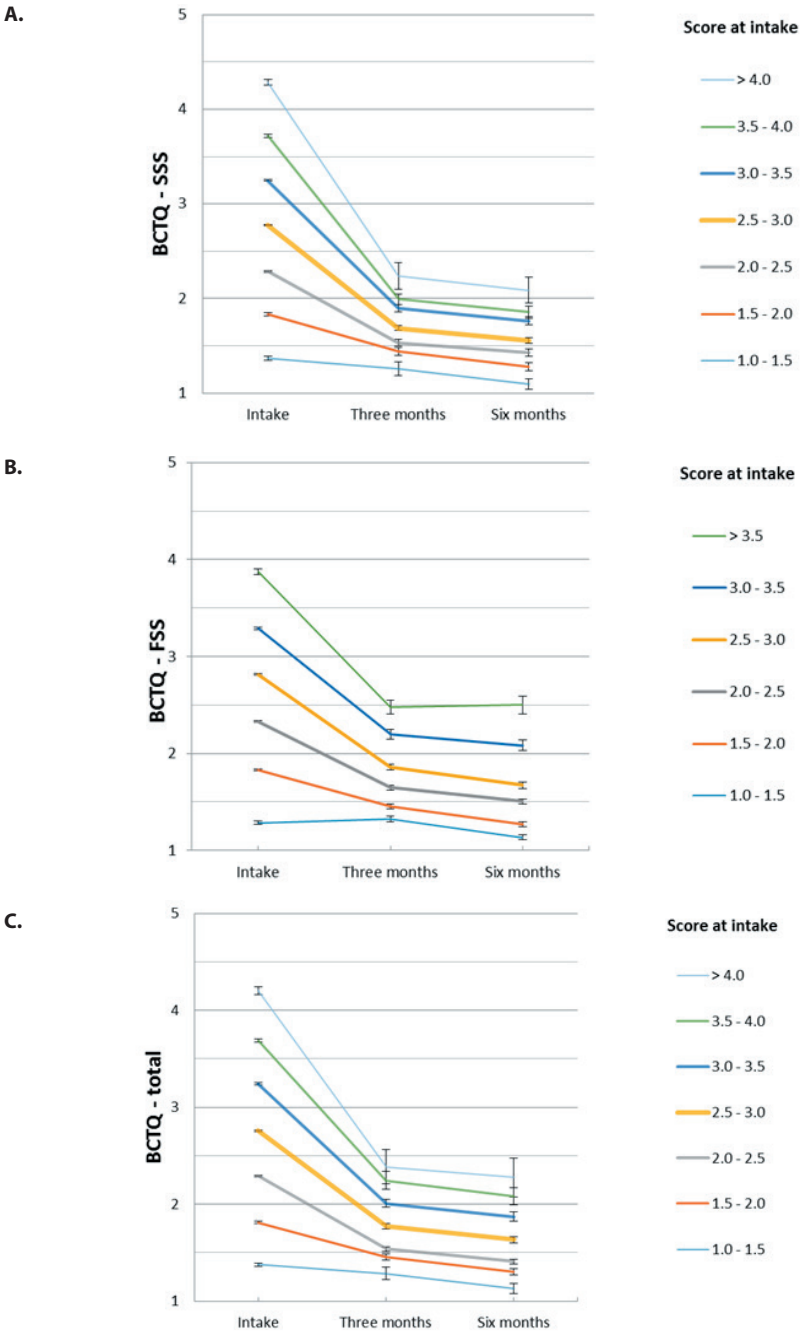


Figure 1. A Postoperative course of the BCTQ-SSS, **B** BCTQ-FSS, and **C** the BCTQ-total score of subgroups of patients grouped on their score at intake, corrected for regression to the mean. The error bars represent the standard error of the mean.

RESULTS

Study sample and baseline characteristics

Between November 2011 and November 2015, 2748 patients underwent a primary CTR. After exclusions, the cohort consisted of 1049 patients (Figure 2). Baseline characteristics of the included patients can be found in Table 1.

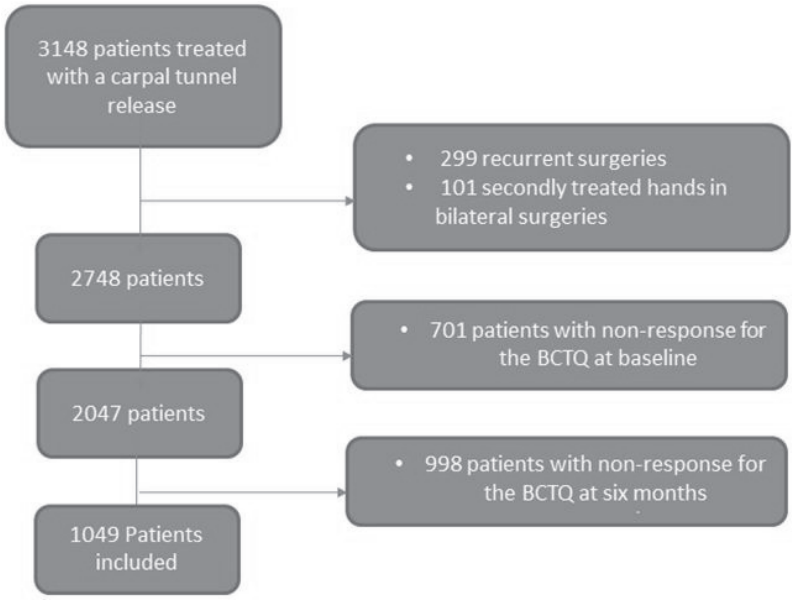


Figure 2. Study flowchart.

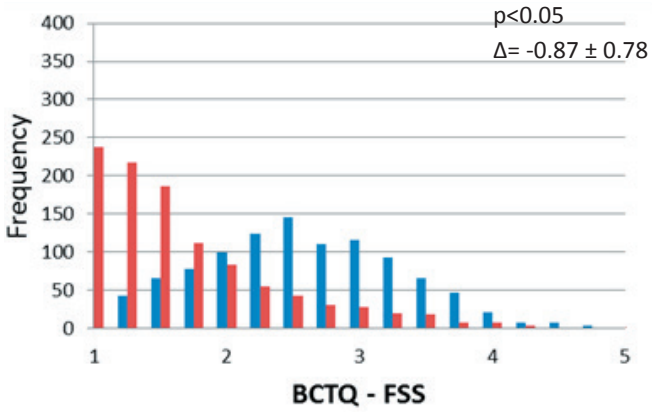
Surgical outcome

Figure 3 shows a significant mean improvement on all primary and secondary outcomes at six months after surgery and shows the distributions of these outcomes at intake and 6 months after surgery. After six months, 985 patients (93.8%) showed improvement on the BCTQ-total score with a mean improvement of 1.15 points (±0.63). However, 64 patients showed a deterioration on the BCTQ-total score at 6 months with a mean increase of 0.31 (±0.26). Furthermore, there were 21 complications in 20 patients, consisting of 14 infections and 6 wound dehiscences. One patient had an infection and a wound dehiscence. All 20 patients with a complication did not show deterioration on the BCTQ-total score at 6 months after surgery.

Table 1. Baseline characteristics of the study population

Categorical Variables	Baseline Characteristics		Study population (n=1049)
			(%)
Sex	**Female**		72
Operated hand	**Right**		61
Smoking			48
Alcohol usage			58
Comorbidities	**Trigger finger**		15
	Trapeziometacarpal joint arthrosis		7
	Diabetes		6
	History of wrist trauma		3
	De Quervain tenosynovitis		3
	Dupuytren's disease		2
	Rheumatic diseases		2
	Guyon's canal syndrome		1
	Cubital tunnel syndrome		2
	Unspecified ulnar nerve neuropathy		1
	Radial tunnel syndrome		1
	Instability and/or arthrosis of the wrist		1
Concomitant procedures	**Trigger finger release**		10
	Cubital tunnel release		2
	De Quervain release		*1*
	Guyon's tunnel release		*1*
Workload	**No work**		37
	Light physical work		24
	Moderate physical work		24
	Heavy physical work		15
Dominance	**Left**		8
	Right		89
	Co-dominant		3
Continuous Variables			***Mean±SD***
Age (years)			53.9 ± 12.1
BMI (kg/m^2)			27.6 + 5.0
BCTQ (1-5)		**Symptom severity scale***	2.87 ± 0.6
		Functional severity scale*	2.48 ± 0.8
		Total*	2.68 ± 0.6
Duration of complaints in months			34.9 ± 61.3

A.



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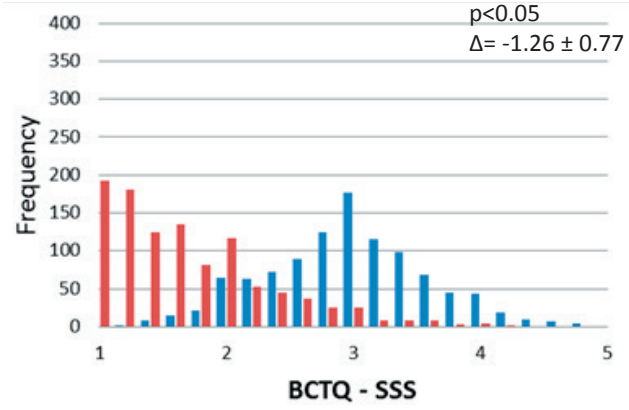

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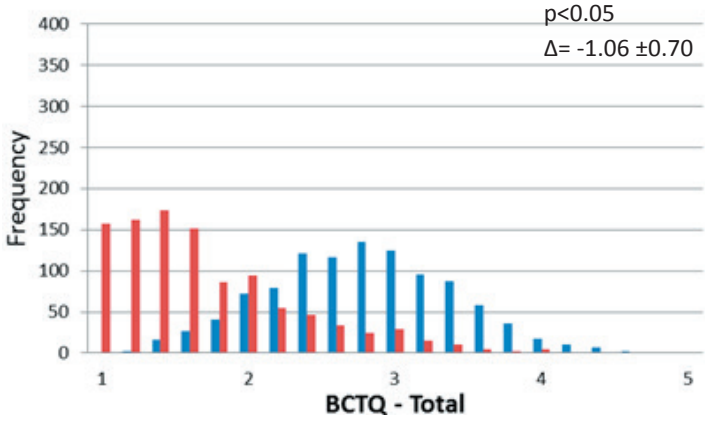

Figure 3. Pre- and postoperative distributions of the **A** BCTQ-FSS, **B** the BCTQ-SSS, and **C** the BCTQ-total score within the study population at intake and 6 months after surgery, with the y axis representing the frequency of the different scores situating on the x axis. Values in the right upper corner represent *t* test *p* values and the deltas for the mean differences between the intake and 6 months postoperative score with the corresponding SD.

Predictive factors

Several potential predictive factors were identified from our bivariable analyses (Table 2). Subsequently, these potential predictive factors were used in creating our multivariable models (Table 3). The multivariable models could explain 42%, 38% and 35% of the variance in the model for the change score of the BCTQ-SSS, BCTQ-FSS and the BCTQ-total score, respectively, at 6 months. Generally, a more severe score at intake was predictive for a greater improvement on the score at 6 months for the BCTQ-SSS score, whereas the presence of trapeziometacarpal joint arthrosis, a trigger finger, ulnar nerve neuropathy on the ipsilateral hand and a high BCTQ-FSS score at intake are predictive for a smaller improvement on the BCTQ-SSS score at 6 months postoperatively. Likewise, a more severe score at intake and a more physically demanding job was predictive for greater improvement at 6 months on the BCTQ-FSS score, while the presence of trapeziometacarpal joint arthrosis, a trigger finger and instability or arthrosis of the ipsilateral hand were predictive for a smaller improvement on the BCTQ-FSS score at six months after surgery. For the BCTQ-total score at six months, a more severe score at intake for the BCTQ-SSS and the BCTQ-FSS are predictive for a greater improvement, while the presence of a trigger finger or trapeziometacarpal joint arthrosis is predictive for a smaller improvement compared with the score at intake.

Figure 1 further illustrates that the clinical severity of CTS at intake is the most important factor in estimating the effect of surgical treatment. This figure shows the effect of surgery on the BCTQ-scores after 3 and 6 months for subgroups of patients defined by their score at intake, corrected for regression to the mean. This figure also indicates that patients with severe CTS symptoms at baseline have approximately the same level of residual symptoms at 6 months after surgery as those with less severe CTS symptoms at baseline.

Table 2. Bivariable analyses with correlation coefficients representing the relation between baseline variables and surgical effect on the BCTQ domains.

Baseline Variables			Six months after surgery		
			Δ SSS score	Δ FSS score	Δ Total BCTQ score
Sex		***Female***	0.065*	0.106**	0.094**
Age				0.117**	0.085**
Dominance operated hand		***Yes/No***			-0.058†
Duration of complaints in months			0.075*	0.046†	0.066*
Workload		***Unemployed (reference)***			
		Light physical labor	-0.043†	-0.062†	
		Moderate physical labor			
		Severe physical labor			
BMI					
Smoking		***Yes/No***	-0.082*	-0.093*	
Alcohol usage		***Yes/No***	0.062†	0.060†	0.067†
Comorbidities	**Trigger finger**	***Yes/No***	0.098**	0.044†	0.078*
	Trapeziometacarpal joint arthrosis	***Yes/No***	0,069*	0.070*	0.076*
	Diabetes	***Yes/No***			
	History of wrist trauma	***Yes/No***	0.075*		0.048†
	De Quervain tenosynovitis	***Yes/No***			
	Dupuytren's contracture	***Yes/No***			
	Rheumatoid arthritis	***Yes/No***	0.045†		
	Radial tunnel syndrome	***Yes/No***			
	Instability and/or arthrosis of the wrist	***Yes/No***		0.042†	
Ulnar nerve neuropathy		***Yes/No***	-0.041†		
	Cubital Tunnel syndrome	***Yes/No***			
	Guyon's canal syndrome	***Yes/No***			
Concomitant procedures	**Trigger finger release**	***Yes/No***	0.062*	0.042†	0.057†
	Cubital Tunnel release	***Yes/No***			
	De Quervain release	***Yes/No***			
	Guyon's tunnel release	***Yes/No***			
BCTQ	***Total***		-0.519**	-0.554**	-0.583**
	SSS		-0.634**	-0.374**	-0.553**
	FSS		-0.302**	-0.605**	-0.500**

*Association found to be significant at a p-level <0.05.
**Association found to be significant at a p-level <0.01.
† Association eligible for multivariable analysis at p-level <0.20.
Empty cells indicate a nonsignificant correlation at p=level >0.20

Table 3. Multivariable regression analysis with beta-coefficients representing the relation between baseline variables and the surgical effect on the BCTQ domains.

Baseline Variables			Six months after surgery		
			Δ SSS score β (SE)	Δ FSS score β (SE)	Δ Total BCTQ score β (SE)
R^2 (% explained variance) for the complete model			**42%**	**38%**	**35%**
Constant			0.834** (0.084)	0.750** (0.070)	0.756** (0.084)
Sex		***Female***			
Age					
Dominance operated hand		***Yes/No***			
Duration of complaints in months					
Workload		***Unemployed (reference)***			
		Light physical labor		-0.057** (0.018)	
		Moderate physical labor			
		Severe physical labor			
BMI					
Smoking		***Yes/No***			
Alcohol usage		***Yes/No***			
Comorbidities	**Trigger finger**	***Yes/No***	0.155** (0.050)	0.111* (0.053)	0.133** (0.049)
	Trapeziometacarpal joint arthrosis	***Yes/No***	0.151* (0.071)	0.174* (0.075)	0.163* (0.069)
	Diabetes	***Yes/No***			
	History of wrist trauma	***Yes/No***			
	De Quervain tenosynovitis	***Yes/No***			
	Dupuytren's disease	***Yes/No***			
	Rheumatoid arthritis	***Yes/No***			
	Radial tunnel syndrome	***Yes/No***			
	Instability and/or arthrosis of the wrist	***Yes/No***		0.552* (0.235)	
Ulnar nerve neuropathy		***Yes/No***	0.182* (0.085)		
	Guyon's canal syndrome	***Yes/No***			
	Cubital tunnel syndrome	***Yes/No***			
Concomitant procedures	**Trigger finger release**	***Yes/No***			
	Cubital tunnel release	***Yes/No***			
	De Quervain release	***Yes/No***			
	Guyon's tunnel release	***Yes/No***			

Table 3. Multivariable regression analysis with beta-coefficients representing the relation between baseline variables and the surgical effect on the BCTQ domains. *(Continued)*

Baseline Variables		Six months after surgery		
		Δ SSS score β (SE)	Δ FSS score β (SE)	Δ Total BCTQ score β (SE)
BCTQ	***Total***			
	SSS	-0.864** (0.036)		-0.432** (0.035)
	FSS	0.137** (0.031)	-0.636** (0.025)	-0.247** (0.030)

*Association found to be significant at a p-level <0.05.
**Association found to be significant at a p-level <0.01.
Empty cells indicate a nonsignificant correlation at p-level >0.05

4

DISCUSSION

In this study, we showed that clinical severity of CTS at intake is the most important factor in estimating the symptom relief after surgical treatment because patients with more severe CTS at intake experienced greater effect of CTR on the BCTQ. Although the amount of symptom relief after CTR is higher for patients with more severe CTS, these patients might also have more residual symptoms. However, Figure 1 shows that the amount of residual symptoms at 6 months after surgery in patients with severe CTS symptoms at baseline is close to the amount of residual symptoms at 6 months after surgery of patients with less severe CTS symptoms at baseline. By using multivariable models, we could explain 37-41% of the variation in treatment effect on BCTQ. This means that the majority of the variation between the outcomes between different patients cannot be explained by the variables included in the present study.

This study confirms that surgical treatment of CTS is, on average, effective for improving function and symptom intensity[1,13,14]. However, our study also shows that mean improvement might not be a relevant measure for individual patients because of the wide variation in symptom relief between individual patients. Our study also shows that the BCTQ score might be influenced by the presence of other, unrelated conditions. The presence of comorbidities might, therefore, not be predictive for the response to CTR because patients with these comorbidities might also have been responding to the BCTQ for their persistent symptoms related to these comorbidities. This could mean that the BCTQ is an insensitive outcome measure as it does not only reflect median nerve dysfunction. Therefore, patients with multiple comorbidities on the hand should also be clearly counseled that they have symptoms related to more than one etiology and that CTR is meant to address only the symptoms related to the median nerve compression. This information could be of importance in adjusting the individual patient's expectations of surgical treatment for CTS[15].

Although we tested 28 variables, only a few variables were found to have predictive value for the effect of surgery on the BCTQ-score. At present, few and relatively small studies have performed similar analyses. Conzen et al. found similar results in the way that the amount of improvement after CTR is largely independent of sociodemographic characteristics[16]. Moreover, our study is in line with Burke et al. who found that patients with more severe symptoms, as determined by patient self-assessment at intake, have a greater improvement in the symptom severity and hand function after surgery[17]. However, this finding might also be explained as a characteristic of the imperfect measurement scales of the BCTQ.

The lack of predictive value of most of our evaluated baseline characteristics, as well as the approximately 60% unexplained variance, may indicate that other variables that were not examined play a role. For example, multiple studies have shown that mental health plays an important role when evaluating treatment effect on self-reported upper extremity health[18,19]. In addition, preoperative expectations influence postoperative patient-reported outcomes and could be of importance when predicting success of CTR in an individual[20]. Furthermore, it could be that the BCTQ shows a relatively small change because of other co-morbidities that are not treated by the CTR influencing its score. Therefore, patient expectations of the effect of CTR on other comorbidities of the hand should be addressed before surgery. Future research should focus on the role of nonphysical factors in predicting treatment outcome after CTR as well as on developing more valid and sensitive outcome measures of CTS.

Several limitations of our study should be considered. First, some comorbidities present within our study sample could have been missed by the physician and, therefore, remained undiagnosed. Second, because the completion of our questionnaires in daily clinical practice was voluntary, we have a high amount of missing data. Because of the amount of missing data, we could not conduct a complete case analysis and only identified 40% of our CTS patients as eligible for inclusion. Because of this missing of data, our study sample might not be a valid representation of our CTS patient population and imputing the data could then give misleading results[21]. However, a nonresponder analysis indicated that the missing data pattern was at random and that there were no differences between included and excluded patients at baseline. We therefore assumed that our study sample is a valid representation of our CTS patient population. Third, our study lacked information on nerve conduction study results. At Xpert Clinic, all patients receive electrodiagnostic testing as a part of routine practice for CTS. However, the outcomes of electrodiagnostic testing were not reported in a consistent and standardized format. Therefore, this information was of insufficient quality to be included in our analyses. Although the predictive value of electrodiagnostic measurements in predicting surgical outcome after CTR is heavily debated in the

literature and does not seem to be of additional value in predicting surgical outcome[22-24], information on median nerve conduction might have improved the explained variance of our model. Fourth, information on chronic pain and centralized pain conditions such as fibromyalgia and complex regional pain syndrome was also not accessible in a consistent and accessible format. Fifth, CTR procedures in our cohort were performed by specialists highly trained in hand surgery and that may lead to a larger effect on the BCTQ than procedures performed by other medical specialists. However, because CTR is considered a relative simple procedure, this is not likely to influence the generalizability of the results of our study. Sixth, the BCTQ might not be able to distinguish between symptoms that are permanent, such as static numbness, from those that are correctable, such as intermittent numbness. Also, caution should be advised for patients who have asymptomatic median nerve entrapment. In addition, although Figure 1 is corrected for regression to the mean, the postoperative course of the BCTQ scores of subgroups of patients might be influenced by ceiling and floor effects of the BCTQ.

In conclusion, this study contributes to a more precise understanding of the capabilities of surgical treatment in relieving symptoms and improving function for different subgroups of patients as well as management of expectations. However, a significant proportion of the variability in symptom relief remains unexplained. Furthermore, our study shows that the BCTQ might be an insensitive outcome measure as it may not only reflect median nerve dysfunction. We suggest that future research on predictive factors focus more on nonphysical factors such as mental health, preoperative expectations and disease awareness. This way, patients at risk for a low postoperative satisfaction can be identified and targeted for expectation management. In addition, future research should focus on developing more valid measures so that the evaluation of outcome in CTS patients is less influenced by unrelated comorbidities of the hand.

ACKNOWLEDGEMENTS

We want to thank the patients and physicians that participated in this study.

Supplementary table 1. Non-responder analysis for completing the BCTQ with the variables representing patient characteristics at intake.

Baseline Characteristics		Non-responder analyses (N=2748)				
		Responders at intake and six months (n=1049)	Responders at intake and non-responders at six months (n=942)	Non-responders at intake and responders at six months (n=93)	Non-responders at intake and six months (n=664)	
Categorical Variables		%	%	%	%	**P-value**
Sex	**Female**	72	74	*68*	*74*	*0.53*
Operated hand	**Right**	61	59	*68*	*55*	*0.02*
Smoking		18	26	*13*	*26*	*0.02*
Alcohol usage		56	56	*52*	*59*	*0.44*
Workload	**No work**	36	34	*36*	*33*	
	Light physical work	24	24	*20*	*25*	*0.29*
	Moderate physical work	24	26	*25*	*27*	
	Heavy physical work	16	16	*19*	*15*	
Dominance	**Left**	8	8	*12*	*7*	
	Right	89	89	*82*	*89*	*0.09*
	Co-dominant	2	2	*6*	*4*	
Continuous Variables		**Responders at intake and six months (n=1049)**	**Responders at intake and non-responders at six months (n=942)**	**Non-responders at intake and responders at six months (n=93)**	**Non-responders at intake and six months (n=664)**	
		Mean±SD	*Mean±SD*	*Mean±SD*	*Mean±SD*	*P-value*
Age (years)		53.9 ± 12.1	55.3 ± 14.2	*55.6* ± 12.4	*53.9* ± 16.0	*0.14*
BMI (kg/m²)		27.5 ± 4.8	27.0 ± 5.0	26.6 ± 4.3	*27.3* ± 5.6	*0.25*
BCTQ (1-5)	**Symptom severity scale**	2.87 ± 0.6	2.87 ± 0.7			*0.91*
	Functional severity scale	2.49 ± 0.8	2.48 ± 0.8			*0.69*
	Total	2.68 ± 0.6	2.68 ± 0.7			*0.80*
Duration of complaints in months		30.6 ± 78.1	35.1 ± 58.9	27.6 ± 37.0	*31.9* ± 50.6	*0.49*

† Significance of comparison between baseline characteristics of the responders and non-responders.
* High scores indicate better outcome

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5

HAND SURGEONS PERFORMING MORE OPEN CARPAL TUNNEL RELEASES DO NOT SHOW BETTER PATIENT OUTCOMES

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Plast Reconstr Surg. 2018 Jun;141(6):1439-1446.

ABSTRACT

Background

Although previous studies have shown that more experienced surgeons have better patient outcomes following a variety of procedures, in hand surgery and carpal tunnel release in particular, this relation remains unknown. We assessed whether there is an association between surgeon volume and patient outcomes following open carpal tunnel release.

Methods

Patients who underwent carpal tunnel release between 2011 and 2015 at outpatient hand surgery clinics in the Netherlands were included. Surgeon annual volume was defined as the average number of carpal tunnel releases performed per year per participating surgeon over the study period. Primary outcome measures were the Symptom Severity Scale (SSS) and Functional Status Scale (FSS) of the Boston Carpal Tunnel Questionnaire 6 months postoperatively. Multilevel random intercept linear regression analyses were performed to assess whether there was an association between surgeon annual volume and outcome measures, with adjustment for patient characteristics, concomitant procedures and intake score on the Boston Carpal Tunnel Questionnaire.

Results

A total of 1345 patients were included, operated on by 17 surgeons. Median annual surgeon volume was 75 (interquartile range, 50 to 149). Only 0.5% to 0.6% of the total variance in patient outcome on the Boston Carpal Tunnel Questionnaire could be explained by random differences between surgeons. We did not find an association between annual surgeon volume and outcome measures 6 months postoperatively (SSS: $\beta = .000$, 95% confidence interval [CI] -.001 - .001, FSS: $\beta = .000$, 95% CI -.001 - .001).

Conclusion

In our sample of highly specialized hand surgeons operating in high-volume centers, we found no differences in outcome between high- and low-volume surgeons.

INTRODUCTION

Previous studies have shown that more experienced surgeons have better patient outcomes following a variety of surgical procedures, including gastrointestinal, cardiac, lung, and vascular operations[1-4]. In addition, such relationships have also been found in surgery of the musculoskeletal system[5-7]. Because it can be challenging to quantify a surgeon's cumulative surgical experience for a specific procedure and cumulative experience can be deceptive, annual operative volume is often used to assess the relationship between surgeon volume and patient outcome[1-4].

Carpal tunnel release is one of the most common surgical procedures and the most frequently performed surgery of the hand and wrist, with estimates of 400.000 to 600.000 carpal tunnel releases performed annually in the United States[8,9]. Nevertheless, in hand surgery in general, and in carpal tunnel release in particular, it remains unknown whether there are outcome benefits to repetition for individual surgeons.

There are various reasons why experience might be beneficial in the context of carpal tunnel release. For example, a higher volume surgeon might be better prepared to handle anatomical variations, extensive fibrosis, or other challenging situations. In addition, incomplete transection of the transverse carpal ligament is a relatively common reason for unrelieved symptoms following carpal tunnel release[10,11], which might be less likely to occur in more experienced surgeons.

Conversely, despite the specific challenges of carpal tunnel release, it has been suggested that trained nurse practitioners might be able to perform carpal tunnel release with the same results on patient outcome as achieved by surgeons[12,13]. A reported argument for having a nurse practitioner operate is reduction in waiting time for carpal tunnel release[12,13]. This suggests that operator's education is not considered a predictor for outcome after carpal tunnel release.

A recent study assessed the effects of hand fellowship training on rates of complications for both endoscopic and open carpal tunnel release[14]. Neither operative technique nor type of fellowship training (hand fellowship training versus non-hand fellowship training) had a statistically significant impact on overall complication rates, suggesting that for carpal tunnel release specifically there is no association between surgeon training and complication rate. However, these results were not adjusted for potential confounding factors or for baseline measurements. Fellows were possibly less likely to treat complicated cases (e.g., patients with comorbidities or more severe symptoms) compared to more-senior hand surgeons. Furthermore, it has not been assessed whether, within the surgeon population, there is an association between surgeon experience and patient outcome. Therefore, the aim of this study was to assess whether there is an association between annual surgeon volume and patient outcomes at 6 months postoperatively after open carpal tunnel release.

METHODS

Data collection

All patients with carpal tunnel syndrome (CTS) who underwent carpal tunnel release between 2011 and 2015 at one of the 11 specialized outpatient hand surgery clinics (Xpert Clinic) in the Netherlands were eligible for the study. As part of routine clinical care, patients were included in a large multicenter web-based database, which contains patient-rated outcome measures. All patients signed informed consent and the study was approved by our local ethics committee. Patients who underwent a primary carpal tunnel release and had at least a baseline measurement and one follow-up measurement on the Boston Carpal Tunnel Questionnaire (BCTQ) were included in the study. Patients where an operative report was not available or the surgeon could not be identified were excluded. In addition, patients operated by a surgeon who performed carpal tunnel releases for less than 1 year in our cohort were also excluded.

Covariates of interest

The following study data were abstracted from the database, because they are known prognostic factors for clinical outcome following carpal tunnel release identified based on literature review[15-20]: age, sex, smoking status, alcohol use, and comorbidities (i.e., rheumatoid arthritis, diabetes mellitus, peripheral neuropathy, cervical radiculopathy, trigger fingers, tendinitis, radiocarpal arthritis, carpometacarpal joint arthritis, scaphotrapezotrapezoidal joint arthritis, history of trauma of the wrist, Dupuytren's disease, cubital tunnel syndrome, ulnocarpal impingement, radial tunnel syndrome and Wartenberg syndrome). For the analysis, cubital tunnel syndrome, radial tunnel syndrome, Wartenberg's syndrome and pronator syndrome were grouped under "other nerve compressions". In addition, a group "other comorbidities" was defined, including the following comorbidities: scaphotrapezotrapezoidal arthritis, radiocarpal arthritis, peripheral neuropathy, cervical radiculopathy, and ulnocarpal impingement. Concomitant procedures (i.e., procedures carried out at the same time as the carpal tunnel releases) were scored as well.

Outcome measures

Our primary outcome measure was the BCTQ score at 6 months postoperatively. The scores at intake were also abstracted, to be able to adjust for score at intake. In addition, to illustrate the course of the outcomes on BCTQ, measurements at 6 weeks and 3 months postoperatively were collected as well. Two domains of the BCTQ were assessed: the Symptom Severity Scale (SSS) and the Functional Status Scale (FSS). The SSS and FSS consist of 11 and 8 items, respectively. All items of both scales have five

response categories ranging from 1 to 5, and higher score represents worse symptoms/ lower level of function. Responses to items were averaged to create an overall score for each domain[21].

The secondary outcome measure was overall pain assessed using the Visual Analog Scale (VAS), ranging from 0 to 100, 6 months postoperatively. Higher score represents greater pain intensity. The VAS was performed at intake and 6 weeks, 3 months and, 6 months postoperatively.

In addition, adverse events were scored, including infections treated with antibiotics, wound dehiscence, postoperative bleeding, and neuroma of the median nerve. We scored only adverse effects directly related to the carpal tunnel release. Information on the presence of adverse events was abstracted from the medical charts (S.E. and M.C.J.).

Main exposure variable: annual surgeon volume

Surgeon volume was defined as all carpal tunnel releases, including reoperations and concomitant interventions, performed by the participating surgeon, divided by the number of years the surgeon performed carpal tunnel releases during the study period. Similar definitions of annual surgeon volume have been described previously [1,7,22]. All procedures were performed by European board-certified hand surgeons or surgeons following a hand fellowship.

Procedure

All patients underwent an open carpal tunnel release. Neither endoscopic procedures nor modifications were performed. In general, the following protocol was used in all treatment centers within the Xpert Clinic group, with only minor variations between surgeons: longitudinal incision was placed through the subcutaneous fat and palmar fascia until Guyon canal. Fibers were revealed in the radial-ward direction and the transverse carpal ligament was divided. The median nerve was separated from the roof of the carpal tunnel in the proximal direction using scissors, where potential transverse fibers could be dissected. Subsequently, the tendons and median nerve were inspected. When hemostasis was obtained, the fat was repositioned and the skin sutured with 4-0 (Ethicon, Inc., Somerville, N.J.). Sterile dressing and compression bandage was applied. All patients received standard postoperative care and hand therapy by a hand therapist consisting of nerve and tendon-gliding exercises.

Statistical analysis

Parametric data were presented as mean and standard deviation (SD) and nonparametric data as median and interquartile range (IQR). We categorized the variable “annual

surgeon volume" for presentation purposes, using tertile-derived categories, into three subgroups: low-volume, medium-volume, and high-volume surgeons. Given the number of missing values, a non-responder analysis at six months postoperatively for baseline variables was performed using chi-square statistics and unpaired T-tests. Based on this analysis we concluded that missing data could be classified as "missing completely at random". Therefore, we used multiple imputation to impute the missing values[23]. Ten versions of the data set were produced and independently analyzed, each with its own set of imputed values. To give a single mean estimate, the pooled estimates of ten imputed data sets were used as statistical results.

Because of the hierarchical structure of the data (level 1 = patients, level 2 = surgeons), multilevel random intercept linear regression analyses were performed to assess whether there was an association between surgeon annual volume and outcome measurements. First, we ran an intercept-only model to assess whether there was a significant difference in patient outcome across surgeons, regardless of surgeon volume. In addition, we calculated the intraclass correlation coefficient (ICC) to assess the overall variability in patient outcomes between surgeons. An ICC close to zero would suggest no substantial variability between surgeons in patient outcomes. To adjust the estimated effect of surgeon volume for known prognostic factors identified based on literature review, the variables age, sex, smoking status, alcohol use, comorbidities, concomitant procedures and intake score for the respective questionnaire were included in the model as fixed factors. Values of $p < 0.05$ were considered statistically significant. Analyses were performed using IBM SPSS Version 21 (IBM Corp., Armonk, N.Y.).

RESULTS

A total of 2057 patients who underwent carpal tunnel release within the specified time window were identified. After exclusions, 1345 patients were eligible for this study (Figure 1), operated on by 17 surgeons: 16 hand surgeons and one surgeon in hand fellowship training. The annual surgeon volume ranged from six to 163 procedures per year, with a median (IQR) volume of 75 procedures (50 to 149) (Figure 2). Some of the variables had missing values due to non-response. Regarding the baseline variables, there were missing values for smoking status (35% missing) and alcohol use (35% missing). The proportion of missing data for all other baseline variables ranged from 0 to 1%. Regarding the outcome measures, there were nonresponse rates of 0%, 52%, 13% and 27% for both the SSS and the FSS score at baseline, 6 weeks, 3 months, and 6 months postoperatively, respectively. These were 3%, 9%, 15% and 28% for the VAS score. Because adverse events were reported in only 23 cases (1.6%), we did not use this variable as an outcome measure. Adverse events included wound infection in 18 cases

and wound dehiscence in 5 cases. There were a total of 212 concomitant procedures. Table 1 shows the demographic, clinical, and procedural characteristics of the cohort.

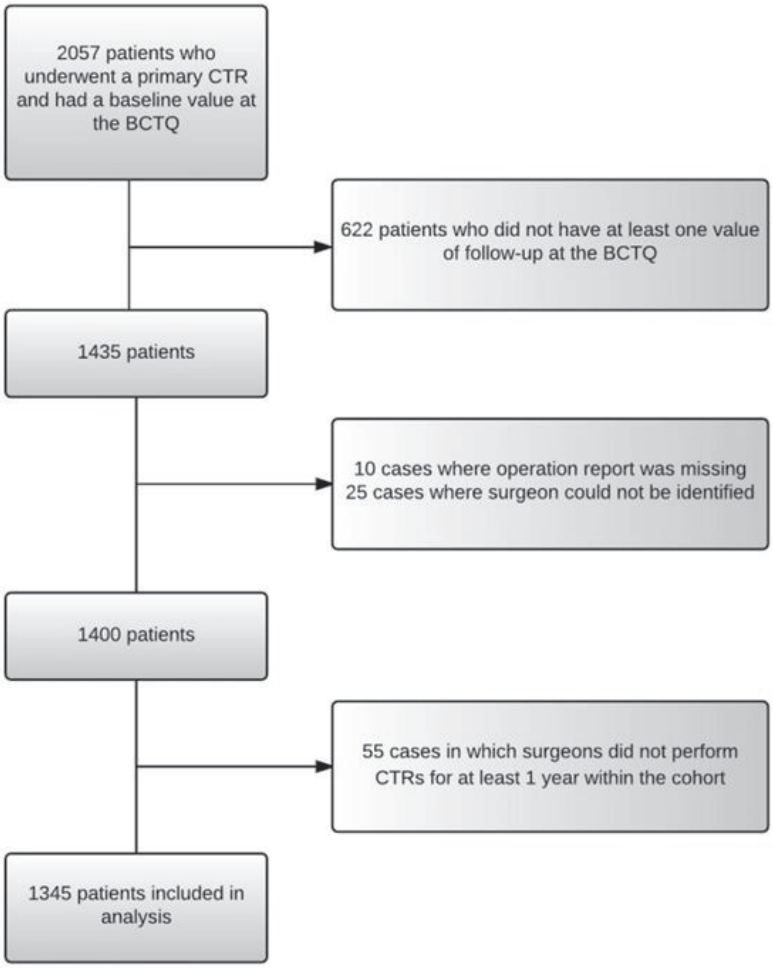

Figure 1. Subject selection flow chart. *CTR*, carpal tunnel release; *BCTQ*, Boston Carpal Tunnel Questionnaire.

Table 1. Demographic, clinical and procedural characteristics of the CTR cohort.

	Total cohort (N= 1345 patients)
Age, years (SD)	54 (13)
Female (%)	986 (73)
BMI (SD)	27 (5)
Smoking status (smoker: yes) (%)	263 (20)
Alcohol use (drinker: yes) (%)	776 (58)
Comorbidities (%)	
Diabetes Mellitus	68 (5.1)
Rheumatoid Arthritis	19 (1.4)
Dupuytren's disease	30 (2.2)
Trigger fingers	190 (14)
CMC1-arthritis	93 (6.9)
Compression Neuropathy	81 (6.0)
Tendinitis	38 (2.8)
History of wrist trauma	43 (3.2)
'Other'	33 (2.6)
Concomitant procedures (%)	
CTR + Trigger Finger Release	122 (9.1)
CTR + Cubital Tunnel Release	29 (2.2)
CTR + Guyon Release	23 (1.7)
CTR + Radial Tunnel Release	8 (0.6)
CTR + fasciotomy Dupuytren	9 (0.7)
CTR + 'other' procedure	21 (1.6)

CTR= Carpal Tunnel Release
The group 'other' comorbidities refers to STT arthritis, radiocarpal arthritis, peripheral neuropathy, cervical radiculopathy and ulnocarpal impingement.

Figures 3 and 4 illustrate the course of the outcome measures, from intake to 6 months postoperatively, grouped by whether the surgeon was a low-, medium- or high-volume surgeon for this procedure. The boundaries for the low-, medium- and high-volume group were 6 to 44, 47 to 71 and 75 to 163 operations annually, and there were 171, 459 and 715 patients in the low-, median- and high-volume group, respectively. The low-, median- and high-volume group included six, six, and five surgeons, respectively.
The intraclass correlation coefficients (SSS, $\rho = 0.005$; FSS, $\rho = 0.006$; VAS, $\rho = 0.002$) indicated that, respectively, only 0.5%, 0.6%, and 0.2% of the patient outcome variance on the SSS, FSS and VAS 6 months postoperatively could be explained by random differences between surgeons. Unadjusted and adjusted models for the association between annual surgeon volume and patient outcome on the BCTQ (SSS and FSS domains) and VAS overall pain indicated no significant association between annual

surgeon volume and patient outcome 6 months postoperatively for any of the outcome measures (Table 2). To assess whether the patient outcomes of the surgeon following a fellowship influenced the overall results, we also ran the analysis on the dataset including board-certified hand surgeons only. The results remained unchanged.

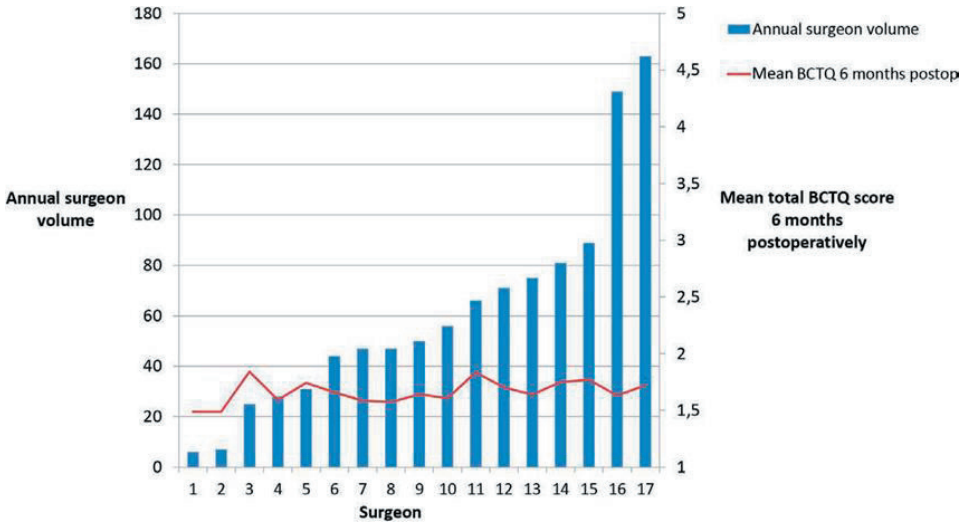

Figure 2. Distribution of number of carpal tunnel releases performed per year (primary y axis) per participating surgeon within the cohort (x axis). Secondary y axis represents the mean total BCTQ score 6 months postoperatively per participating surgeon. *BCTQ*, Boston Carpal Tunnel Questionnaire.

Table 2. Uni- and multivariable analysis for association between annual surgeon volume (continuous variable) and the three outcome measurements: Symptom Severity Score (SSS), Functional Status Score (FSS) and Visual Analog Scale (VAS) overall pain at 6 months postoperatively.

Dependent variables	**Unadjusted model†** **β (95%, CI)** for annual surgeon volume effect	**Adjusted model*** **β (95%, CI)** for annual surgeon volume effect
BCTQ: SSS	.000 (-.001 - .001)	-.000 (-.001 - .001)
BCTQ: FSS	.000 (-.001 - .001)	-.000 (-.001 - .001)
VAS: overall pain	.006 (-.025 - .037)	-.002 (-.027 - .023)

CI, confidence interval

†Unadjusted model: univariable analysis for the association between annual surgeon volume and patient outcome.

*Adjusted model: adjusted for score at intake for respective questionnaire, age, sex, smoking status, alcohol use, concomitant procedure, comorbidities: diabetes mellitus, rheumatoid arthritis, CMC1-arthritis, Dupuytren's disease, trigger fingers, tendinitis, history of trauma of the wrist, compression neuropathy, and the group 'other' comorbidity.

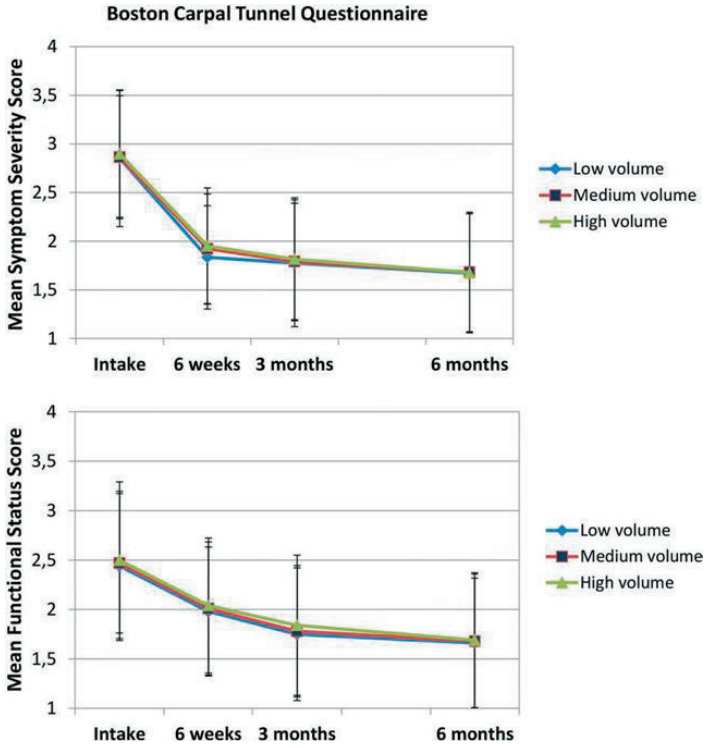

Figure 3. (*Above*) Mean Symptom Severity Score (SSS) and (*below*) mean Functional Status Score (FSS) preoperatively and at 6 weeks, 3 months, and 6 months postoperatively in patients undergoing open carpal tunnel release grouped. Outcomes are divided by whether the surgeon was a low-, medium- or high-volume surgeon for this procedure. *Error bars* = 1SD.

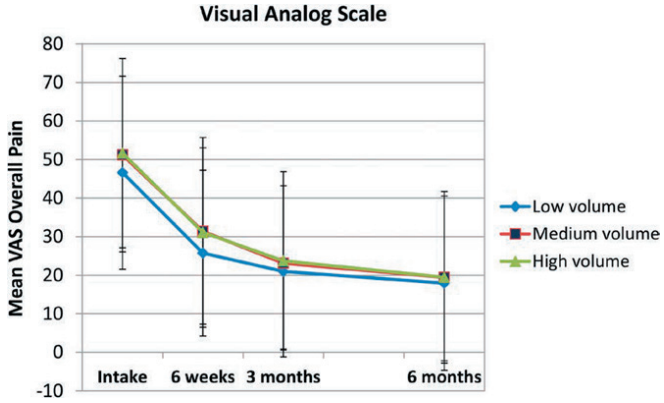

Figure 4. VAS overall pain preoperatively and at 6 weeks, 3 months, and 6 months postoperatively in patients undergoing open carpal tunnel release. Outcomes are divided by whether the surgeon was a low-, medium- or high-volume surgeon for this procedure. Error bars = 1SD.

DISCUSSION

This study, based on a large cohort and including highly specialized surgeons only, did not show an association between annual surgeon volume and patient outcome after an open carpal tunnel release assessed using the BCTQ and the VAS. In addition, we found that only 0.6% of the variance on the BCTQ 6 months postoperatively could be explained by random differences between surgeons, regardless of surgeon volume.

Previous studies have shown an association between surgeon volume and patient outcome, suggesting that centralization of some types of surgery in a small number of centers is beneficial[2,22]. In hand surgery specifically, it is unknown whether there is an association between surgeon volume and patient outcome. It could be argued that surgeon experience might mainly be beneficial in technical challenging procedures, but data are lacking for both more challenging, more complex procedures as well as for more simple procedures in hand surgery.

The overall improvement in functional status and symptom severity found in our study is in line with the literature[24]. Katz et al. described patient outcomes after an open carpal tunnel release carried out by 26 surgeons in different offices in Maine[24] with symptom severity and functional status 6 months postoperatively similar to our results despite symptom severity and functional status at intake being slightly higher compared to our cohort. Mack et al. reported patient outcomes at 3 months after open carpal tunnel release on 134 patients[25] and found a slightly larger change from baseline compared with our results. The total number of reported adverse events was slightly higher compared with our results, with wound dehiscence in 4% and infection in less than 1% of cases compared with 0.4% and 1.3%, respectively, in our study. Smetana et al. reported a similar incidence of wound dehiscence of 1.2% and median nerve palsy or injury in 0.22% of 28.086 cases of isolated open carpal tunnel release while infection rate was not reported[14].

The main strength of our study is the size of the study population and the detailed outcome assessment, compared with many studies only focusing on symptom or pain reduction[26]. We were able to test our hypothesis on a relatively large database because of the unique registration system on clinical outcomes that Xpert Clinic uses. This leads to very small confidence intervals in the main analysis, where clearly indicating a volume effect are lacking. Several limitations of our study should, however, also be considered. The major limitation of our study is the surgeon cohort in which all the procedures were performed (i.e., the cohort of surgeons are highly specialized and the procedures were carried out in highly specialized centers). In contrast, there was still a wide range (6 to 163) in the number of carpal tunnel releases performed by each of the participating surgeons. In addition, it has been recognized that endoscopic carpal tunnel release has a steep learning curve[27-29]. Considering the complexity of this procedure compared with

open carpal tunnel release[30], the learning curve for open carpal tunnel release might flatten out at a relatively early stage that had already been passed by the surgeons in our cohort. Furthermore, because all the procedures were performed within one group of uniformly organized clinics with a similar patient population, we could not account for a potential hospital volume-outcome relation. Previous studies have shown an association between hospital volume and patient outcome beyond surgeon's experience; the relation between the number of patients undergoing a specific surgery at a specific hospital and their postsurgical outcomes indicate that larger-volume hospitals yield better patient outcomes, despite individual surgeon volume[3,31].

In conclusion, our study shows that specialized hand surgeons have similar patient outcomes following open carpal tunnel release and their annual volume does not influence patient outcome. However, whether our results apply to orthopedic surgeons, neurosurgeons, and plastic surgeons in general and, for example, to residents and nurse practitioners still has to be investigated in further studies.

ACKNOWLEDGEMENTS

This study was funded by a grant from the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (RO1 AR62613).

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PART II

ULTRASONOGRAPHIC ASSESSMENT OF CTS

6

SPECKLE TRACKING OF TENDON DISPLACEMENT IN THE CARPAL TUNNEL: IMPROVED QUANTIFICATION USING SINGULAR VALUE DECOMPOSITION

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IEEE J Biomed Health Inform. 2019 Mar;23(2):817-824.

ABSTRACT

Background

Ultrasound is a real-time image modality enabling the analysis of tendon dynamics for diagnosis of carpal tunnel syndrome. Automatic tendon displacement quantification algorithms based on speckle tracking generally suffer from underestimation due to stationary background present in the tendon region. We propose an improved quantification method using Singular Value Decomposition (SVD) filtering to suppress the clutter.

Methods

The accuracy of our Improved Speckle Tracking (IST) method was validated against a ground truth and compared to the accuracy of our Original Block Matching (OBM) algorithm and Commercial Tissue Tracking (CTT) software. The methods were evaluated in experiments involving six human cadaver arms. The ground truth displacements were generated by tracking metal markers inserted in the tendons.

Results

The relative displacement errors with respect to the ground truth for IST were 12 ± 16.9%, which was significantly lower than for OBM (19.7 ± 20.8%) and for CTT (25.8 ± 18.4%).

Conclusion

These findings show that SVD filtering improves the tendon tracking by reducing the underestimation due to clutter.

INTRODUCTION

Current non-invasive examination of tendon pathology is mostly based on subjective judgment of the physician after examination of the ultrasound or MRI images of the tendon. MRI provides high-quality images but is not as easily accessible and is relatively expensive compared to ultrasound[1-3]. Moreover, MRI images are generally static. Ultrasound provides high-resolution, high frame rate imaging that can be used to examine dynamic behavior of the tendon in real time. Therefore, ultrasound is a natural choice for motion analysis[4-7].

There is also expanding evidence for the added value of ultrasound in managing carpal tunnel syndrome (CTS)[8]. Carpal tunnel syndrome is the most common entrapment neuropathy with a cumulative lifetime incidence of roughly 30%[9]. Literature shows that dynamic ultrasound imaging has the ability to detect biomechanical alterations of structures within the carpal tunnel in patients with CTS[10-12]. Carpal tunnel biomechanics can be quantified with several techniques. Manual tracking of anatomical landmarks over an image sequence or the use of tissue Doppler have been described[13]; however, these methods have clear limitations. Manual tracking is laborious, and depends on visibility of landmarks. Tissue Doppler only measures motion in the direction of the ultrasound beam, while tendons generally move almost perpendicular to the beam. Most approaches for tendon motion quantification employ techniques known as speckle tracking or block matching[14-19]. Speckle tracking is a method in which the speckle patterns generated by the scattered ultrasound beams are tracked from frame to frame to measure the motion of tissues. Speckle tracking offers a two-dimensional displacement estimate and is virtually independent of the angle of the ultrasound beam. Since the method exploits the inherent speckle patterns in the tendon tissue, anatomical landmarks or implanted markers are not required.

The longitudinal tendon fibers produce a pattern that has more laterally elongated speckles than that produced by other tissues. However, this need not be a problem for successful block matching: as long as the pattern is unique and moves with tissue motion, tracking by block matching is feasible. Yoshii et al. first reported assessment of the relative motion of the flexor tendon and surrounding sub-synovial connective tissue (SSCT) in the carpal tunnel of healthy subjects using speckle tracking[20]. For the analysis, they used a speckle tracking algorithm called Velocity Vector Imaging (VVI) Syngo software[21,22]. The correlation between speckle tracking measurements and ground truth tendon displacement was reported to be 0.642 with a mean difference of 1.07 ± 0.27 cm.

Korstanje et al. developed and validated a speckle tracking algorithm optimized for tracking of tendon motion[14]. The novelties of the algorithm included a stationary region of interest (ROI) over the tendon path and the combination of multiple overlapping kernels within the ROI to estimate frame-to-frame displacement. Speckle tracking measurements in ex-vivo porcine legs and human cadaver wrists were compared to the motion of surgically inserted metal markers. In-vivo speckle tracking measurements of the tendon displacement in human wrists were compared to the motion of anatomical landmarks as a reference. The use of this algorithm showed small errors in both ex-vivo and in-vivo tracking measurements, with a mean relative error between the ex-vivo marker measurement and speckle tracking of 1.3%. Although Korstanje et al. found relatively small errors in their small-size validation study of the speckle tracking algorithm, it was also found that the algorithm tended to underestimate the true motion due to noise and semi-static artifacts (stationary background, clutter, and shadowing) in the images which limits the performance of the speckle tracking algorithm. To increase the robustness of the tracking method presented by Korstanje et al., we investigated in this paper a novel technique to mitigate the effects of the clutter and noise: Singular Value Decomposition (SVD)[23]. Classically, clutter suppression is used in Doppler imaging by temporal high-pass filtering to remove the stationary or slowly moving tissue signals. However, SVD uses both temporal and spatial information by performing a Principal Component Analysis of the whole image sequence[23]. The basic principle behind this method is that it allows extracting the motion of interest by removing other spatiotemporal components (stationary, slow moving and noise).

In this paper, we validated the improvement in the speckle tracking accuracy using SVD filtered images in a human cadaver hand model (six specimens) with actuator-controlled displacement of the flexor digitorum superficialis (FDS) tendon.

To evaluate the effect of SVD on tendon tracking, this improved speckle tracking (IST) method was compared to our original block matching (OBM) and to a standard, commercial tissue tracking (CTT) tool (discussed in Section IIIC). For this comparison, the ultrasound recordings of the six specimens were analyzed.

METHODS

The overall block diagram of the proposed algorithm is shown in Figure 1. Individual blocks of Figure 1 are explained below. We define an ROI manually within the tendon path and estimate the frame-to-frame tendon displacement inside the ROI. Since the tendon displacement is often larger than the ultrasound image size, we use a fixed ROI, with the tendon tissue moving through the ROI.

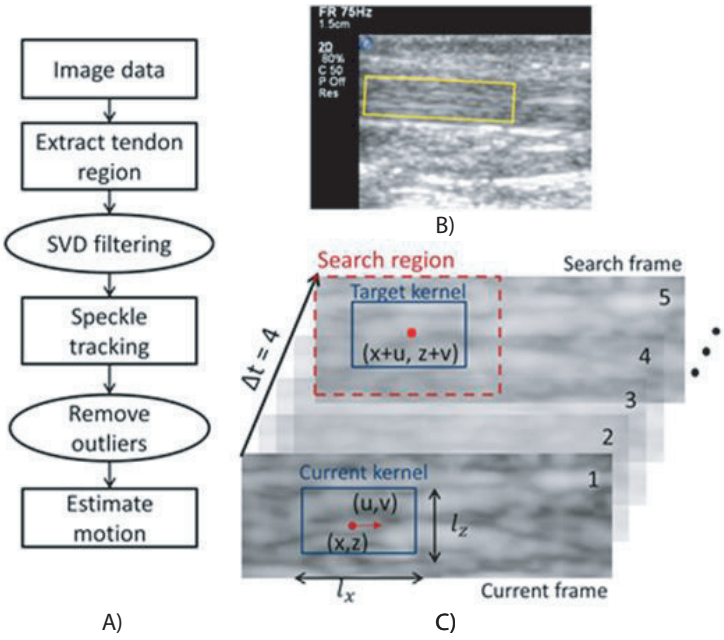

Figure 1. A) Overview of the proposed method (new parts in ovals), **B)** Tendon ROI, **C)** Schematic of block matching method.

A. Speckle Tracking

We represent the sequences of ultrasound data as sets of 2D frames *I(x, z, t)*, where *x* stands for lateral dimension of the 1D ultrasound probe, *z* stands for depth in the medium in front of the ultrasonic probe, and *t* stands for frame number (sampled at $F = 75$ Hz). A multi-kernel 2D block matching method was applied to track the tendon motion inside the ROI [11]. Each kernel was of size (l_x,l_z), as shown in Figure 1 c). The kernels (where *C* is the number of kernels) were equally distributed over the ROI.

Normalized Cross Correlation (NCC) [24] was used for block matching for each kernel within its search region. NCC was evaluated for all possible integer pixel displacements by calculating equation 1 for all displacements (*u, v*). The sub-pixel displacement vector (d_c) for the c^{th} kernel was found by interpolating the resultant correlation matrix with a 1:10 cubic spline interpolation,

$$y_c(u,v) = \frac{\Sigma_{x,c}[g_c - \bar{g}_c(x,z)][f(x+u,z+v) - \bar{f}_{u,v}]}{\{\Sigma_{x,z}[g_c(x,z) - \bar{g}_c]^2 \Sigma_{x,z}[f(x+u,z+v) - \bar{f}_{u,v}]^2\}^{0.5}} \quad (1)$$

$$d_c = \underset{u,v}{\operatorname{argmax}}\, y_c(u,v) \quad (2)$$

where $g_c(x, z)$ is the c^{th} kernel inside the ROI in the current frame *I(x,z,t)*; *(x, z)* are all pixel locations within the kernel; *f*_is the target kernel (displaced kernel) inside the search region of search frame *I(x,z,t+Δt)*; *(u, v)* is a vector of search displacement; $\bar{g}_c$ is the mean of the kernel g_c; and $\bar{f}_{u,v}$ is the mean of the target kernel corresponding to the current kernel g_c.

The incorrect kernel displacements were detected and discarded in two stages. In the first stage, kernel displacements with a correlation value < 0.5 were considered unreliable and discarded. In the second stage, displacements that were statistically distant (outliers) from others were removed using a Tukey test[25,26]. The tendon displacement per frame, *d(t)*, was estimated by taking the mean of all valid individual kernel displacements. The cumulative displacement, *D(t)*, up to a certain frame *t* was estimated by integrating the per-frame-displacements *d(t)* over the previous frames:

$$D(t) = \Sigma_0^t d(t) \tag{3}$$

Note that the block matching can be applied between consecutive frames, or between frames further apart in the sequence (frame interval *Δt*). If there is considerable motion between frames, it is best to use consecutive frames (*Δt*=1), to limit the decorrelation of patterns due to out-of-plane motion. On the other hand, if the motion is very small (sub-pixel), the correlation will be high but the peak estimate may be too coarse (quantization error) to detect the subpixel motion component accurately. The accuracy for lower velocities can be improved by increasing the frame interval. Although, the block matching was applied on frames *Δt* apart, the displacement estimation is adapted to the original frame rate.

B. SVD Filtering

In the SVD algorithm, the sequence of 2D ultrasound images I(x, z, t) with dimensions (n_x, n_z, n_t) are rearranged in a spatiotemporal fashion into a Casorati matrix form (A) with dimensions ($n_x \cdot n_z$, n_t), where one dimension represents space and the other dimension time. The SVD method is used to decompose the Casorati matrix into singular values as shown in equation 4,

$$A = U_{(n_x \cdot n_z, n_x \cdot n_z)} S_{(n_x \cdot n_z, n_t)} V^*_{(n_t, n_t)} \tag{4}$$

where *S* is a diagonal matrix of ordered singular values σ, *U* and *V* are orthonormal matrices and * stands for conjugate transpose. The signal *I* is decomposed as shown in Figure 2. The columns of *U* correspond to spatial singular vectors of *A* and the columns of *V* correspond to temporal singular vectors (sorted by decreasing singular values *σ*) of

A. Only the first n_t columns of *U* and *S* contain nonzero values, because there are only n_t singular vectors. Each column of U represents a spatial 2D image of size $n_x \cdot n_z$ which we will call a component image.

The matrix *A* can also be represented as a weighted, ordered sum of matrices:

$$A = \sum_{i=1}^{n_t} \sigma_i . U_i . V_i^* \tag{5}$$

where σ_i represents the ith order singular value, U_i is the ith order singular vector (component image) and V_i its associated time pattern.

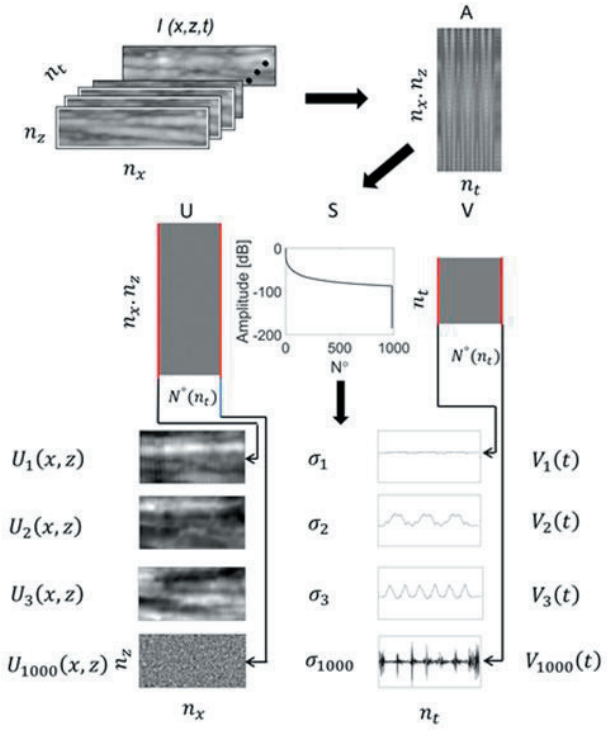

Figure 2. Image sequence decomposed by Singular Value Decomposition. Examples of component images U_i are shown on the lower left side of the figure. The graphs V_i, on the lower right side, represent their associated time patterns.

Stationary Signal and Noise Removal

All the different component images (U) mentioned above are associated with different temporal (V) characteristics. Stationary background, clutter, shadows and very slow tissue motion are generally represented by the lower order SVD component images with a low frequency temporal behavior. True tendon motion is represented by the middle

order SVD components. On the other hand, the relatively fast temporal changes (noise) correspond to higher order SVD components. Different motions described can indeed be seen in the frequency domain as shown in Figure 3. The tendon signal of interest can be extracted by removing the lower *n* clutter-related components and the higher *m* noise-related components and subsequently the image sequence is reconstructed based on the selected range as shown in equation 6.

$$a_{tendon}(x,z,t) = \Sigma_{i=1}^{n_t-m} \sigma_i U_i(x,z) V_i(t) \tag{6}$$

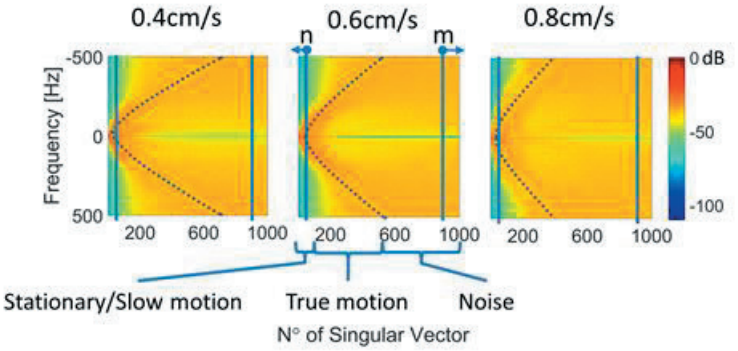

Figure 3. Spectral content estimation (using Fast Fourier Transform) of all the right singular vectors V_i, estimated for three different sequences (Test set 1) with different velocities. The dotted blue line indicates the primary frequency content (true motion) which is associated with the orders from *n* to *m* (chosen after parameter optimization as explained in Section III.D). The chosen (*n*, *m*) parameters indeed preserve the true motion.

Motion enhancement

Extraction of the tissue motion (equation 6) from the range *n* to *m* may not be fully suitable for speckle tracking. In practice, there will be parts of the image sequence where the tendon is moving and parts where it is almost stationary as shown in Figure 4. These parts may respond very differently to the proposed SVD approach. For example, the images are reconstructed for different *n* and *m* ranges at a stationary (*t=50)* and moving time points *(t=100*) as shown in Figure 4. Image a4 suppresses most of the clutter, leaving almost nothing in the still frame (t=50). However, this is counterproductive in a block-matching scenario, where a blank area cannot be tracked. In other words, for improved block matching, we want to suppress stationary clutter obscuring moving tendons, but we do not want to completely eliminate stationary (tendon) tissue. Our solution is to partly suppress the lower order and take out the higher order components, by creating a weighted sum of the different components where we lower the weight of the lower-

order, as shown in equation 7. The values we have chosen for the variables *m, n* and *w* are shown in Table 1. The choice of the parameter values is described in section III D.

$$a'_{tendon}(x,z,t) = \mathrm{w}.\sum_{i=1}^{n-1}\sigma_i.U_i(x,z).V_i(t) + \sum_{i=1}^{n_{t-m}}\sigma_i.U_i(x,z).V_i(t) \quad (7)$$

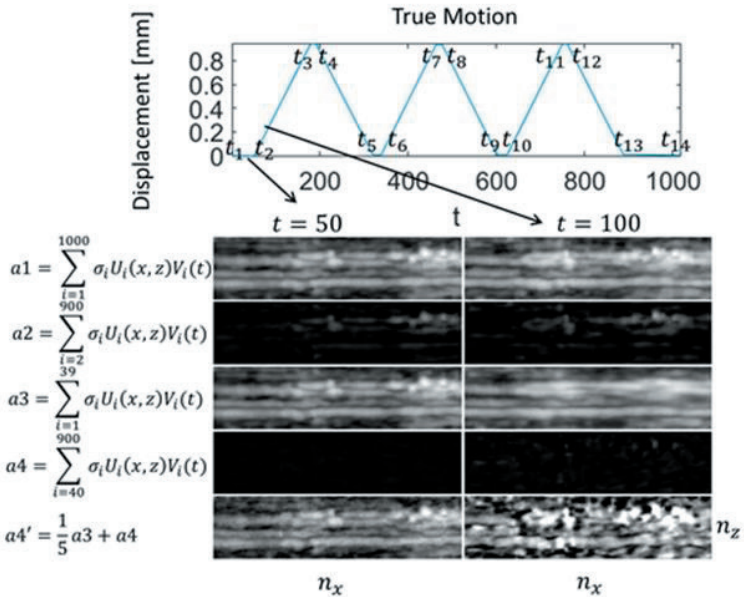

Figure 4. Reconstruction of stationary (left) and moving (right) tendon images generated from different SVD components. Top graph shows displacement pattern over time with the 14 time points where the marker position was manually indicated. Bottom images show different image reconstructions (rows *a1-a4'*) for time points *t=50* (left, stationary) and *t=100* (right, moving). Original image *a1* is reconstructed from all the components; *a2* from first 900 components except the first; *a2* still contains a significant 'stationary' contribution inside the tendon; *a3* from first 39 components; a4 from the first 900 components except 39 from the beginning; and *a4'* is a linear combination of *a4* and a3.

EXPERIMENTS

A. Experimental Setup

In this study design, we strived to validate our methods in a well-controlled model that closely matches the practical clinical application of our tools. Therefore, we chose to validate on a set of human cadaver hands with injected markers and controlled mechanical actuation. Six human cadaver hands were obtained from the Mayo Clinic [Rochester, USA] anatomical bequest program for use in this study, with approval from

the institutional bio specimen committee (IRB 15-005357). The power calculation was performed based on the measurement variability of CTT as reported by van Doesburg et al.[12]. It was concluded that with more than 30 sequences an average tracking difference of 0.37mm would be sufficient to show significant differences between the methods. Therefore, six cadaver hands (54 sequences) were considered as sufficient. Human cadaver hands, without a history of CTS, rheumatoid arthritis, osteoarthritis or traumatic injuries of the ipsilateral arm, were used. The fresh-frozen specimens were thawed prior to the experiment. The mean age was 78 ± 9 years. The cadavers were amputated approximately 10 cm proximal to the wrist joint. A customized fixture, clamping the proximal ends of the ulna and the radius, was used to hold the specimen in place. The wrist joint was held in a neutral position using an external fixator. All digits were fixed in extension with 1.5mm diameter Kirschner wires. The FDS tendons of the index, middle, ring and little fingers (FDS2 to 5) and the middle finger flexor digitorum profundus (FDP3) tendon were exposed proximal to the proximal wrist crease and the severed ends of all tendons besides the FDS3 were connected to a 50 gram weight using a Vicryl 4.0 suture to maintain tension. The severed proximal end of the FDS3 tendon was connected to a stepper-motor driven mechanical actuator controlled by a microcontroller (Arcus Technologies, Livermore, CA). The distal end of the FDS3 tendon was exposed and connected to a 50 gram weight suspended over a pulley to maintain tension (figure 5), which assisted in providing consistent tendon motion between trials. The carpal tunnel was kept intact over its entire length.

A metal marker (the tip of a 20 gauge needle approximately 4-5 mm in length; Figure 5) was inserted transversely into the FDS3 tendon by injecting the marker at the level of the proximal carpal tunnel using an 18 gauge needle. The actuator displaced the tendon with three different target velocities (0.4 cm/s, 0.6 cm/s and 0.8 cm/s) over three displacement amplitudes (0.5 cm, 1 cm and 1.5 cm) in the proximal direction. As a result, nine combinations of velocity and displacement were investigated for each specimen. Actuator displacement was recorded at a sample rate of 50Hz. The longitudinal motion of the FDS tendon was recorded using an iE33 ultrasound machine (Philips Electronics, Best, The Netherlands) with an L15-7io linear transducer in fundamental mode (high-resolution mode, up to 15MHz), which was held in a fixture and placed at the level of the proximal outlet of the carpal tunnel. For each of the nine combinations of displacement and velocity, three motion cycles (motion in the proximal direction and then returning to the neutral position) were recorded. A warm up cycle was performed before each trial of a certain velocity and displacement to precondition the tendon, since the structure of the tendon can change in response to loading. Preconditioning of soft tissue is a widely applied element in biomechanical testing procedures, since gliding resistance can change between the first pull and subsequent pulls[27]. This change can be attributed to

non-linear effects such as poroelasticity and viscoelasticity. Since that first cycle can be different because of these effects, looking at subsequent cycles is more representative of repeated hand motions. Given the known high stiffness of the FDS tendons[28] and the relatively small load of 50 gram that is able to retract the tendon, we can safely assume unobstructed motion of the tendon with negligible strain over the imaging area and displacement ranges. The displacement pattern of the marker is assumed to be identical to that of any position within the tendon.

Images were acquired at a frame rate F = 75Hz in DICOM format (1024 x 768 pixels, 2.55cm width x 1.5cm depth, 25 x 25 μm^2 pixel spacing). 600 to 1000 frames (depending on velocity and displacement applied) were acquired for each sequence.

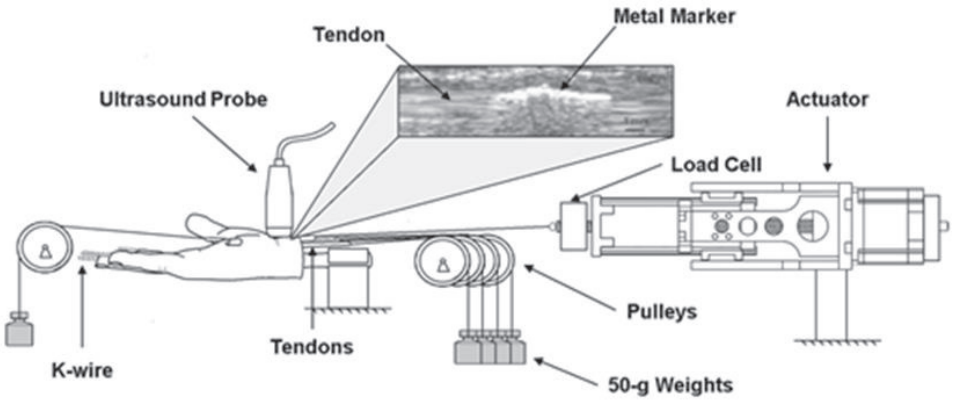

Figure 5. Experimental set-up. The cadaver hand is fixed in a neutral position, with the proximal end of the FDS3 connected to the actuator and the distal end to a 50 gram weight. The proximal end of FDS2, 4, 5 and FDP3 are connected to a 50 gram weight as well. The ultrasound probe is placed at the level of the proximal carpal tunnel inlet. An example of an ultra-sonographic image of the FDS3 with inserted marker is shown.

B. Manual ground truth motion analysis

The ground truth (GT) motion was measured by manually indicating the physical marker position at 14 time points (*t1-t14* in Figure 4) in the original DICOM image series. Two observers performed the manual GT measurements. The time points *t2-t13* were located at the start and end of each of the six tendon displacement half-cycles. The marker displacement was measured by taking the Euclidean distance between the pair of 2D start and end points of each half-cycle. The average of the six half-cycles was taken as the ground truth displacement value. We chose not to use the motion that was applied via the actuator as a ground truth, because we expected differences between actuator and tendon displacement due to friction and deformations of soft tissue that would occur during testing.

C. Manual initialization of OBM, IST and CTT

User interaction in OBM and IST

The ROI selection is as described in the Methods section. We made sure that the metal marker was never entering the ROI. A rectangular ROI was positioned manually over the tendon (no specific anatomical landmarks were used) and rotated and scaled to be coaxial with and within the tendon path. This region of the image along with the search region was exported as a rectangular image sequence of fixed ROI size (scaled using cubic interpolation) where the tendon was moving horizontally. The mean pixel spacing of the exported sequence was 14μm. The size of the exported ROI and the search region are given in Table I. The maximum speed that can be detected is dependent on the maximum search region and the exported pixel spacing. The detectable mean velocity was 5.6 cm/s.

User interaction in CTT

For CTT, we used Syngo VVI software (Siemens Medical Solutions USA Inc.) to analyze the images. As opposed to the OBM and IST, the CTT software applies a dynamic ROI. An ROI was selected manually by placing three markers on the tendon with an approximate distance between the markers of 1 mm. The markers were placed on the central axis of tendon motion, far away from the inserted metal marker [12]. To minimize the difference in ROI placement between methods, we verified that the ROI at some point in the tracking approached the ROI selected for the OBM and IST software. The CTT software's free trace mode was selected to perform the analysis, providing velocity time series data and ROI coordinates at each frame. The displacements were derived based on the area under the velocity curve. Ultrasound clips analyzed with CTT were exported at 30 Hz due to a practical limitation of the file size that can be uploaded into the CTT software [12].

D. Tracking accuracy evaluation and parameter selection

Our proposed tracking method (IST) with the optimized set of parameters was applied to the 6 test sets to estimate its accuracy and compared to our previous method (OBM, optimized for parameters) and commercial tissue tracking tool (CTT). The parameter values of the OBM method were already optimized by Korstanje *et al.* [14]. Some parameters were slightly adapted to allow a fair comparison between OBM and IST. We used a larger ROI in our study to accommodate more kernels for the Tukey filter to perform better (more statistical information). The rest of the IST parameters were copied from the OBM method. The other parameter values were chosen after a limited-range optimization on all nine image sequences of one of the six cadavers, for best accuracy of the IST tracking; further details about the optimization can be found in [29]. All the parameters used are shown in Table 1.

Table 1. Optimized paramter values usedf or IST and OBM methods.

Parameter	IST	OBM
Frame difference, Δt (frames)	4	4
SVD start, n	40	-
SVD end, m	100	-
SVD weight, w	1/4	-
Number of kernels C [C_x, C_z]	28 [7, 4]*	12 [6, 2]*
Kernel size, [l_x, l_z] *(pixels)*	[71, 31]	[101, 51]
ROI (*x, z*) [pixels]	[400, 100]	[400, 100]
Search region (x, z) [pixels]	[800, 600]#	[500, 120]

* adapted to a larger ROI size. Korstanje et al. [14] used (3, 2) for a ROI size of (200, 90) pixels.
# this search region corresponds to the maximum tendon velocity that can be detected between frame t to frame $t+\Delta t$. A search region of 800 pixels in X-direction, corresponds to a maximum velocity of around 10 cm/sec

E. Analysis

The cumulative displacement, *D(t)*, was estimated for all the frames of the full motion sequence (3 cycles). However, small systematic underestimations, as well as instantaneous errors could lead to a drift (at the end of each cycle, estimated position is different from initial position). If the motion is known to be cyclic, it is common to compensate for such drift. Therefore, to evaluate the accuracy of the tracking, we compared the drift free displacement (DFD) as well as the drift to the manual tracking. We reported the relative drift as the final displacement found at *t14* expressed as a percentage of the GT displacement. We observed in our study this drift was mostly linearly accumulating and compensated the displacement curves accordingly. The DFD was then found by taking the absolute mean of the 6 relative displacements (*t2* to *t3*, *t4* to *t5*, *t6* to *t7*, etc.) The relative DFD error was the difference of DFD from GT expressed as a percentage of the GT displacement.

The DFD displacements, DFD errors and relative drifts in all 9 sequences of the 6 test studies were measured using IST, OBM and CTT methods. Agreement of displacement estimation between each of the three methods and the GT was evaluated for each sequence of the 6 test studies using Bland-Altman 95% limits of agreement[30], in which the difference between the respective method and GT was plotted against the mean of the two measurements, describing the distribution of variance.

RESULTS

The DFD errors and the drifts of all the test sets are shown in Fig 6 for each method. The mean relative DFD error was 19.7 ± 20.8% using the OBM method and 25.8 ± 18.4 % using the CTT method, but notably lower, 12 ± 16.9% using the IST method. The median relative DFD error was only 4.6% using the IST method vs 14% and 20.7% using the OBM and CTT methods, respectively. The mean relative drift observed was 8.7 ± 7.2%, 7.7 ± 9.0% and 8.3 ± 11.0% using the OBM, CTT and IST methods respectively.

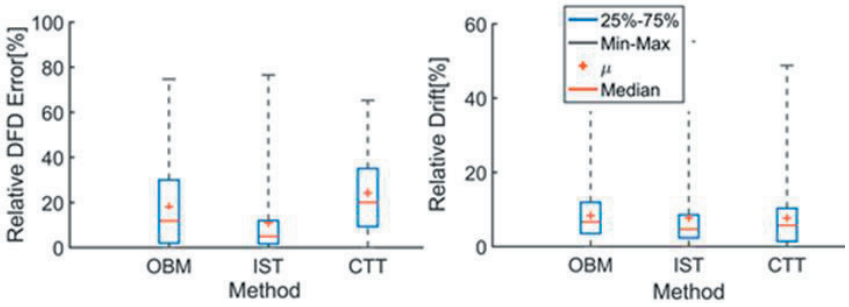

Figure 6. Relative DFD error (left) and relative drift (right) of three tracking methods (OBM, IST, and CTT) compared to the ground truth. Per method, the bar represents the results over all velocities and displacements and over all test sets.

The Bland-Altman plots comparing the three methods (OBM, IST, CTT) to GT are shown in Figure 7. Typical differences between OBM tracking and GT ranged from –0.52 to 0.22 cm (95% confidence interval) with a mean error of –0.15 cm. The results of the CTT method are very similar to the OBM method with the 95% confidence interval ranging from –0.6 to 0.17 cm and a larger mean error of –0.21 cm. Typical differences between IST tracking and GT tracking were found ranging from –0.41 to 0.24 cm (95% confidence interval) with a mean error of –0.07 cm. The mean underestimation error by IST was significantly smaller than that of OBM and CTT (one-sided paired Student T-test on means, $p<<0.001$); also the confidence interval for IST was significantly smaller (F-test on variance, $p<<0.001$). The mean underestimation error of OBM was significantly smaller than that of CTT ($p=0.034$), but the confidence intervals were not significantly different ($p=0.30$). It must be noted that the upper limits of the confidence intervals are a bit misleading because of the skewed distributions of data: almost all estimations are lower than the ground truth, so positive error values are very rare.

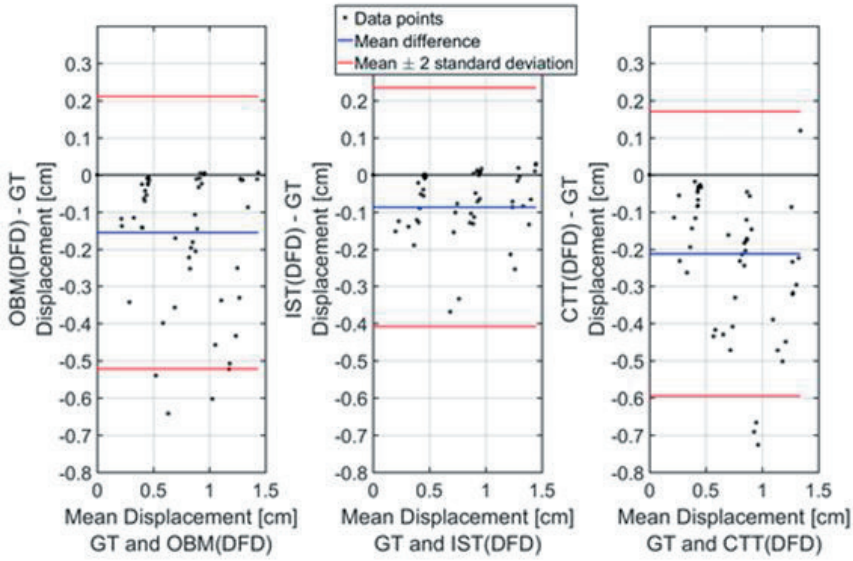

Figure 7. Bland-Altman plots of OBM, IST and CTT methods with respect to manually tracked ground truth (GT). X-axis represents the mean DFD displacement of the automatic and GT tracking, and y-axis represents difference between automatic and GT.

DISCUSSION

In this paper, an improved speckle tracking method for tendon tracking was described and validated using human cadaver experiments. The proposed method uses SVD to suppress the stationary background from the ultrasound sequences that affects the speckle tracking accuracy. The experimental results showed that the IST method resulted in a higher accuracy in estimating tendon motion compared to our original method (OBM) and commercially available tissue tracking software (CTT).

The manually measured GT displacements were accurate, with a standard deviation of 0.0062 cm of the 6 absolute half displacements measured by one observer within each sequence and the standard deviation of the difference of the mean absolute GT displacements between two observers was 0.087 cm.

Comparison with literature

It should be noted that the DFD errors we found using the OBM method were considerably higher than those reported originally by Korstanje et al.[14]. This could be due to four reasons. Firstly, we used 3 excursion cycles, unlike a single one-directional excursion in [14]. Secondly, we tested in a realistic setup with 6 human cadavers, in contrast to the 2 fresh porcine cadavers in [14]. Our measurement in the human carpal tunnel region

might be more prone to artifacts than the superficial porcine FDS tendons. Thirdly, we found that the success of the OBM tracking can vary from case to case depending on the image quality. For example, Test set 4 resulted in a mean relative DFD error of 43.1% using OBM, whereas Test set 2 and Test set 6 resulted in a mean relative DFD error of only 1.9% using OBM. CTT also showed a large variability between specimens, with average DFD errors per specimen ranging from 15% to 50%. IST showed less variability between specimens, with average DFD errors ranging from 1 to 26%. Fourthly, the size of the search region we used was much larger.

IST findings

The IST method successfully improved the estimation compared to the OBM method in all the cases (best and worst). Indeed, the reconstruction of image frames using SVD decomposition improved extraction of the true tendon motion by suppressing the background. However, IST tended to produce extreme outliers in situations where there is a sudden transition in motion. The OBM produced extreme outliers in very few cases but tended to underestimate the motion systematically. For this reason, the Tukey outlier remover was important in the IST method, more than in the OBM method.

The optimized parameters of IST ($C[C_x{*}C_z]$, $[I_x I_z]$ and Search region) we used were different from the optimized parameters of OBM method. Therefore, we applied the new parameters settings of IST on the OBM method as well and found that the accuracy was slightly degraded (19.7 ± 20.8% using the optimized parameters of OBM and 21.6 ± 21.0% using the optimized parameters of IST given in Table I). In conclusion, the new parameters did not improve the OBM method so the improved results of IST are not attributable to them.

The primary step of the IST method is to remove semi-static artifacts like clutter. There are various methods available in literature to suppress the clutter using a simple frequency-based finite impulse response (FIR) high-pass filter, where the clutter and the desired signal are assumed to have distinct frequencies. However, the frequencies in most cases overlap, making high-pass filtering unreliable. Moreover, others have already reported that SVD-based clutter suppression outperforms simple high pass filtering in such cases[23,31].

Limitations and further research

A main limitation of the current study is that the method was validated on datasets where the motion was limited to a maximum velocity of 0.8 cm/sec. These velocities were chosen because it was shown earlier that in cadaver experiments, higher velocities and excursions resulted in permanent damage to the cadaver tissue (not in-vivo)[32]. Furthermore, the intended use is in well-controlled patient exercise protocols, where the speed can be kept low. However, we actually skip frames for best accuracy at these

velocities (Δt=4). At four times higher velocities, skipping no frames should result in the same accuracy. We showed in our earlier study[29] that the accuracy of the method was best at the given velocities of 0.4-0.8 cm/s when Δt = 4-6 frames, which corresponds to velocities up to 1.6-4.8 cm/s with no frames skipped. However, the accuracy worsened for Δt > 6 frames, which implies that a higher frame rate is advised for experiments with actual velocities >5 cm/s.

A limitation of the IST method is that while it produced overall smaller relative DFD errors and relative drifts compared to OBM and CTT, it produced large drifts in some cases, as seen in Figure 7; the standard deviation of the drifts using IST was 10.94% whereas it was only 7.21% using OBM. In most cases, the relative drifts were below 10% for all three methods, but there are more cases with large drift for the IST method compared to OBM and CTT. As we have seen, the IST method, in general, tracked more accurately but produced more incidental tracking outliers, which needed to be handled by our Tukey outlier removal. We presume the drifts are caused by imperfect outlier removal in these cases. Further optimization of SVD parameters or Tukey settings might improve the results; this could be investigated further.

Demene et al.[23] applied the SVD filter for separating the blood and tissue responses in a Doppler image and hence they required large ensemble data lengths (RF) and high frame rate for Doppler sensitivity. The SVD filter was therefore able to discriminate between tissue and blood with very similar velocities. However, the purpose of our study is not Doppler, but only to remove the slow moving tissue from the sequence of B-mode images and hence a lower frame rate was sufficient for the SVD filter to perform well.

A limitation in all three methods that we studied is the inability to account for out-of-plane motion. If the image sequence has an out-of-plane motion, the true motion will be underestimated; moreover, out-of-plane motion causes decorrelation of the image content between frames. This is an inherent problem in the imaging itself and IST will not be more helpful than other methods in that case. In our human cadaver experiment, we tried to limit the out-of-plane motion, but included all the studies for the analysis in this manuscript. However, it is more difficult to avoid out-of-plane motion in studies on healthy subjects or patients, where a tendon may not be moving in the same plane throughout the conditions that are studied.

It should be noted that the IST method uses a different tracking technique and a different frame rate compared to the CTT method. We only intend to demonstrate that the accuracy of IST was higher than the commercially available software (CTT). Moreover, we used a frame difference of 4, which corresponds to an effective frame rate of 18.75 only.

Some potential improvements may be further investigated. Although the different IST parameters were optimized for a human cadaver study, we intend to further investigate

the parameters while applying on in-vivo patient data where a more diverse motion (higher velocities and irregular motion cycles) is expected. Higher velocities would result in faster change in speckle pattern from frame to frame which might require using higher frame rates. For example, a change in acquisition rate could influence the choice of Δt. Moreover, the content of the ROI was manually selected with a fixed size to include only tendon area. A change in the dimensions and content might require fine-tuning in kernel size and number of kernels. Repeatability and reliability should also be further investigated. Although we had enough sequences to validate our method, it would be also interesting to further investigate inter-specimen variability using more cadaver arms.

In this study, we intend to use only post processing methods on the images acquired from a commercial ultrasound machine operated in high frequency mode with the best possible resolution. However, the tracking accuracy could also be limited due to lower lateral resolution. In order to improve the lateral resolution, the use of imaging techniques like compounding or transverse oscillations could improve the lateral resolution and therefore the tracking accuracy. This might be studied in future research. The use of RF data has also been shown to improve speckle tracking, but only in the direction of the ultrasound beam. This direction is perpendicular to the tendon motion and it is not expected to give any improvement in our case.

Moreover, based on our spectral analysis of the resultant singular vectors from three different tendon velocities, we came up with overall useful IST filter parameters (m, n, w). However, we believe that a large change in tendon velocity range as well as a large change in the clutter composition could affect these IST parameters. Therefore, adaptively tuning the IST filter parameters could further improve the tracking accuracy.

CONCLUSION

In summary, we have proposed an improved correlation-based speckle tracking method for tendon tracking, using a Singular Value Decomposition filter to remove the stationary background. The relative performance of three speckle tracking algorithms was evaluated on 6 cadaver test sets, by using manual tracking as the ground truth. The mean relative DFD error of IST (12 ± 16.9%) was significantly better than that of our original block matching method (19.7 ± 20.8%) and that of commercially available software (25.8 ± 18.4%).

ACKNOWLEDGEMENT

The project was supported NIH/NIAMS Grant RO1 AR62613.

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7

IMPROVED TENDON TRACKING USING SINGULAR VALUE DECOMPOSITION CLUTTER SUPPRESSION

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Conference Paper September 2017: IEEE International Ultrasonics Symposium (IUS)

ABSTRACT

Ultrasound imaging is a real-time and high frame rate modality suitable for the analysis of tendon dynamics, e.g. for diagnosis of carpal tunnel syndrome. Tendon displacement quantification algorithms based on speckle tracking are sensitive to underestimation due to stationary clutter present in the tendon region. In this study we propose an improved speckle tracking method based on Singular Value Decomposition to suppress the stationary background. The method was optimized using image sequences from a human cadaver arm experiment. The ground truth displacement was found by tracking a metal marker inserted in the tendon. Various parameters involved in our method were optimized for best accuracy. Overall relative error of 3.2±2.3% was observed using our method compared to 7.4±4.8% using our previous speckle tracking method.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common wrist neuropathy. Current non-invasive examination of tendon pathology is mostly based on subjective judgment of the physician after examination of the ultrasound or MRI images of the tendon. MRI provides high-quality images but is not easily accessible and relatively expensive as compared to ultrasound[1]. Furthermore it is less suitable for imaging tendon dynamics.
Ultrasound provides high-resolution, high-frame rate imaging that can examine the tendons in real-time enabling analysis of tendon dynamics[2-4]. Manual tracking of anatomical landmarks over an ultrasound image sequence or the use of tissue Doppler have been described[5]. However, manual tracking is laborious, and depends on visibility of landmarks. Tissue Doppler has the limitation of measuring the motion component only in the direction of the ultrasound beam, while tendons generally move almost perpendicular to the beam. Most approaches for tendon motion quantification employ techniques known as speckle tracking or block matching[6-8]. Speckle tracking is a method in which the speckle patterns generated by the scattered ultrasound are tracked from frame to frame to measure the motion of tissues. Speckle tracking offers a two-dimensional displacement estimate and is virtually independent of the angle of the ultrasound beam. Since the method exploits the inherent speckle patterns in the tendon tissue, anatomical landmarks or implanted markers are not required.
We earlier developed and validated a speckle tracking algorithm using Normalized Cross Correlation (NCC) on a stationary region of interest (ROI) over the tendon path [6]. However, the NCC is sensitive to semi-static artifacts (stationary background, clutter, and shadowing) in the images which lead to motion underestimation. In this study, we use an improved speckle tracking method based on Singular Value Decomposition (SVD) filtering to suppress the semi-static artifacts[9]. The parameters of the SVD based image reconstruction and speckle tracking were optimized for best accuracy using the human cadaver study.

MATERIALS

A human cadaver hand was obtained from the Mayo Clinic [Rochester, USA] anatomical bequest program for use in this study, with approval from the institutional bio specimen committee (IRB 15-005357). A metal marker (the tip of a 20 gauge needle approximately 4-5 mm in length; Figure 1) was inserted transversely into the Flexor Digitorum Superficialis-3 (FDS3) tendon by injecting the marker at the level of the proximal carpal tunnel using an 18 gauge needle. The FDS3 tendon of the human cadaver arm was displaced mechanically at 3 speeds and with 3 excursion amplitudes, resulting in 9 unique sequences. A sequence consisted of 3 cycles of forward and backward displacement. Ultrasound sequences were acquired at 75Hz framerate (Philips iE33, L7-4).

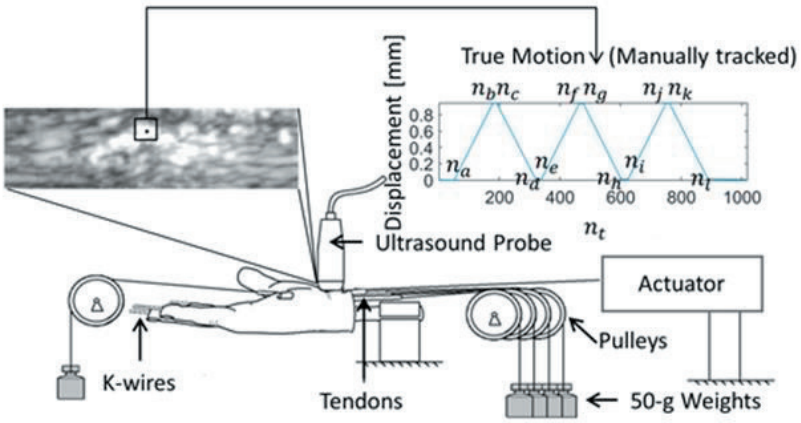

Figure 1. Experimental set-up. The cadaver hand is held in place with a customized fixture by clamping the proximal ends. The proximal end of FDS2, 4, 5 and FDP3 are connected to a 50 gram weight and FDS3 is connected to the actuator. The distal end is connected to a 50 gram weight. The ultrasound probe is placed at the level of the proximal carpal tunnel inlet. An example of an ultra-sonographic image of the FDS3 with inserted marker is shown on top left. The manually tracked marker displacement (True Motion) pattern over time (n_t) at the 12 time points of the marker position is shown on the top right.

METHODS

The tendon ultrasound image sequences generally consist of different components (moving tendons, slow moving connective tissues, and stationary tissue) along with artifacts (noise, clutter, stationary background, and shadow regions in the image). Due to the presence of these artifacts, a standard block matching method suffers from under-estimation of motion. We therefore used an SVD algorithm to filter out the clutter-like components in the images, before applying the block matching method.

A. SVD Filtering:

The 2D ultrasound image sequences, *I(x,z,t)* of dimensions (n_x, n_z, n_t) were reformatted into a spatiotemporal data representation known as a Casorati matrix (*A*) as shown in Figure 2, where (*x, z*) stands for lateral and depth dimensions respectively and t stands for frame number. The matrix *A* is decomposed by SVD into individual spatio-temporal components (*U, S, V*) as shown in equation 1.

$$A = U_{(n_x \cdot n_z, n_x \cdot n_z)} S_{(n_x \cdot n_z, n_t)} V^*_{(n_t, n_t)} \quad (1)$$

where *S* is a diagonal matrix of ordered singular values σ (eigen values), *U* and *V* are orthonormal matrices representing spatial and temporal singular vectors of *A* respectively, and * stands for conjugate transpose.

The matrix A can also be represented as a weighted, ordered sum of matrices:

$$A = \sum_{i=1}^{n_t} \sigma_i . U_i . V_i \tag{2}$$

where *i* corresponds to the column number of each matrix *U, S, V*.

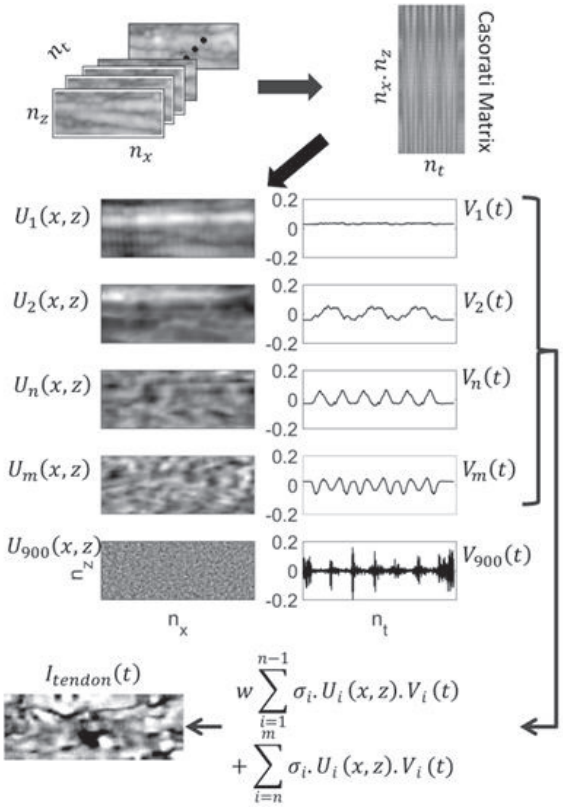

Figure 2. The ultrasound sequence *I(x,z,t)* is decomposed into spatio temporal singular vectors *U* and *V* using SVD method. The tendon motion is reconstructed from the component range [*n=40, m=800*] with a percentage (*w*) of the slow moving components [1, n-1] added. The components above m are considered noise and are rejected.

The lower order components generally correspond to stationary tissue and clutter, where $U_1(x, z)$ and $V_1(t)$ is the most dominant. The highest components correspond to noise and can be discarded. The tendon motion of our interest lies in the components in the middle range [*n, m*] as shown in Figure 2. The original image sequence can be reconstructed back from all the components using equation 2. The tendon image sequence of our interest (representing only motion) can be extracted by removing the

lower n and higher m components, discarding the upper (noise) and lower (clutter) components. However, in practice, there will be parts of the image sequence where the tendon is moving and parts where the tendon is stationary. For that matter, the range [*n, m*] may not be suitable for reconstructing the part of the image sequence where there is no motion, as this could result in empty images. This could be counterproductive in a block-matching scenario while transitioning from a still frame (empty) to a moving frame (enhanced motion). Therefore, we added back a down weighted (*w*) (cf. Figure 2) set of lower-order components while reconstructing the tendon images. This suppressed the artifacts without obstructing the tracking of semi-stationary tissue. The parameters [*n, m*] and *w* are subject to optimization.

B. Displacement estimation using Block matching:

A multi-kernel 2D block matching method based on NCC[10] was applied to track the tendon motion inside the defined ROI[6]. The tendon displacement per frame, *D(t)*, is estimated by taking the mean of all the valid kernel displacements $d_c(t)$, where *c* is the kernel number. The invalid kernel displacements were filtered out based on two filters. The kernels with normalized correlation lower than 0.5 are considered unreliable and are discarded by the first filter. The second filter removed the displacement outliers (kernels with extreme displacements) based on a Tukey outlier filter[11].

Note that the block matching can be applied between consecutive frames, or between frames further apart in the sequence (frame interval *Δt*). The selection of a proper frame interval is important for the quality of tracking. Since the continuous motion of the tendon is spatiotemporally quantized in a digital image sequence, the frame rate may be too low or too high for the tendon displacement. If the frame rate is too low, frame-to-frame displacement and deformation is large and decorrelation will deteriorate the matching. In our study, since we tested relatively slower tendon velocities (maximum of 0.8 cm/sec) the frame-to-frame displacement may be too small (subpixel) and matching may lead to quantization errors. Therefore, the tendon displacement per frame was estimated by correlating the current frame with a frame further away in the sequence by a frame interval Δt. The parameter Δt was subject to optimization.

C. Parameter Optimization

The nine sequences with different velocities and excursions were used to optimize algorithmic parameters, by evaluating for each parameter setting the accuracy of the estimated displacement with respect to the ground truth. We first established a set of default parameters (cf. Table I) that produced overall good results and fine-tuned these values by estimating the accuracy of the result for changes in each specific parameter.

The parameters were varied over a range of values in the order of decreasing sensitivity as shown in Table I. Δt was the first factor to optimize, as it was found to be the most sensitive parameter. The next logical choice was the SVD parameters as they control the image quality of the generated frames. Finally, kernel size and number of kernels were changed together. The default parameters were updated in each step and used in the next parameter analysis. The evaluated values of each parameter are shown in Table I.

Table 1. Parameter values for optimization of the improved speckle tracking accuracy.

Parameter	Default	SVD based tracking
Frame difference, Δt (frames)	4	[1 to 9] in steps of 1
SVD start, n	40	[0, 5, 10, 20, 40, 80, 90]
SVD end, m	400	[100, 200, 400]
SVD weight, w	1	1/[1, 2, 3, 4, 5]
Number of kernels *c*[*x* z*]	28 [7*4] *	[6(3,2), 12(4,3), 20(5,4), 28(7,4), 40(8,5), 66(11,6), 153(17,9)]
Kernel size, [c_x] *(pixels)*	71	[15, 31, 71, 91, 111]
Kernel size, [c_z] *((pixels)*	31	[9, 15, 31, 51, 71]

*Adapted to a larger ROI size. Korstanje *et al.* used (3, 2) for a ROI size of (200, 90) pixels.

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D. Accuracy Analysis

The ground truth (GT) motion was measured by manually tracking the metal marker's position at 12 time points (n_a-n_l in Figure 1) in the original image sequence. The time points n_a-n_l were located at the start and end of each of the six tendon displacement half-cycles. The marker displacement was measured by taking the Euclidean distance between the pair of 2D start and end points of each half-cycle. The mean of the six half-cycles was taken as the ground truth displacement value.

In order to perform the automated tracking, a stationary ROI of size (400,100) pixels was positioned manually such that the tendon region was included in all the frames and the metal marker was never entering the ROI. The ROI was rotated to be coaxial with the tendon path. This region of the image was exported as a rectangular image sequence where the tendon was moving horizontally.

The cumulative tracking displacement, *D(t)*, was estimated for all the frames of the full motion sequence (3 cycles). However, small systematic underestimations, as well as instantaneous errors could lead to a drift at the end of each cycle. Therefore, we estimate the displacement as absolute mean of the 6 relative displacements (n_a to n_b, n_c to n_d, n_e to n_f, etc.) The relative error (displacement) was the difference of estimated relative displacement from the GT, expressed as a percentage of the GT displacement.

RESULTS

The results of the parameter optimization for the three different velocities are as shown in Figure 3 and Figure 4 and the optimized parameters are summarized in Table II.

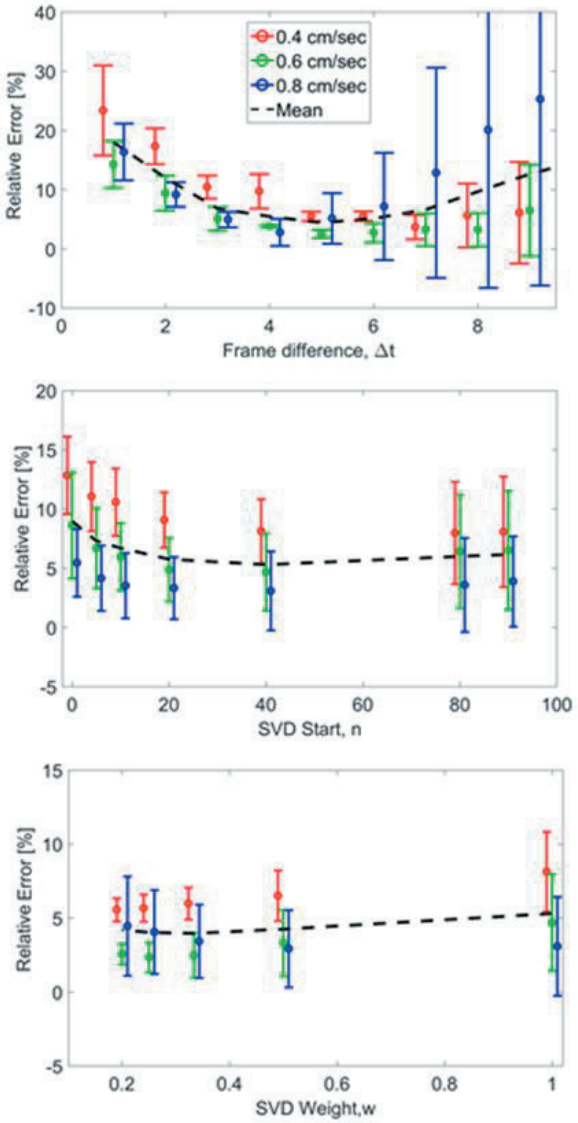

Figure 3. Speckle tracking parameter optimization of Frame difference *Δt*, SVD Start *n* and SVD weight *w*. The relative error bars indicate the mean and standard deviation of the relative displacement errors for different GT displacements for each velocity. The overall mean of the relative errors is shown as the black dotted line.

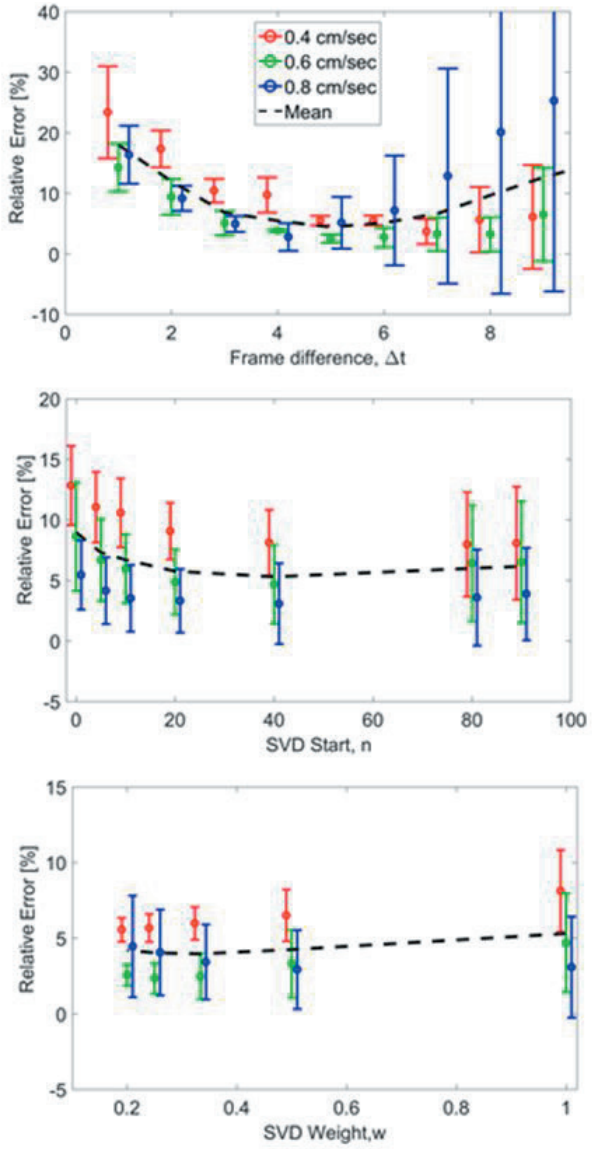

Figure 4. Speckle tracking parameter optimization of number of kernels *c* and kernel sizes ($c_x c_z$). The relative error bars indicate the mean and standard deviation of the relative displacement errors for different GT displacements for each velocity. The overall mean of the relative errors is shown as the black dotted line.

For the SVD parameters, down weighting the 40 lower-order components to 20% resulted in best accuracy. The results of parameter *m* did not change for the range of values tested and were not shown. An overall minimum relative error of 3.2±2.3%

was observed using the improved speckle tracking with SVD filtering, where as it was 7.4±4.8% using our previous speckle tracking [6].

Table 2. Optimum parameters

Parameter	Optimized
Frame difference, Δt (frames)	5
SVD start, n	40
SVD end, m	100
SVD weight, w	1/4
Number of kernels *c*[*x* z*]	28 [7*4]
Kernel size, [c_x]*(pixels)*	71
Kernel size, [c_z]*(pixels)*	31

DISCUSSION

In this paper, an improved speckle tracking method for tendon tracking was described and optimized using a human cadaver experiment. The proposed method uses SVD to suppress the stationary background from the ultrasound sequences that affects the speckle tracking accuracy.

A large number of parameters are used in the block matching method. However, in the current study we limited the optimization to a few critical parameters that are the most influential. The *Δt* was found to be the most critical factor. A smaller *Δt* could increase tracking errors due to the quantization error when the displacements are in the order below the pixel size. It can indeed be seen in Figure 3 that a lower *Δt* performed better for higher velocity (0.8 cm/sec) and higher *Δt* for lower velocity (0.4 cm/sec). A *Δt* of 5 resulted in the best accuracy over all the datasets. The size of each search region for a given *Δt* was estimated by assuming that the maximum ground truth velocity was 10cm/sec. The number of kernels *c* and kernel sizes (c_x,c_z) are other important parameters to consider. The performance of the method was improved with increased *c* and (c_x,c_z). However, since the kernels are placed within a fixed-size ROI, increasing c will result in more kernel overlap. Using smaller kernels will increase the chance of false matches. Also, the calculation time is heavily dependent on these three variables. Therefore, we chose (c_x,c_z) of (71, 31) with the best accuracy, with the lowest possible *c* of 28 for lesser computation time.

A main limitation of the current study is that the method was optimized on a few datasets of a single cadaver study. Accuracy is also subject to change from study to study. We intend to validate the method on more cadaver studies to verify its robustness. Also, the motion was limited to a maximum velocity of 0.8 cm/sec. The parameters might need

to be re-established for protocols where faster motions are essential. The choice of *n* has shown to be a complex issue in other SVD studies and no automated method of selecting *n* is reported yet.
Further investigation of the parameters is needed while applying on in-vivo patient data where a more diverse motion (higher velocities and irregular motion cycles) is expected.

CONCLUSION

We proposed an improved speckle tracking method using Singular Value Decomposition to track tendon motion. Various parameters of the method were optimized for best performance using a cadaver data set. A relative displacement error of 3.2±2.3% was observed using the improved speckle tracking with SVD filtering, compared to 7.4±4.8% using previous speckle tracking.

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8

RELIABILITY OF ULTRASOUND SPECKLE TRACKING WITH SINGULAR VALUE DECOMPOSITION FOR QUANTIFYING DISPLACEMENT IN THE CARPAL TUNNEL

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J Biomech. 2019 Mar 6;85:141-147.

ABSTRACT

Background

Inhibited movement patterns of carpal tunnel structures have been found in carpal tunnel syndrome (CTS) patients. Motion analysis on ultrasound images allows us to non-invasively study the (relative) movement of carpal tunnel structures and recently a speckle tracking method using singular value decomposition (SVD) has been proposed to optimize this tracking. This study aims to assess the reliability of longitudinal speckle tracking with SVD in both healthy volunteers and patients with CTS.

Methods

Images from sixteen healthy volunteers and twenty-two CTS patients were used. Ultrasound clips of the third superficial flexor tendon and surrounding subsynovial connective tissue (SSCT) were acquired during finger flexion-extension. A custom made tracking algorithm was used for the analysis. Intra-class correlation coefficients (ICCs) were calculated using a single measure, two-way random model with absolute agreement and Bland-Altman plots were added for graphical representation.

Results

ICC values varied between 0.73-0.95 in the control group and 0.66-0.98 in the CTS patients, with the majority of the results classified as good to excellent. Tendon tracking showed higher reliability values compared to the SSCT, but values between the control and CTS groups were comparable.

Conclusion

Speckle tracking with SVD can reliably be used to analyze longitudinal movement of anatomical structures with different sizes and compositions within the context of the carpal tunnel in both a healthy as well as a pathological state. Based on these results, this technique also holds relevant potential for areas where ultrasound based dynamic imaging requires quantification of motion.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common compression neuropathy, with an estimated prevalence of 1-5%[1,2]. CTS is predominantly a clinical diagnosis, often supported by electrophysiological measurements. However, this is an invasive, uncomfortable method that has been criticized since it has limited negative predictive potential[3], with up to 50% of electrophysiological-negative patients still benefitting from treatment[4]. More recently, ultrasound (US) imaging has emerged as an interesting alternative with sensitivity and specificity rates almost matching electrophysiological testing[5]. Transverse and static ultrasound parameters have been studied most extensively, with median nerve area showing the highest sensitivity rates[6,7]. However, longitudinal and dynamic assessment of the carpal tunnel structures has also gained interest. A common finding in CTS patients is non-inflammatory thickening and fibrosis of the connective tissue around the median nerve and flexor tendons[8]. The fibrotic changes in this subsynovial connective tissue (SSCT) alter the mechanical response of the tissue surrounding the median nerve to loading of the flexor tendons. Previous research has focused on measuring these patterns of (relative) motion[9-11]. Compared to non-CTS volunteers, relative median nerve motion appears inhibited, worsening with more severe symptoms[12]. Since the decision for conservative or surgical treatment is influenced by disease severity, being able to measure this non-invasively could thus aid the clinical diagnosis process and support intervention choice. However, measuring the SSCT has been challenging due to its small size.

Speckle tracking is an image analysis technique that has been applied mostly to cardiac imaging[13] but is now also under investigation in the musculoskeletal field due to its ability to describe features of moving structures[14]. Doppler imaging is similar to this technique, but is limited by its angle dependency. This method tracks the displacement of speckle patterns, the grainy texture in the ultrasound image that results from interfering ultrasound waves that are backscattered by the inhomogeneity of the tissue. Speckle tracking of tendons has been described for the Achilles tendon[15-20], the tibialis anterior[21], the patellar[22], the flexor digitorum superficialis (FDS)[17,23,24] but also for the median nerve[12,25].

Relative SSCT motion has been assessed using commercial tracking software in both healthy volunteers[26] as well as in patients with CTS[11], but this type of tracking is limited because the software limits the settings that the user can change manually in order to optimize the tracking on individual patient basis.

Recently, a custom made speckle tracking algorithm was extended with a background suppression technique based on Singular Value Decomposition (SVD)[27] in order to minimize the effect of clutter and noise of stationary background. This improved approach could provide a cleaner look at the differential movement of the FDS and how

the relationship between the SSCT and neighboring structures changes in CTS. Since ultrasound imaging and speckle tracking are both subjected to operator interpretation, variability in image acquisition and analysis needs to be assessed. If reliability can be established, it also provides interesting potential applications in the image processing of any musculoskeletal assessment where dynamics and biomechanics play a role. Therefore, using the context of the carpal tunnel structures, this study evaluates three aspects of reliability of speckle tracking with SVD: 1) intra-rater, reflecting the variation in measurements done by a single rater, 2) inter-rater analysis, reflecting the variation between two raters who measure the same subjects[28], and 3) repeatability (also referred to as test-retest reliability), reflecting the variation in measurements acquired at multiple time points.

METHODS

Data collection

Ultrasound images were obtained from a sample of patients with CTS and from volunteers without CTS, referred to as control group. The Mayo Clinic Institutional Review Board approved both studies (control group IRB#06-002950, patients with CTS IRB#14-003444). Written consent was obtained from all participants.

Control Group

Seventeen subjects between the ages of 18-85 years were included. Exclusion criteria were: history of CTS, rheumatoid arthritis, osteoarthritis or traumatic injuries of the ipsilateral hand or wrist. All imaging was done according to a preset imaging protocol described below.

Patients with CTS

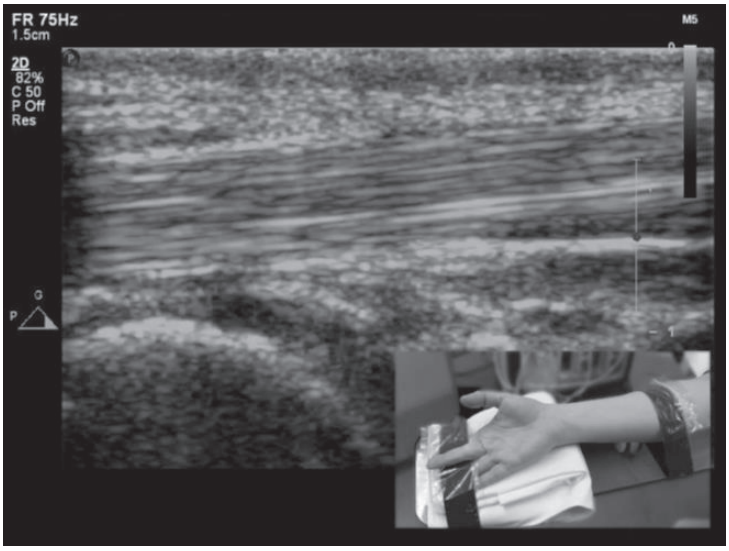
A dataset was constructed by randomly selecting twenty-two patients included in a prospective randomized controlled trial (ClinicalTrials.gov, identifier: NCT02219555). Patients were recruited after being diagnosed with CTS in a hand clinic by any of the hand physicians. Diagnoses were made based on clinical presentation and EMG results as described in the guideline from the American Academy of Orthopaedic Surgeons[29]. Inclusion criteria were clinical diagnosis of CTS, age between 21 and 80 years, symptoms of numbness or tingling for at least 4 weeks, and indication for treatment with injection or surgical release. Exclusion criteria were a previous surgical release, tumor, deformity in hand/wrist, previous history of steroid injection, and any known risk factor for non-idiopathic CTS (including pregnancy, diabetes, rheumatoid arthritis). Clinical evaluations

included two point discrimination, Phalen's test, Tinel's sign, manual muscle testing of the abductor pollicis brevis, and notation of the presence of thenar muscle atrophy.

Imaging protocol

Ultrasound recordings were collected from the patients prior to their treatment. Each subject was imaged in supine position on a bed with the elbow (of the affected hand in CTS cases) fully extended, the shoulder in abduction (70-80 degrees) and the forearm supinated stretched out on an acrylic glass board. One strap was used to minimize forearm movement and another to inhibit overextension of the third digit and flexion of the second and fourth digit. An ultrasound scanner Philips iE33 (Royal Philips Electronics, Amsterdam, the Netherlands) equipped with 15L7 linear array transducer was used. The transducer was placed at the wrist in a sagittal plane over the proximal wrist crease with the wrist in the neutral position. If necessary, a folded pillowcase was placed under the hand to straighten the wrist. The transducer was applied to the skin without additional pressure and with plenty of gel. Participants were asked to flex and extend the third digit corresponding to a frequency of fifty beats per minute under guidance of a metronome (Fig. 1, Suppl video 1). After a practice round, three ultrasound clips with each three flexion-extension cycles were recorded. All images were taken following the same ultrasound protocol, with the same machine by two different ultrasonographers (VS & SE) who were both trained in using the protocol.

Figure 1. Example of start (left) and end (right) position of the third digit during the flexion-extension cycle. Each recording contained three cycles.



Video 1. Synchronized ultrasound recording with participant flexing and extending the third digit to illustrate the relation between the movement and the image.

Data analysis

After image acquisition, all images were analyzed using a Matlab based custom made algorithm developed at the Erasmus MC for speckle tracking with singular value decomposition which had already been tested in an animal model and validated for tendon tracking[23,30]. Before setting the region of interest (ROI), the complete clip was reviewed to identify the median nerve, the SSCT, the FDS and the flexor digitorum profundus (FDP). Then, image analysis took place in three stages (Fig. 2). First, the ROI was manually placed with its proximal border at the level of the radial head, covering the width of the tendon, but without incorporating movement of the adjacent FDP. The ROI was fixed during motion with a pre-set 1:4 size ratio, and could be rotated to ensure a position parallel to the tendon fibrils. Immediately after placement, a feedback video would play with the ROI added for the analyst to review whether it correctly captured the desired structure throughout the entire clip (Fig. 3). In some cases, the tendon would show apparent movement in the volar-dorsal plane in which case, if possible, the ROI would be adjusted in size. Differences in ROI box sizes were negligible, since tendon widths were comparable. In cases where additional kernel size and number fine tuning were deemed necessary, images were excluded. For the SSCT, a similar method was used, but with a separate ROI covering the visible SSCT. The position of the ROI was placed directly volar to the tendon ROI to measure relative motion. The SSCT's organization shows multiple horizontal sheets[8] and to account for different speeds

at different levels, the analysis was performed over five evenly-spaced vertical layers within the SSCT ROI. After placing both ROIs, a temporary video file was created that was used as input for the speckle tracking. The algorithm has been described in detail before[30], but in short, consists of first the SVD filtering followed by the speckle tracking. The SVD filter is an improvement on the more classically used high-pass clutter filter; It decomposes the sequence into specific motion components, which allows noise (incoherent-high frequency signals) as well as clutter removal (high intensity- low frequency), minimizing the signal of static and slow moving structures in the image sequence. Then, within the ROI, a set of overlapping 2D kernels was defined and block matching with normalized cross correlation was applied for each of them to find the frame-to-frame displacement vector. Finally, as described by Bandaru et al.[30], unreliable kernel results were removed based on their correlation values and discordant vectors. The average of the displacement vectors of the reliable kernels gave the final frame-to-frame displacement vector.
The analyses were done using Matlab (R2016a, The MathWorks Inc., Natick, MA, 2000). The Euclidean length of the total displacement vector was calculated in mm. The input used for reliability analyses were the excursion and shear index over 3 cycles (equal to six movements). The shear index is a measure for relative motion between the third FDS and SSCT and was defined as:

$$\text{Shear index} = \frac{\textit{Tenndon Excursion} - \textit{SSCT excursion}}{\textit{Tenndon Excursion}} * 100\%$$

An index value of 0% indicates that the SSCT moved in equal amount with the tendon whereas 100% would indicate a complete dissociation. All analyses were done in random order and the rater who performed the analyses was blinded to the results of their previous assessment and the results of the other rater.

Three aspects of reliability were analyzed:
Intra-rater reliability: For measurement of the main rater-dependable factor of the speckle tracking (placement of region of interest), the recordings from both groups were analyzed in random order twice by the same rater with a time interval of three-four weeks. The first set of results was also used for the inter-rater reliability and the repeatability. *Inter-rater reliability*: In order to measure the variance between different raters, a second analyst measured the same set of clips derived from both the control group and the CTS patients. *Repeatability*: Repeatability was defined as the variation in measurements derived from the same subject, under equal circumstances, directly after an initial clip was recorded. Any differences measured therefor must be the summation of the variance in the recording and the analysis.

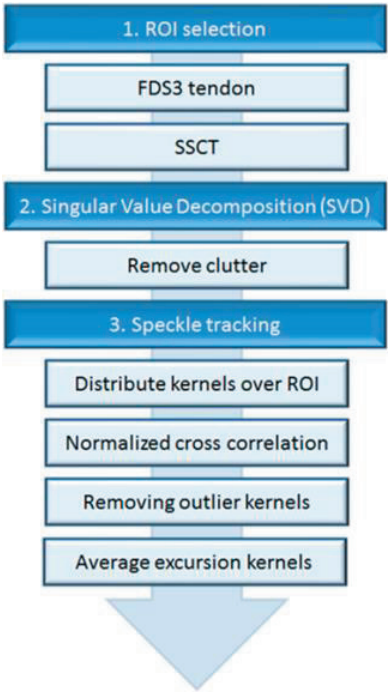


Figure 2. General overview of the image analysis sequence including the singular value decomposition.

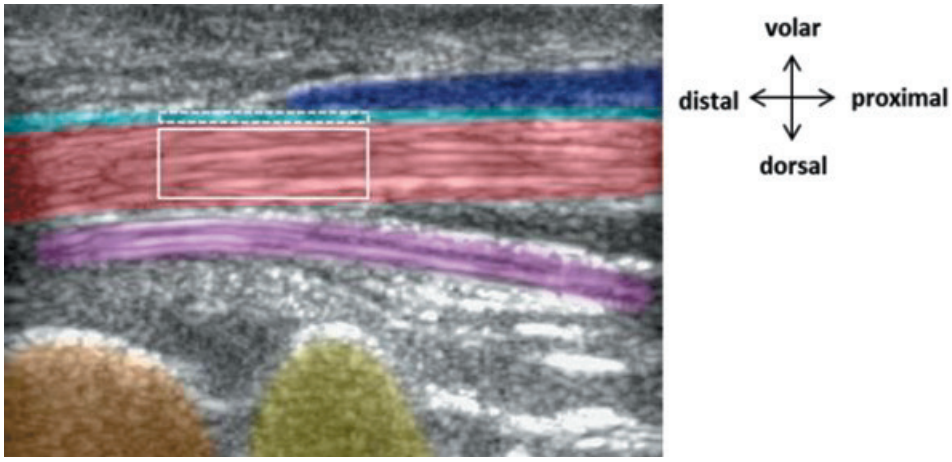


Figure 3. Ultrasound B-mode image with color overlay to indicate the anatomical structures in a sagittal plane. From volar to dorsal, dark blue: median nerve, light blue: SSCT between tendon and median nerve, red: FDS3, purple: FDP 3, orange: lunate, yellow: radius. The box with the solid demarcation depicts an example of a ROI over the entire width of the superficial tendon. The box with the interrupted line shows the ROI for the SSCT.

Statistical Analyses

To quantify reliability, intra-class correlation coefficients (ICCs) including the 95% confidence interval were calculated, using a two way random effects model with single measure and absolute agreement. In general, ICC values above 0.75 are considered as excellent, values between 0.40–0.74 are fair to good and values below 0.40 are considered as poor, in accordance with the classification proposed by Fleiss[31]. Agreement was evaluated using Bland Altman plots with 95% limits of agreement[32]. Distribution of the difference of means was tested for normality visually with histograms and normal quantile plots and statistically with the Shapiro-Wilk test of normality[33]. In case of normality, the plots were made with limits of agreement as calculated by the mean difference ± 1.96 x SD of the difference. In case of non-normal distribution, a logarithmic transformation of the data was performed after which the same calculation for the limits was done[34]. Statistics were done using IBM Statistical Package for Social Sciences software version 22 (SPSS, Chicago, IL, USA).

RESULTS

In total, images from seventeen healthy volunteers and twenty-two CTS patients were analyzed. The clips of one control participant were labeled as too low image quality to include since the tendon and SSCT moved significantly in volar-dorsal direction and out of plane, causing the structures of interest to fall out of the ROI. After exclusion, the remaining sixteen healthy volunteer clips were used for analyses.

The absolute values for the tendon, SSCT and shear index are summarized in Table 1. The shear indices are arguably the parameter of most interest since it is the disturbance of the relative motion due to fibrosis of the SSCT that would underlie the hypothesized pathophysiology of idiopathic CTS. The shear index values found in the control versus the CTS group ranged between 56%-90% with an average of 78% versus 41%-93% with an average of 73% respectively.

The intra-rater, inter-rater and repeatability ICCs of the tendon and SSCT are shown in Table 2. All tendon ICC values can be classified as excellent, as well as the majority of the SSCT comparisons. Only SSCT inter-rater and repeatability in the CTS patients classified as good with 0.70 and 0.74 respectively. In the control group, values for the shear indices ranged between good and excellent (intra-rater: 0.87, inter-rater: 0.74, repeatability: 0.73). This was also found in the CTS group except for a lower ICC value of 0.66 for the inter-rater reliability. Bland Altman plots for the intra-, inter-rater and repeatability reliabilities of the shear index are shown in Figure 4A-F. By plotting the average between two measurements against the difference between those measurements, any funnel-like shapes would indicate a more profound disagreement with either a decrease or

increase in the average value. Only in the inter-rater comparisons and the repeatability of the CTS group (Fig. 4C, D & F) can a slight tendency of more disagreement be found with lower values. However, most values still fall within the 95% confidence limits.

Table 1. Summary of absolute displacement results and shear indices in both groups. Means were calculated based on measurements over three consecutive flexion-extension cycles derived from the first data set from one of the raters. FDS: Flexor digitorum superficialis, SSCT: Subsynovial connective tissue, Shear index: ratio of the difference in motion between FDS and SSCT over the total motion of the FDS.

	Control group	**CTS patients**
Number of participants	**16**	**22**
FDS displacement in cm; mean (SD)	6.8 (2.4)	8.4 (2.5)
SSCT displacement in cm; mean (SD)	1.5 (0.7)	2.1 (0.8)
Shear index in %; mean (SD)	78 (9.7)	73 (13.2)

Table 2. Reliability of structure displacement measurements including relative motion (shear index) for both the control **(A)** and the CTS group **(B)**. ICC's were calculated using two way random model with absolute agreement and include the 95% confidence intervals. Control group n=16, CTS patient group n=22. FDS: Flexor digitorum superficialis, SSCT: Subsynovial connective tissue, CI: Confidence interval, Shear index: ratio of the difference in motion between FDS and SSCT over the total motion of the FDS.

A.	**Control group**					
	FDS		**SSCT**		**Shear Index**	
	ICC	95% CI	**ICC**	95% CI	**ICC**	95% CI
Intra-rater	0.94	0.84-0.98	0.93	0.82-0.98	0.87	0.66-0.95
Inter-rater	0.95	0.86-0.98	0.82	0.56-0.93	0.74	0.41-0.90
Repeatability	0.89	0.72-0.96	0.82	0.55-0.93	0.73	0.40-0.90

B.	**CTS patients**					
	FDS		**SSCT**		**Shear Index**	
	ICC	95% CI	**ICC**	95% CI	**ICC**	95% CI
Intra-rater	0.98	0.95-0.99	0.81	0.59-0.92	0.82	0.61-0.92
Inter-rater	0.82	0.59-0.92	0.70	0.38-0.87	0.66	0.32-0.85
Repeatability	0.88	0.74-0.95	0.74	0.47-0.88	0.82	0.61-0.92

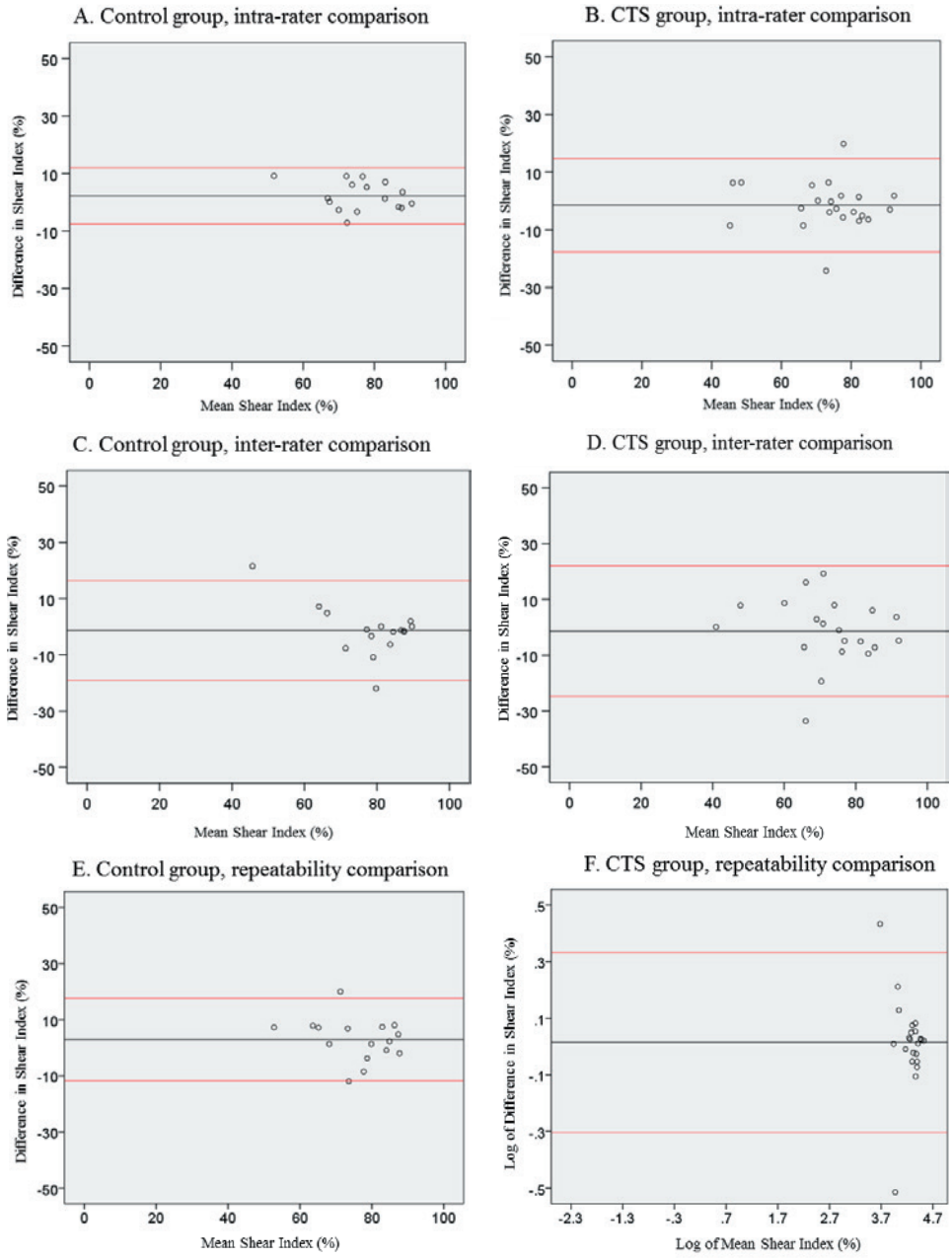


Figure 4A-F. Bland Altman plots showing the intra- **(A and B)**, inter-rater **(C and D)** and the repeatability **(E and F)** data of the shear index for both tested groups. These plots have the mean of two measurements on the x-axis plotted against the difference between the two values. The black line and red lines indicate the average difference and the 95% upper and lower limit respectively for the compared samples. Data for figure **F** was logarithmically transformed due to the non-normal distribution of the data.

DISCUSSION

This study assessed the reliability of a speckle tracking algorithm with singular value decomposition to track absolute and relative motion of longitudinal structures inside the carpal tunnel. Based on our sample of both CTS and non-CTS subjects, we found mostly good to excellent reliability. The lowest ICC value, for the inter-rater comparison of the shear index, can still be classified as moderate to good.

Although several publications describe speckle tracking for analysis of carpal tunnel structures, not many have described reliability. Filius et al. have used a similar speckle tracking analysis without SVD and published test-retest values for both the third FDS tendon and its superficial layer of SSCT. They note ICC values of 0.70 and 0.73 respectively[12]. Their repeatability measurements were done in a larger group (n=50) and reliability data was from both healthy and CTS patents combined. Using Doppler imaging, FDP excursion reproducibility was assessed in both a healthy group[35] as well as a patient group with tendon injury[36]. They presented ICC values of 0.81 and 0.88 respectively at ten days post intervention. Despite the difference in imaging depth, their results are similar to ours.

In general, our SSCT ICC values tended to be lower than those for the tendon which was also the case in similar research[12]. This can in part be explained by the anatomical differences; The FDS tendon has a width of about ten times the SSCT (<1mm) and thus can accommodate a larger ROI which is less susceptible to movement in the volar-dorsal plane. In addition, the SSCT is a layered structure, so during tracking the displacement can differ based on the position. This should receive extra consideration when imaging patients with CTS, because higher levels of fibrosis have been found to occur in the layers closest to the tendon[37].

In this study, an average of 1.1 cm (control group) and 1.4 cm (CTS group) excursion of the tendon was found per flexion / extension movement (data shown in the results is total over three cycles with two movements each), which is comparable to what colleagues have found; Korstanje et al. used a similar algorithm, without SVD, on CTS patient-derived clips and found a mean tendon excursion of 1.98 cm but do not report any ICC values[10]. Filius et al. published two studies with CTS patients[9,12] where they used the same algorithm without SVD, and found average tendon excursions of 1.88 cm and 1.44 cm (calculated based on published values). Control data showed 1.56 cm and 1.43 cm FDS3 excursion. To test whether the difference in tendon excursion in the present study could be due to anthropometric differences between the groups, post hoc hand measurements from the distal wrist crease to the tip of the long finger were made. This indeed showed a small but significant size difference (CTS: 20.3±1.8 cm, controls: 18.7±1.0 cm). However, the quality of the CTS patient pictures was suboptimal, leading to less accurate measurements. Perhaps more importantly, we do not have data on the

individual amount of finger flexion during the trials. Someone with a large hand could still have a small tendon excursion if their maximum finger flexion was smaller. Although there is evidence that hand morphology is associated with CTS, it seems to be the ratio between wrist width and depth that differs most between controls and CTS patients[38]. So far, this seems to hold limited diagnostic and prognostic value[39].

Excursion values for SSCT were published in two articles, 1.55 cm and 0.74 cm for CTS groups and 1.30 cm and 0.76 cm in control groups[10,12]. Although Korstanje found a significant difference in SSCT excursion between the most and least affected hand ($p=0.025$), this was not found in the study by Filius et al. and explained by possible greater inter-subject variability. Our study found an average of ~0.3 cm SSCT excursion in both the patients with CTS as the healthy group, but all results are susceptible to noticeable standard deviations. Additionally, our study was not primarily designed for absolute value comparison and our absolute values represent the total excursion over three cycles. Previously, a validation of the speckle tracking[30] was done for tendons and ideally the same would be done for the SSCT. However, this is challenging, even with a phantom or cadaver model, due to the small size of the SSCT and the likelihood of disrupting the complex microstructure with markers.

Strengths of this study are that we tested an innovative technique to measure ultrasonically captured motion of small anatomical structures, expanding the boundaries of what speckle tracking can detect and be utilized for. Insights gained into the limitations of speckle tracking can help contextualize results whether acquired for research or clinical purposes. In addition, utilizing dynamic features and interrelations of the carpal tunnel structures to support CTS therapy choice is a novel approach. Limitations of the study include that speckle tracking inherently does not take out of plane motion into account, which may result in underestimation of the actual motion. We also used a high frequency probe to allow visualization of the SSCT, which might have supported the high ICC values. Additionally, it was reported that the tracking depends on the balance between tendon velocity and acquired frame rate, with a decrease in validity if these parameters fall outside of predetermined boundaries[30]. In our situation this was, prevented by adding a metronome during acquisition, but this does not eliminate the variation in the participant's cooperation and ability to perform a repeatable movement. If, in a clinical application baseline images are compared to a follow-up, changes in finger movement should be taken into account via either a rigid acquisition protocol or an outcome measure insensitive to total excursion (like shear index). Additionally, the ICC values presented in this study do indicate that future data on shear index in the carpal tunnel should be re-evaluated within different contexts. For example, for a study-based purpose, a single rater would be fine, but for clinical application, more research including multiple raters would be needed.

In conclusion, this study shows that SVD enhanced speckle tracking can reliably be used to analyze (relative) longitudinal SSCT displacement both in participants with and without CTS. Together with the validation data, our results imply that dynamic ultrasonic measurements of carpal tunnel structures can be used to further explore the potential of using this technique to help guide and predict CTS treatment outcomes. Although our study focuses on CTS related anatomical structures, the principles of the image analysis could be extrapolated to other research areas involving pathologies where the assessment of dynamic imaging is of relevance.

ACKNOWLEDGEMENT

The authors would like to thank Raja Bandaru for his technical assistance during the experimental phase of the study.

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9

MEDIAN NERVE TRANSVERSE MOBILITY AND OUTCOME AFTER CARPAL TUNNEL RELEASE

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Submitted

ABSTRACT

Background

The prognostic potential of ultrasound (US) in carpal tunnel syndrome (CTS) has shown conflicting results. Fibrotic changes around the nerve could limit its physiological movement which can be assessed with US imaging. This study aims to explore differences in nerve dynamics after surgical intervention and to test the association with patient-reported outcome.

Methods

Patients diagnosed with idiopathic CTS between 2014 and 2017 were included. Data was collected before and three months following surgery. Both static measurements as well as nerve mobility during finger and wrist flexion in the transverse plane were acquired. Changes were tested using paired t-tests. Adjusted linear regression models were used to assess prognostic value. Differences in the symptom and functional scales of the Boston Carpal Tunnel Questionnaire were primary outcomes.

Results

A total of 85 patients were included (mean age 57.1±13.5), of whom 93% completed the three month follow up. Median nerve area (-1.3 mm^2, $p<0.001$) and perimeter (-0.6 mm, $p<0.01$) decreased significantly after surgery, while displacement in dorsal direction during wrist flexion (0.54 mm, $p<0.01$) increased. A larger cross-sectional area at baseline was significantly associated with more functional improvement, but not with symptomatic relief. None of the baseline mobility parameters were significantly associated with the outcome.

Conclusions

Nerve mobility increases in a dorsal direction after surgery in CTS patients but only pre-surgical cross-sectional area was associated with outcome. The added value of dynamic ultrasound as part of a more extensive prognostic model should be a topic of future research.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a common compression neuropathy with an estimated prevalence of 3-12% in a working population[1,2]. Carpal tunnel release (CTR) surgery is the best option for some patients in order to prevent progression of motor nerve dysfunction, but also the next treatment in line after conservative treatment fails[3]. Although CTR is effective in reducing pressure, there is wide variation in reported success rates of CTR, ranging from as low as 27% to as high as 100%[4]. Failure can in part be attributed to intra-surgical and post-surgical factors, but the wide range indicates that *a priori* case selection is essential as well.

To date, it has been difficult to identify specific factors that support surgical outcome prediction[5-7]. It seems likely that not a single, but a multitude of preoperative factors, could potentially help support consideration for surgical intervention.

So far, the role of ultrasound has been established for the diagnosis of CTS and includes the (relative) cross-sectional nerve area and circularity just proximal to the carpal tunnel inlet[8]. However, the prognostic potential, of these static, morphological parameters has shown conflicting results on short term and little relation with long-term surgical outcome[9,10]. In addition to nerve size, transverse dynamic ultrasound has successfully been used to evaluate the flexor tendon and nerve movement in response to finger and hand movement[11-14].

There is evidence that fibrosis of the subsynovial connective tissue (SSCT) plays an important pathological role in CTS[15-18]. The SSCT is a multilayered tissue surrounding the tendons and nerve within the carpal tunnel. As the tendons move, the SSCT moves along, but it is prone to damage with excessive excursions[19-21], which can lead to a non-inflammatory response with progressive fibrosis[22-24]. Although the presence of causality or direction of association between CTS development and SSCT fibrosis is still unknown, CTS patients have been found to have thicker SSCT compared to controls[25] and dynamic ultrasound studies have shown decreased mobility patterns of the median nerve during finger and wrist motion in patients with CTS[26-31]. Hypothetically, these differences could be attributed to the mechanical constrain of the fibrotic SSCT, with the nerve "sticking" to the transverse carpal ligament as it is inhibited in its physiological path of movement during tendon loading. A relation has been shown between decreasing median nerve motion with increasing CTS severity in a longitudinal plane[32] and Nanno et al. showed significant changes in median nerve motion after CTR[31]. Nerve dynamics may thus perhaps hold useful information pertaining to CTS pathophysiology, but so far there has been limited research associating this with clinical outcome.

In this study we aim to build on these findings by exploring the prognostic potential of a combination of static and dynamic nerve characteristics using patient reported outcomes as the primary outcome. In addition, nerve mobility before and after CTR

will be compared, hypothesizing an increase in excursion at the three month time point.

MATERIALS AND METHODS

General

This is a prognostic, prospective (level I) study with a sample of surgical patients from a larger clinical trial (CT.gov identifier NCT02219555) which was reviewed and approved by our Institutional Review Board. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki[33].

Subjects and disease characteristics

All patients with idiopathic CTS were approached and recruited from a single institution with a specialized hand clinic. The diagnosis and surgical indication was determined by the attending hand physicians based on a combination of symptoms at presentation, clinical tests and supporting electro-diagnostic tests. Clinical evaluations included sensibility (two point discrimination) in the median nerve distribution of the hand, Phalen's test, Tinel's sign, pinch and grip strength, and thenar muscle atrophy. After the diagnosis of CTS was made and the decision for surgical treatment was agreed upon, patients were approached for the study. This was an open label study, so no restrictions based on type of surgical procedure or post-operative protocol were applied. Patients were recruited if they met the following inclusion criteria: clinical diagnosis of CTS, age between 21-80 years, symptoms of numbness or tingling for at least four weeks in at least two digits on one hand including the thumb, index, long or radial border of ring finger, full understanding of English language, and indication for surgical release surgery. Exclusion criteria were a previous surgical release, tumor, mass or deformity in hand/wrist, pregnancy induced CTS, and either of these diagnoses: cervical radiculopathy, peripheral nerve disease, thyroid disease, rheumatoid arthritis or other inflammatory arthritis, osteoarthritis in wrist, diabetes, renal failure, sarcoidosis, amyloidosis or major trauma to ipsilateral hand or wrist. Clinical evaluations included sensibility (two point discrimination) in the median nerve distribution of the hand, Phalen's test, Tinel's sign, pinch and grip strength, and thenar muscle atrophy. After the diagnosis of CTS was made and the decision for surgical treatment was agreed upon, patients were included in the study. This was an open label study, so no restrictions based on type of surgical procedure or post-operative protocol were applied. If patients experienced bilateral CTS, only the hand with most severe symptoms was included. No exclusions based on previous treatment, except surgical intervention, were applied.

As part of routine diagnostic medical care, all patients underwent, all patients underwent electrodiagnostic tests using the Viking Select or Viking EDZ EMG machine (CareFusion, San Diego (CA), USA) according to the guidelines from the American Association of Neuromuscular and Electrodiagnostic Medicine . Part of the recording included measuring the sensory latency, velocity and sensory nerve action potential amplitude, the distal motor latency, velocity in forearm and compound muscle action potential from the abductor pollicis brevis muscle. The severity grade was based on the results of the individual NCS components with values ranging between 1 and 5 with 1 indicating normal test results and 5 very severe CTS.[34]

Patient reported outcomes

The Boston Carpal Tunnel Questionnaire (BCTQ)[35] was used to assess patient reported clinical outcome at both baseline level and three months after surgery. The questionnaire consists of 19 questions divided over symptom severity (SSS; 11 questions) and functional status scales (FSS; 8 questions). Each answer can range from 1 (no symptoms) to 5 (most severe) and are averaged to result in two separate scores.

Ultrasound acquisition protocol

Ultrasound images were acquired at two time points; first before surgery and the second three months after surgery. Patients were placed in supine position with the affected arm stretched out in 70-80° abduction on a Plexiglas board. A Velcro strap was used around the mid forearm to minimize movement and pillow cases under the hand were used to place the wrist in neutral position. All images were made using a Philips iE33 (Royal Philips Electronics, Amsterdam, the Netherlands) ultrasound machine with a L15-7io linear transducer. Images were taken, all in a transverse plane, just proximal to the level of the carpal tunnel inlet defined as the proximal margin of the flexor retinaculum, using the pisiform and the scaphoid tubercle as landmarks. To minimize compression to the carpal tunnel structures, the transducer was applied to the skin without additional pressure and with a surplus of gel. Patients were asked to perform two tasks: finger flexion and palmar wrist flexion (Fig. 1). For the first, starting from a neutral position, patients were asked to make a fist: start from a full extension position, flex the four fingers, without thumb adduction, over the course of seven seconds. For the latter, again starting from a neutral position, patients were asked to keep the fingers extended and flex the hand until a maximum range of motion was reached. Movements were chosen based on their clinical relevance, with CTS patients often complaining of symptom aggravation after a period of wrist flexion and physicians using this feature as part of their diagnostic exam (Phalen's test). No formal quantification of range of motion

was done, assuming similar movements within patients and reflecting clinical practice. After a practice round, a set of three clips was recorded for each movement and the best quality image selected for analyses. All measurements were done by ultrasonographers with a minimum of 1 year US experience and two physicians (SE, VS) who were blinded to the clinical outcome and who were trained by the same ultrasonographers while using a predetermined protocol.

Figure 1. From left to right: Wrist in neutral position, finger flexion, wrist flexion.

Image analysis

Images were analyzed using an in-house software package (Analyze v12.0, Biomedical Imaging Resource, Mayo Clinic, Rochester MN, USA). Clips were selected based on clarity of the nerve epineurium, completion of the full potential movement within the seven-second lapse and minimization of probe displacement. All parameters were measured by manually placing a polygon region of interest (ROI) around the inner edge of the nerve epineurium. Parameters acquired from static images included median nerve cross sectional area (CSA), perimeter and circularity. Circularity was calculated by

$$\frac{perimeter^2}{area} \times \frac{1}{4n}$$

A perfect circle would present with a value "1" whereas non-circular / irregular shapes having higher values. The static parameters were derived from the first frame of the first finger flexion clip (considered neutral position). Nerve mobility parameters were based on Cartesian coordinates x and y from the center point of the median nerve polygon (Fig. 2). Data is presented in both individual vectors reflecting movement in the two main axes; the palmar-dorsal direction which reflects the y-axis and radio-ulnar direction given by the direction on the x-axis. In terms of polarity, positive values correspond to palmar and ulnar direction and negative values correspond to dorsal and radial directions. Overall displacement will be graphically presented in a two dimensional plot including the standard ellipse and Hotelling's confidence ellipse (α=0.05) of the average start and end positions. The initial start position of the nerve varies per patient and time so this point was used for normalization and pinned to the midpoint of the plot (coordinate 0,0). Additionally, Pythagorean theorem was used to calculate the

gross displacement including *overall displacement* during a movement (end position – initial position) and *summed displacement*. The *summed displacement* is the summed difference in coordinates between ten time points within a complete clip of 331 frames (Fig. 2, right image).

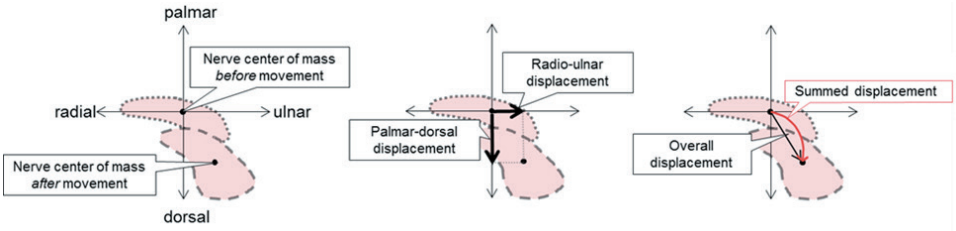


Figure 2. Schematic representation of how nerve mobility was quantified based on transverse US images. Left: The nerve's center of mass was determined first in a dual plane field and used to normalize the start position in neutral wrist and finger posture. Middle: Displacements in radio-ulnar and palmar-dorsal direction. Right: Mobility was defined both as the difference in end-start position of the nerve (black arrow; overall displacement) and as a cumulative parameter describing the entire course of the nerve (red arrow; summed displacement).

A randomly selected set of ten images from the study cohort were used to confirm intra- and inter rater reliability; the test-retest assessment images were acquired with an identical protocol from seventeen volunteers without CTS symptomology. This was done in order to test repeatability without surgical interference.

Statistical analysis

The sample size calculation was made fitting the aims of the main clinical trial of which this is a subset and henceforth is less relevant to this work. Continuous variables were compared before and after surgical treatment using paired t-tests. Association of the baseline US parameters as well as the change in US parameters versus the change in BCTQ were tested using sex and baseline BCTQ-adjusted linear regression models. Potential confounders tested were age, sex, BMI, duration of symptoms, NCS based severity, and the respective BCTQ baseline scores (e.g. the adjusted model for the FSS only had baseline FSS score included). The dependent variable was the change in BCTQ scales after three months. White robust variance estimators[36] were used to obtain consistent estimates of the variance of the model parameters due to heteroscedastic residuals. For secondary analysis, logistic regression models were created using a cut-off score of 1 on the SSS subscale as dependent variable, based on the minimal important difference described for this subscale[37,38]. These were also adjusted for baseline SSS and sex. Intra-rater data was collected by a single rater (VS) by measuring the same images

twice with a four week interval. Inter-rater measurements were based on the same images made and analyzed by two raters (VS, SE). For the test-retest data, clips were collected from healthy volunteers with a four week interval and then analyzed in sets by either of the two raters (VS, SE). All agreement measurements were calculated using intra-class correlation coefficients (ICCs) including the 95% confidence interval using a two-way mixed effects model assuming single measure and absolute agreement. ICC values above 0.75 are considered as excellent, 0.40–0.74 are fair to good and values below 0.40 are considered as poor[39]. Type 1 error rate was set at 0.05; no multiple testing corrections were done. All analyses were done using SAS™ (version 9.4; SAS Institute, Cary NC) and JMP (Version 13. SAS Institute Inc., Cary, NC, 1989-2007.).

RESULTS

Patient characteristics

A total of 85 patients were included in the study of whom 79 (92.9%) completed the three month follow up visit. Baseline characteristics including age, sex, duration of symptoms, whether the included hand was the dominant hand and NCS categorized severity are summed in Table 1.

Table 1. Patient demographics(n=85)

Characteristics	
Age, years (mean, SD)	57.1± 13.5
Sex (female)	65%
Duration of symptoms, months (median, IQ_{1-3})	24 (10-44)
Surgery on dominant hand	58.3%
BMI (mean, SD)	30.9 (6.5)
NCS severity	
Normal	3.5%
Mild	24.7%
Moderate	49.4%
Severe	15.3%
Very severe	2.4%
No NCS available	4.7%

BMI: body mass index, NCS: nerve conduction study

Reliability

Overall reliability of the ultrasound images of the CTS patients was labeled good to excellent with ICC values ranging between 0.75-0.99. Test-retest data using ultrasound images of healthy volunteers was high for the static measurements (ICC: 0.88-0.96), but moderate for the dynamic assessment (ICC: 0.56-0.76). All ICC values are described in Table 2.

Table 2. Reliability data for ultrasound parameters

	Intra-rater ICC (95% CI)	Inter-rater ICC (95% CI)	Test-retest ICC (95% CI)
Nerve CSA	0.94 (0.76-0.99)	0.94 (0.79-0.84)	0.96 (0.90-0.99)
Nerve perimeter	0.97 (0.81-0.99)	0.75 (0.18-0.93)	0.91 (0.76-0.97)
Nerve circularity	0.97 (0.89-0.99)	0.92 (0.41-0.98)	0.88 (0.69-0.95)
Finger flexion – overall displacement	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.69 (0.31-0.88)
Finger flexion – summed displacement	0.99 (0.96-0.99)	0.99 (0.97-0.99)	0.69 (0.21-0.89)
Wrist flexion – overall displacement	0.99 (0.97-0.99)	0.99 (0.97-0.99)	0.56 (0.13-0.82)
Wrist flexion – summed displacement	0.98 (0.93-0.99)	0.98 (0.93-0.99)	0.76 (0.45-0.91)

Intra-class correlations (ICC) values calculated using two-way mixed effects model assuming a single measure and absolute agreement. CI: Confidence interval, CSA: Cross sectional area.

Changes in patient reported outcome and US parameters after CTR

Patient reported outcomes improved (decreased in score) significantly after carpal tunnel release surgery to a score of 1.5 on both the SSS and FSS (mean difference -1.6 and -1.1 resp. with $p<0.001$ for both). Fig. 3 shows the mean differences of the ultrasound parameters (exact data can be found in S-1). Nerve CSA was on average 14.5±4.2 mm^2 before surgery and decreased significantly to 13.3±3.8 mm^2 ($p<0.001$). Of the dynamic measurements, the abstracted palmar dorsal axis showed a significant increase in displacement from 1.9 to 2.4 mm in dorsal direction (mean difference: 0.54 mm, $p<0.01$). A visual example of the change in nerve displacement is given in Supplement 2. Additionally, the summed displacement of the nerve during wrist flexion increased on average with 0.7 mm ($p<0.05$). Figure 4 shows the end position of the nerve after flexion of the fingers and wrist relative to where it started. Note that these plots do not depict the entire pathway but only the end position and that these are limited to the individual representation of both baseline and follow up data points. These plots indicate that finger flexion causes a median nerve translation in mostly ulnar and slightly palmar direction which does not change significantly after surgery. Wrist flexion induces a movement that ends more in ulnar-dorsal direction. The individual data points

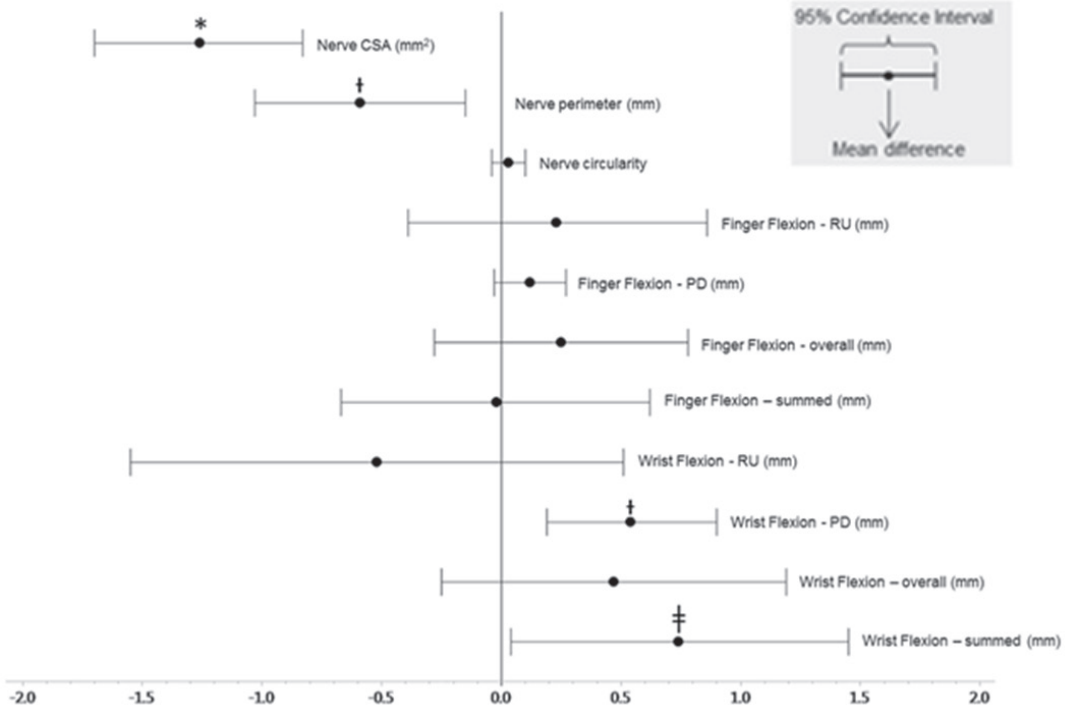


Figure 3. Change in US parameters after carpal tunnel release surgery visualized as the mean difference with the 95% confidence interval. Units are defined behind the data labels. Mean differences were calculated by subtracting baseline values from follow up values. RU: radial-ulnar, PD: palmar-dorsal, CSA: cross-sectional area, *p<0.001, ǂ p<0.01, ǂǂp<0.05.

show that there is a large variation between patients in nerve end points in wrist flexion both before as well as after surgical intervention.

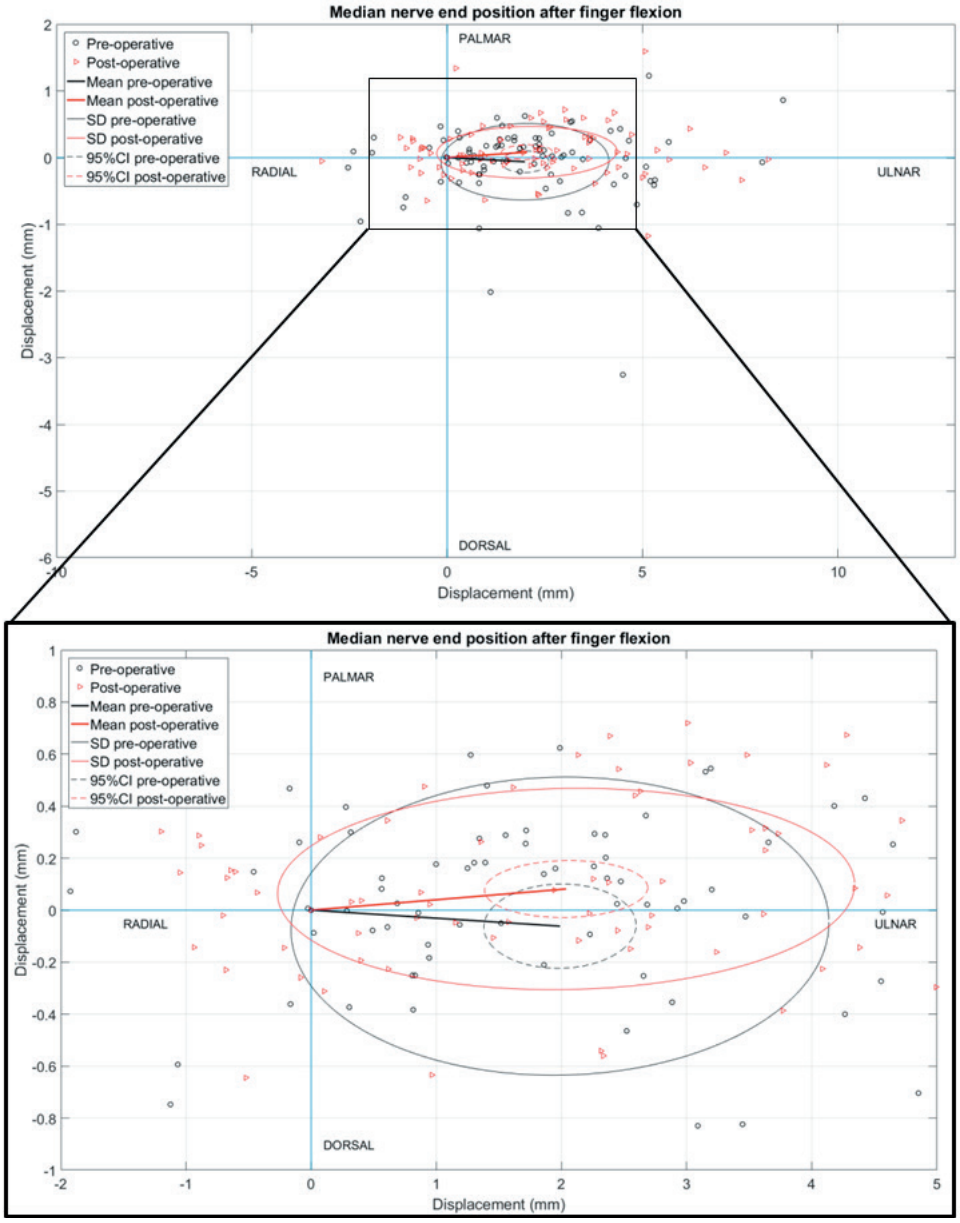
Association between baseline US and BCTQ changes

All static and dynamic US parameters have been assessed in a linear regression model adjusted for their corresponding BCTQ baseline scores and sex. The outcome of choice for the primary analysis was the change in the individual BCTQ scales. Detailed results are shown in Table 3 (presented after the References). Of the static measures, only nerve CSA and perimeter showed a significant association with the function scale difference (β= -0.024, p=0.02 for CSA and β= -0.049, p=0.02 for perimeter). None of the baseline measures showed a significant association with the symptom severity score difference in the linear regression. Using a gradient map to indicate the size of the change in symptom score per individual in relation to the displacement end point, no obvious subsets of patients can be identified (Figure 5). Similar plots were also made for the FSS, but no subsets were directly visible (figures not shown). A formal comparison using logistic regression also indicated no parameters to be associated with a specific type of outcome.

Table 3. Linear regression model for baseline US versus clinical outcome

	Δ Symptom Severity Score		**Δ Functional Status Score**	
Static parameters	**Estimate (β)**	**p-value (adjusted for baseline symptom score and sex)**	**Estimate (β)**	**p-value (adjusted for baseline function score and sex)**
Nerve CSA	-0.006	0.44	**-0.024**	**0.02**
Nerve perimeter	-0.042	0.70	**-0.049**	**0.02**
Nerve circularity	-0.011	0.49	-0.225	0.13
Dynamic parameters				
Finger flexion - RU displacement	0.024	0.27	0.060	0.15
Finger flexion - PD displacement	0.019	0.80	0.077	0.52
Finger flexion – overall displacement	0.036	0.17	0.075	0.13
Finger flexion – summed displacement	0.015	0.40	0.037	0.18
Wrist flexion - RU displacement	-0.003	0.76	0.011	0.55
Wrist flexion - PD displacement	0.023	0.42	0.039	0.28
Wrist flexion – overall displacement	0.001	0.94	0.031	0.22
Wrist flexion – summed displacement	0.004	0.79	0.030	0.23

CSA: Cross sectional area, RU: radio-ulnar, PD: palmar-dorsal.


Median nerve end position after finger flexion
Pre-operative
Post-operative
Mean pre-operative
Mean post-operative
SD pre-operative
SD post-operative
95%CI pre-operative
95%CI post-operative
PALMAR
DORSAL
RADIAL
ULNAR
Displacement (mm)
Displacement (mm)
Median nerve end position after finger flexion
Pre-operative
Post-operative
Mean pre-operative
Mean post-operative
SD pre-operative
SD post-operative
95%CI pre-operative
95%CI post-operative
PALMAR
DORSAL
RADIAL
ULNAR
Displacement (mm)
Displacement (mm)

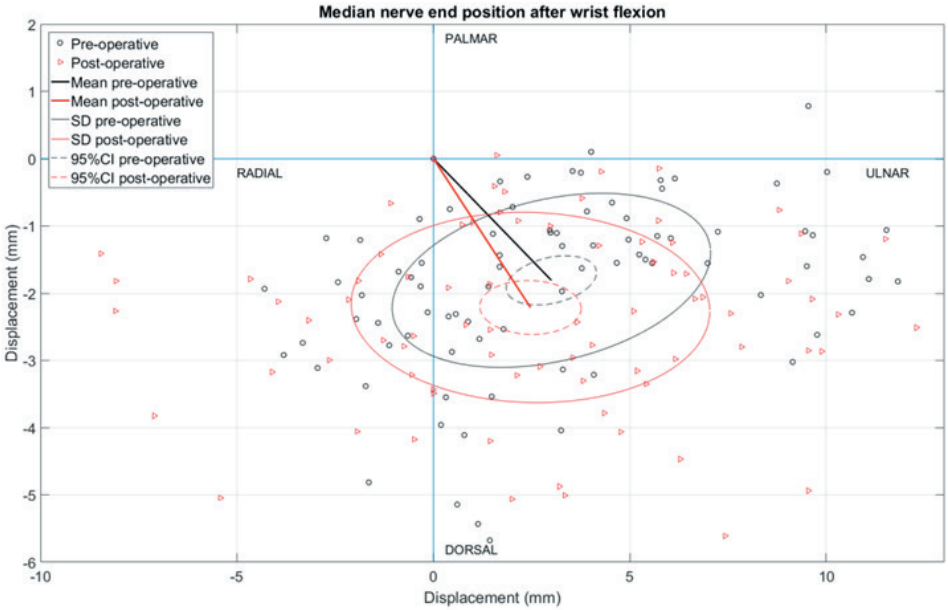


Figure 4. Cartesian plots of both the individual as well as the average nerve displacement end points before and after surgery. Within the plots, both the baseline (red) and the follow up (black) data are depicted. Circles and triangles represent the individual cases with the solid straight line showing the average difference in end position of the nerve. Note that all end points have been normalized to where the nerve originally started, so changes in start position between before and after surgery cannot be seen in these plots. The standard deviation (SD; solid ellipse) and 95% confidence ellipse (interrupted ellipse) are shown as well. The left plot shows the data for the finger flexion with a zoomed in box at the bottom and the right plot shows the data for the wrist flexion.

Association between changes in US and BCTQ changes

Results for the difference in US parameters between baseline and three months post-surgery and the association with the BCTQ difference scores are described in Table 4 (presented after the References). The change in overall displacement of the nerve during finger flexion showed a significant association with change in function score (β= -0.060, p=0.04). The same parameter as well as the change in displacement in radio-ulnar direction during finger movement were associated with the change in symptom severity score (β= -0.050, p=0.01 and β= -0.035, p=0.03 respectively). All associations were also tested using a percent change in score, but showed no additional significant relations.

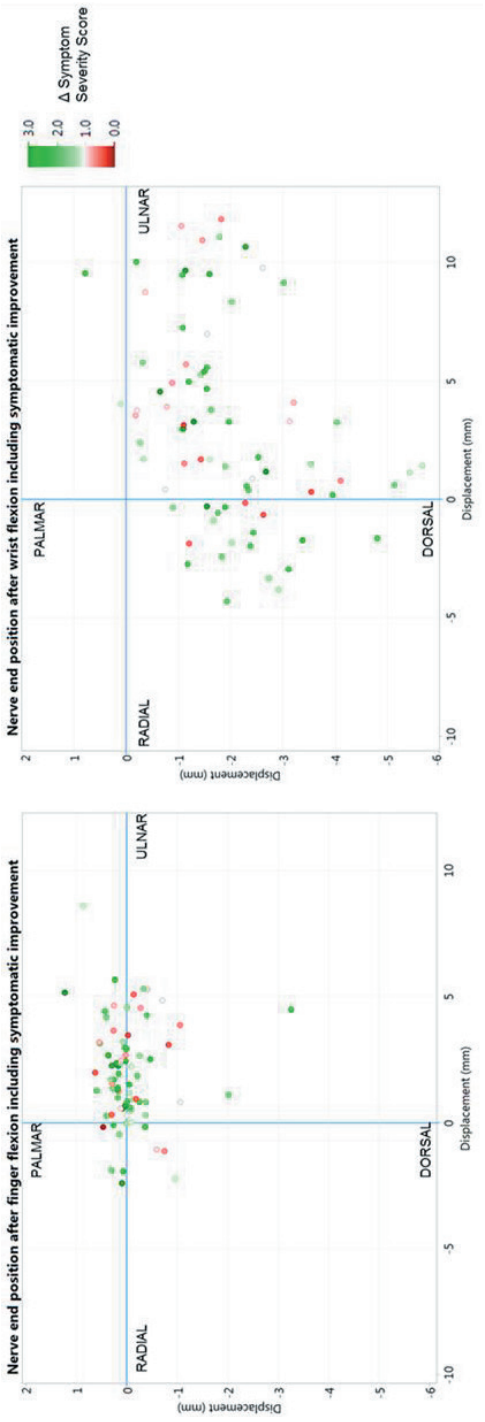


Figure 5. Cartesian plots showing the end position of the nerve after finger (left) and wrist (right) flexion. The color gradient indicates the change in SSS score between baseline and follow up measurement.

Table 4. Linear regression model for difference in Δ US versus clinical outcome

	Δ Symptom Severity Score		Δ Functional Status Score	
Static parameters	**Estimate (β)**	**p-value (adjusted for baseline symptom score and sex)**	**Estimate (β)**	**p-value (adjusted for baseline function score and sex)**
Δ Nerve CSA	0.008	0.69	0.046	0.06
Δ Nerve perimeter	0.005	0.98	0.034	0.85
Δ Nerve circularity	0.001	0.98	0.025	0.43
Dynamic parameters				
Δ Finger flexion - RU displacement	**-0.035**	**0.03**	-0.036	0.12
Δ Finger flexion - PD displacement	-0.016	0.83	-0.111	0.41
Δ Finger flexion – overall displacement	**-0.050**	**0.01**	**-0.060**	**0.04**
Δ Finger flexion – summed displacement	-0.019	0.23	-0.035	0.11
Δ Wrist flexion - RU displacement	-0.012	0.22	-0.001	0.95
Δ Wrist flexion - PD displacement	-0.018	0.49	-0.043	0.40
Δ Wrist flexion – overall displacement	-0.016	0.32	-0.022	0.29
Δ Wrist flexion – summed displacement	0.000	0.99	0.000	0.99

CSA: Cross sectional area, RU: radio-ulnar, PD: palmar-dorsal.

DISCUSSION

This study provides evidence that the median nerve gains mobility in a transverse plane in dorsal direction in CTS patients after surgical intervention as measured with US. The predictive value of baseline static parameters for short term outcome has been shown for functional improvement, but pre-operative dynamic parameters alone have no significant association with patient reported outcome. Only an increase in radio-ulnar displacement and higher overall nerve mobility after surgery during finger flexion showed an association with improved symptoms.

As our main outcome, we choose a patient reported outcome measure to keep the patients' perspective as a primary goal. It was decided to keep the two subscales of the Boston Questionnaire separated to allow conclusions on the different aspects of clinical improvement. Interestingly, it was on the FSS scale that we found a positive association between larger pre-surgical nerve size and increased improvement. We hypothesized that underlying pathological severity would be reflected in increased nerve size and would be directly correlated to clinical symptoms as tested in the SSS, but we found no significant association.

Dynamic imaging of the wrist has been done before, using imaging techniques including MRI and ultrasound. In non-CTS volunteers, Wang et al., showed that finger flexion alone

does not induce a large nerve displacement, but that wrist flexion with extended fingers causes about 2.7 mm displacement[29]. We found similar results in terms of magnitudes, but where they note a straight dorsal translation with wrist flexion, we found the nerve on average to move just as much in an ulnar direction. Whether this difference in angle is due to the CTS is difficult to say since their sample was relatively small (n=10), but their findings did illustrate that normally during wrist flexion, the nerve is inclined to move in dorsal direction, potentially to "escape" compression between the superficial flexor tendons and the transverse carpal ligament during tendon loading. A previous study from our group compared CTS patients with non-CTS controls (n=20 CTS cases, n=10 controls) and showed significantly inhibited dorsal translation for the cases[30], but this effect was lost in a follow-up study with a larger sample size (n=90 CTS cases, n=42 controls)[26]. The fact that our study found a significant increase in dorsal translation after surgical intervention supports the notion that the nerve regains mobility in that direction.

Our nerve mapping system was based on the hypothesis that after CTR, any increases in displacement would be visible by using the center point of the nerve as the start position. This poses a limitation if one of the effects of the surgery is not disruption of the connective tissue, but rather the repositioning of the nerve. In a study done by Nanno et al., the transverse displacement of the nerve was assessed using the hamate and trapezium to define the absolute position of the nerve within the carpal tunnel. They report that after surgery, the nerve tends to have a more palmar location[31]. In contrast to our data, they find a decrease in nerve displacement after CTR during similar motions. This could in part be due to differences in location of the measurement as well as methodological timing as they acquired their imaging at the mid-level of the carpal tunnel at one month post-surgery.

So far, there has been conflicting evidence on the predictive potential of nerve CSA ranging between a negative association (smaller nerve is associated with better outcome)[40,41], no predictive value[42,43], and a positive association (larger nerve is associated with better outcome)[9,44]. Bland et al., like in our study, used the two isolated subscales as their main outcomes, and discussed that based on all the conflicting evidence it seems very unlikely that a single US parameter would provide enough evidence to support treatment counseling for the individual patient[42]. The other studies mentioned used a variety of outcomes, making direct comparisons challenging. Marschall et al. looked at a >25% increase in the overall result on the Boston questionnaire and their surgical sample contained only a small subset of the total sample (n=23)[9]. They found that a larger nerve size at baseline did not maintain its positive association at 12 months follow-up. El Miedany et al. found that a nerve CSA > 14mm^2 before surgery was associated with a poorer outcome and persistence of symptoms at 6 months[40]. Smaller nerve sizes were

associated with a better response at 6 months based on a functional assessment and VAS score.

Possible explanations for the lack of predictive value of the ultrasound parameters and absence of differences in dynamic measurements between baseline and follow up could be the disconnection between US based features of the nerve and symptoms as reported by patients as well as timing of the assessments. Follow up was conducted at three months and although this might have been potentially too short term to find significant changes in the mobility of the nerve, we did see a significant decrease in nerve size, as reported by many before us. Pressure decrease in the carpal tunnel is found directly after surgery[45], indicating that neuro-edema caused by intra-carpal tunnel compression can start normalizing after a relatively short time, but it is currently not known what the time line is for any changes to occur in the fibrotic SSCT or what it would constitute. Assuming this plays a pivotal role in the mechanism of the nerve being confined in its movements; perhaps the lack of understanding of the healing process is reflected in the results.

Another challenge with the dynamic recordings of the nerve as it translates to a different position is the large variation between patients and the lower ICC values between measurements of the same participants. Based on the Cartesian plots, after wrist motion, we saw movement in an almost 180° field, indicating that we are testing a heterogeneous variable. Notably, the test-retest reliability data came from healthy volunteers and indicate that even without surgical intervention, there is a physiological variation in the mobility of the nerve during our finger and hand movements. Since the nerve moves in a three dimensional plane, it would be interesting to see if the addition of a sagittal view would be a better proxy for nerve mobility. Intra-and inter cross correlations found in this study were excellent for both static as well as dynamic parameters. Possible explanation for the high values could be the absence of noise in the selected US parameters and the detailed protocol for the image analyses. Similarly high values have been reported before in healthy participants[11].

Limitations of the study include the focus on idiopathic CTS, limiting translatability to those with CTS not due to secondary causes. Additionally, this study only focuses on short term effects of surgical intervention and we limited the analyses to nerve mobility in a transverse plane. No restrictions were applied on the type of surgical procedure or post-surgical care, allowing variation in the patient sample. However, we do not expect that any potential effects on our outcomes would hold at three months after surgery. Conservative treatment including splinting and corticosteroid injections have a profound role in the management of mild-moderate CTS and should be topic of similar studies with sufficient follow up. Strengths of the study include the homogeneous nature of the patient sample, thorough analysis of the transverse mobility with the

addition of a follow up ultrasound, the inclusion of reliability data, the high follow up rate and the large sample size.

In summary, after carpal tunnel release the median nerve mobility increases in CTS patients in a dominantly dorsal direction at a level proximal to the carpal tunnel. Not only on average but also at the extremes, our data indicates that there is no clear nerve movement threshold that evidently captures a subpopulation that is enriched in either clinically excellent or less excellent outcomes. However, with high frequency ultrasound systems becoming more popular in daily clinical use, and increasing possibilities with image analyses, more opportunities for studies on small anatomical structures and differences are ahead of us. Also, with more studies prospectively collecting a wide array of data including pre-intervention patient characteristics, patient reported outcomes, longer term follow-up, and a better understanding of previously unknown confounders, a multivariable model serving a clinical advisory role for treatment seems possible. We anticipate that the added prognostic value of ultrasound, both statically and dynamically, acquired in multiple directions could add to such a model, rather than have added value as a single modality.

ACKNOWLEDGEMENT

The authors would like to acknowledge the National Institute of Health for providing funding for this work.

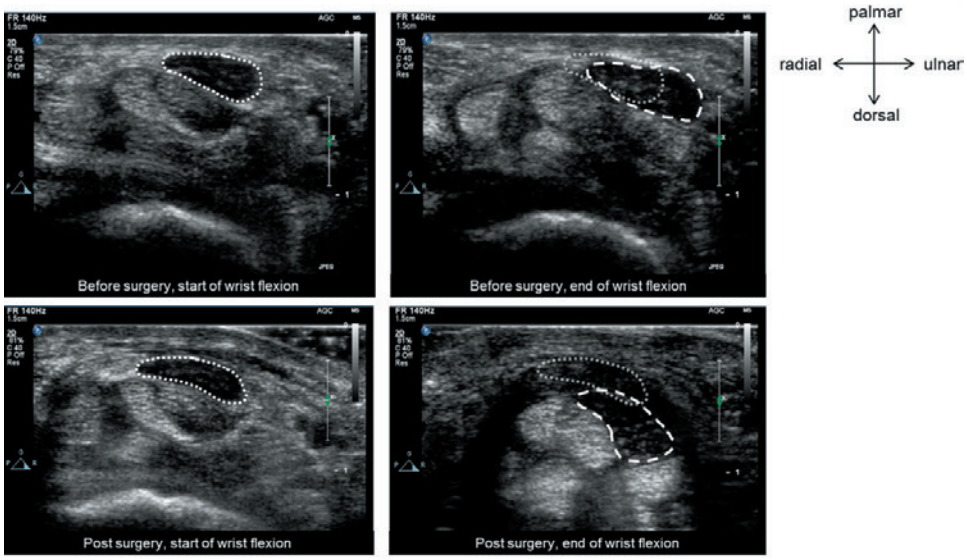
SUPPLEMENTS

Supplement 1. Changes in BCTQ and US parameters after CTR

	Mean pre-operative (SD)		Mean post-operative (SD)		p-value	Mean difference (95% CI)
BCTQ						
Symptom Severity Scale	3.1 (0.7)		1.5 (0.5)		**<0.001**	-1.6 (-1.8, -1.5)
Functional Status Scale	2.6 (0.8)		1.6 (0.6)		**<0.001**	-1.1 (-1.3, -0.9)
Static US parameters						
Nerve CSA, mm^2	14.5 (4.2)		13.3 (3.8)		**<0.001**	-1.3 (-1.7, -0.8)
Nerve perimeter, mm	17.7 (2.6)		17.1 (2.8)		**<0.01**	-0.6 (-1.0, -0.2)
Nerve circularity	1.7 (0.3)		1.8 (0.3)		0.41	0.03 (-0.04, 0.10)
Dynamic US parameters		**Directionality**		**Directionality**		
Finger flexion - RU displacement, mm	2.0 (2.2)	Ulnar	2.2 (2.3)	Ulnar	0.46	0.23 (-0.39, 0.86)
Finger flexion - PD displacement, mm	0.1 (0.6)	Dorsal	0.1 (0.4)	Palmar	0.12	0.12 (-0.03, 0.27)
Finger flexion – overall displacement, mm	2.4 (1.8)	Dorso-ulnar	2.6 (1.9)	Palmo-ulnar	0.35	0.25 (-0.28, 0.78)
Finger flexion – summed displacement, mm	4.8 (2.2)	NA	4.7 (2.3)	NA	0.94	-0.02 (-0.67, 0.62)
Wrist flexion - RU displacement, mm	3.1 (4.1)	Ulnar	2.7 (4.7)	Ulnar	0.32	-0.52 (-1.55, 0.51)
Wrist flexion - PD displacement, mm	1.9 (1.3)	Dorsal	2.4 (1.3)	Dorsal	**<0.01**	0.54 (0.19, 0.90)
Wrist flexion – overall displacement, mm	4.9 (2.8)	Dorso-ulnar	5.4 (2.7)	Dorso-ulnar	0.20	0.47 (-0.25, 1.19)
Wrist flexion – summed displacement, mm	7.2 (2.5)	NA	8.0 (2.8)	NA	**0.04**	0.74 (0.04, 1.45)

Overall displacement is the excursion of the nerve defined as the difference in position between the start of the finger/wrist flex movement and the end. Summed displacement is defined as the summation of segmented nerve excursion over the full finger/wrist flex movement. Comparisons done using paired t-tests, absolute values pre and post-operative have been rounded to the nearest single decimal.
RU: radial-ulnar direction, PD: palmar-dorsal direction with the directionality of the displacements indicated in the next column. NA: Not applicable, since the summed parameter represents the summation of different vectors, no directionality is applicable. BCTQ: Boston Carpal Tunnel Questionnaire, SD: Standard deviation, CI: Confidence interval.

Supplement 2. Example of ultrasound images and median nerve displacement during wrist flexion



Four transverse carpal tunnel ultrasound images from the same patient with moderately severe CTS. Upper row shows the start (left) and end (right) position of the nerve before and after wrist flexion with extended fingers. The row below shows two frames from de clip acquired three months after surgery. The median nerve is indicated with the interrupted line. In the post-operative images the change in end position to a more dorsal level can be seen.

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PART III

ULTRASOUND GUIDANCE IN THE TREATMENT OF CTS

10

EFFECTIVENESS OF ULTRASOUND-GUIDED COMPARED TO BLIND STEROID INJECTIONS IN THE TREATMENT OF CARPAL TUNNEL SYNDROME

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Arthritis Care Res (Hoboken). 2017 Jul;69(7):1060-1065.

ABSTRACT

Objective

To compare the effectiveness of ultrasound-guided injections to blind injections in the treatment of carpal tunnel syndrome (CTS) in a large community-based cohort.

Methods

This study evaluated residents of Olmsted County, Minnesota, treated with a corticosteroid injection for CTS between 2001 and 2010. The proportion of patients receiving retreatment and the duration of retreatment-free survival between blind and ultrasound-guided injections were compared. Propensity score matching was used to control for confounding by indication.

Results

In the matched data set consisting of 234 (of 600) hands treated with a blind injection and 87 (of 89) ultrasound-guided injection cases, ultrasound guidance was associated with a reduced hazard of retreatment (hazard ratio 0.59 [95% confidence interval (95% CI) 0.37-0.93]). In addition, ultrasound guidance was associated with 55% reduced odds of retreatment within 1 year compared to blind injections (adjusted odds ratio 0.45 [95% CI 0.24-0.83]).

Conclusion

This study indicates that ultrasound-guided injections are more effective in comparison to blind injections in the treatment of CTS.

INTRODUCTION

Corticosteroid injection is frequently used to treat carpal tunnel syndrome (CTS) and is effective in reducing symptoms[1]. However, there is only strong evidence for benefits of steroid injection in the short term and about half of the patients require further treatment within one year[1,2].

Injections into the carpal tunnel are commonly performed palpation-guided using anatomical landmarks[3-7]. While the most common techniques have been described as being safe and reliable[5-7], this 'blind' intervention does not provide certainty on whether the injected steroid is adequately placed in the carpal tunnel. Moreover, cadaveric studies have indicated that there is wide variability of injectate distribution following carpal tunnel injection[8,9]. Misplaced injectates or injectates that cannot distribute freely within the carpal tunnel will likely result in residual symptoms or early recurrence of symptoms. Ultrasound, a nonionizing and relatively inexpensive imaging tool, may improve the accuracy and consequently the efficacy of the injection in CTS[10]. It may allow physicians to place the needle tip and injectate closer to the median nerve, without damaging the surrounding tissue or the median nerve itself. The few studies that have investigated ultrasound guidance for injections in CTS[11-13], generally indicate that ultrasound-guided injections result in better symptom relief and increased therapeutic duration compared to non-ultrasound-guided injections. However, these studies were limited by small sample sizes and short term follow-up. Therefore, the purpose of this study was to compare the effectiveness of ultrasound-guided injections with palpation-guided injections in patients with CTS in a large community-based cohort over a longer period of follow-up.

METHODS

Data collection

This retrospective study evaluated residents of Olmsted County, MN, USA, treated with a corticosteroid injection for CTS between 2001 and 2010. Subjects were identified using the resources of the Rochester Epidemiology Project[14] with selection based on a Current Procedural Terminology (CPT) code for diagnosis of carpal tunnel syndrome (ICD-9 354.0) and carpal tunnel injection (CPT 20526). Subjects were followed through their medical record until 2014.

Patients with an age of 21-80, diagnosis of carpal tunnel syndrome and a follow up of at least one year after initial injection were included in the study. Patients were excluded if they received surgical carpal tunnel release prior to injection. Study data were collected and managed by three physicians (SE, AB, TS) using Research Electronic Data Capture (REDCap)[15]. Data were collected independently and for inter-rater agreement between

reviewers Cohen's kappa coefficients were calculated for a subset of the cases. Cohen's kappa was 0.845 for our primary outcome measure[16]. Any discrepancies between the information extracted by the three reviewers were resolved through discussion.

Data collection included the following patient factors: age, gender, diagnosis of primary carpal tunnel syndrome and laterality, and the presence of pregnancy, diabetes mellitus, rheumatoid arthritis, peripheral neuropathy, cervical radiculopathy or other comorbidities such as previous trauma to the affected hand or wrist, Kienbock's disease, or volar ganglion cyst. The severity of CTS was assessed using available EMG data, classified in the following categories; normal, mild, moderate and severe, by a neurologist or physiatrist. For reports not mentioning severity, the reviewers scored severity based on the classification of Stevens[17]. Treatment-specific characteristics included volume of injection, type and concentration of steroid and the use of ultrasound guidance. To compare the effective dose of the steroids, we converted the concentration of each steroid to the equivalent of triamcinolone using a conversion table of the relative potency of steroids[18], since triamcinolone was the most common type of steroid in our cohort. We also collected information about any injections and surgical interventions following the initial injection.

Outcome measurements

The outcome measure in this study was 'failure' of injection, defined as either a second injection or surgical carpal tunnel release that was performed within one year after the initial injection. Additionally a survival analysis was performed to compare the duration of retreatment-free survival by initial treatment groups.

Statistical analysis

Propensity score matching was used to control for confounding by indication[19]. The propensity score (PS) was defined as the likelihood of receiving a blind injection or an ultrasound-guided injection based on baseline characteristics. The following covariates were included in the model: age, gender, EMG severity, pregnancy related CTS, comorbidities such as rheumatoid arthritis, diabetes mellitus, neuropathy, and 'other' comorbidities.

The propensity scores were used to match blind injection cases to ultrasound-guided injection cases on a one-to-three basis using nearest-neighbor matching with a tolerance width of 0.2 SD of the logit of the propensity score. A one-to-three ratio, as compared to a one-to-one ratio, was used to maximize statistical power because our sample had much more non-ultrasound-guided subjects. Significance testing and a comparison of the standardized mean differences were performed to assess whether

the balance in baseline characteristics improved. Standardized mean differences were calculated using the formulas for continuous covariates and dichotomous variables described by Austin et al.[20].
The unmatched subjects were excluded from further analyses and the remaining subjects were treated as independent samples, because the theory behind propensity score matching implies that only within groups of subjects with similar propensity scores, the distributions of the covariates will be similar, not within the individual pairs[21,22].

Kaplan-Meier survival curves were plotted for each treatment group separately to evaluate the unadjusted effect of ultrasound guidance and a log-rank was performed for comparing the treatment groups on long term outcome. Adjusted time to retreatment was tested using a cox mixed effects model, with a random subject effect to account for the correlation between outcomes of hands in bilateral cases and adjustment for volume of injection, effective dose of injection and any baseline characteristic with standard mean difference greater than 10% after matching. Proportional hazard assumptions were tested with a cox.zph test.

The effect of ultrasound guidance on retreatment within one year was estimated by fitting a logistic model applied to the PS-matched dataset using generalized estimating equations with robust variance estimator and an exchangeable structure for the working correlation matrix. This approach allows adjustment for bilateral cases. In this multivariable model we also adjusted for volume of injection, effective dose of injection and any baseline characteristic with a standardized mean difference greater than 10% after matching[23]. In addition, the number needed to treat (NNT) was calculated using the following formula; NNT= (1-(PEER*(1-OR))) / ((1-PEER)*(PEER)*(1-OR)), whereas PEER stands for 'Patient Expected Event Rate'.

A p-value of < 0.05 was considered statistically significant and the statistical analyses and propensity score matching were performed using R (version 3.2.4-revised) with survival package (version 2.38-3) and package 'coxme' version (2.2-5), IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, N.Y.) and the Thoemmes algorithm[24] (version 3.04).

RESULTS

Patient selection and baseline characteristics

A total of 756 subjects with CTS diagnosis and a CTS injection within the specified time window were identified. Among the 756 subjects, 232 patients had bilateral CTS resulting in a total of 988 treated hands (Figure 1). Cases with an injection volume greater than 4

mL were excluded from the analysis, since 4 mL was the maximum amount used in the ultrasound-guided injection group. We excluded 186 injections with a volume greater than 4 mL and 97 cases in which information about volume or effective dose of injection was missing, since all missing data was found to be random. After exclusion of another 16 cases that had less than 1 year follow-up due to death or relocation, the dataset consisted of 533 eligible subjects (689 hands), of which 89 ultrasound-guided cases.

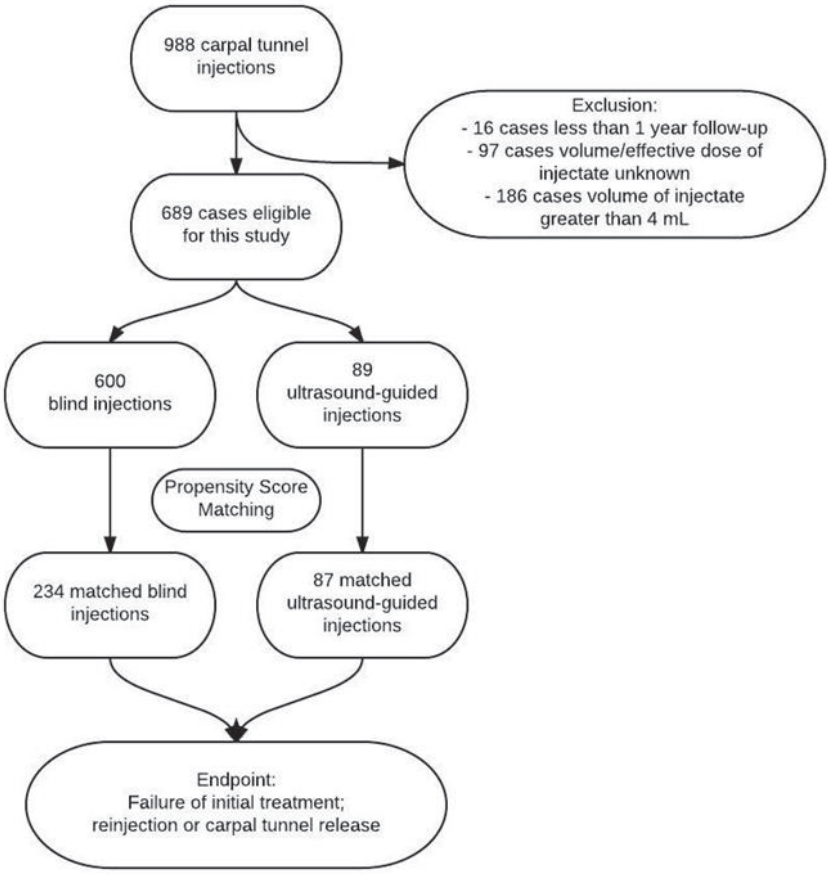

Figure 1. Subject selection flowchart.

Table 1 shows the baseline characteristics of the subjects before and after matching and the treatment characteristics of the matched dataset. Before matching, the proportion of patients who had 'normal' EMG-result was significantly greater in the ultrasound-guided group. Additionally, the proportion of patient with rheumatoid arthritis associated CTS was significantly greater in the ultrasound-guided treatment group.

Based on the estimated propensity scores, we were able to match 234 hands treated with a blind injection to 87 ultrasound-guided injection cases.

Table 1. Baseline characteristics before and after matching and treatment characteristics after matching.

	All subjects				Matched subjects			
Characteristic	Blind injection (n=600)	US-guided injection (n=89)	*Standardized differences*	*p*	Blind injection (n=234)	US-guided injection (n=87)	*Standardized differences*	*p*
Demographics								
Female (%)	72	78	0.139	.24	73	77	0.092	.43
Age, mean yr (SD)	50 (14)	50 (15)	0.067	.37	50 (15)	50 (15)	0.006	.93
EMG severity (%)								
Mild	29	18	0.262	.03	17	18	0.034	.79
Moderate	40	36	0.082	.52	40	37	0.007	.58
Severe	6	7	0.105	.83	8	7	0.031	.81
Normal	9	19	0.304	.00	14	17	0.100	.42
Unknown	17	20	0.090	.41	21	21	0.017	.90
Comorbidities (%)								
Diabetes Mellitus	9	6	0.114	.29	7	6	0.041	.63
Rheumatoid Arthritis	6	19	0.401	.00	13	17	0.112	.31
Peripheral neuropathy/ Radiculopathy	6	3	0.145	.34	5	3	0.102	.63
Other	3	0	0.249	.09	0	0	NA	NA
Pregnancy induced CTS (%)	3	0	0.249	.11	0	0	NA	NA
Treatment characteristics								
Volume of injection, mean mL (SD)					3.1 (0.7)	2.6 (0.7)	0.689	.08
Effective dose (mg) (%)								.08
< 30					29	16	0.315	
40					24	25	0.023	
60					44	57	0.262	
80					2	1	0.082	

Comparison between groups

Mean (standard deviation) follow-up period was 7.2 years (±2.9) for the blind injection group and 5.6 years (±2.5) for the ultrasound-guided injection group. In the unadjusted Kaplan-Meier curves for retreatment (Figure 2), the difference in retreatment between blind- and ultrasound-guided subjects occurred mainly within the first 1.5 years

after initial injection. The log-rank test indicated a significant better retreatment-free survival curve for the ultrasound-guided group. Multivariate cox mixed effect analysis of retreatment-free survival, showed an adjusted decreased hazard of retreatment in favor of the ultrasound-guided group (hazard ratio, 0.59; 95% confidence interval [CI], 0.37 - 0.93).

Within the ultrasound-guided group 55% (N=48/87) received retreatment with eventual surgery in 44% (N=38/87) of the cases. Within the blind injection group retreatment was 72% (N=169/234), with eventual surgery in 64% of the cases (N= 150/234).

As the vast majority of the failures occurred within one year, the odds ratio (OR) of failure within one year was calculated. Binary logistic analysis indicated that, after adjustment for bilateral cases and covariates, ultrasound guidance was associated with 55% reduced odds of retreatment within one year compared to blind injections (adjusted OR, 0.45; 95% CI, 0.24 - 0.83). Since there was still a slight difference in the proportions of 'normal' EMG after matching, we applied additional adjustment for EMG results to this analysis, with similar results. Retreatment within one year was performed in 41% (N=36/87) of the cases within the ultrasound-guided group and 58% (N=135/234) of the cases within the blind injection group. The number needed to treat to prevent one patient from retreatment within one year was five.

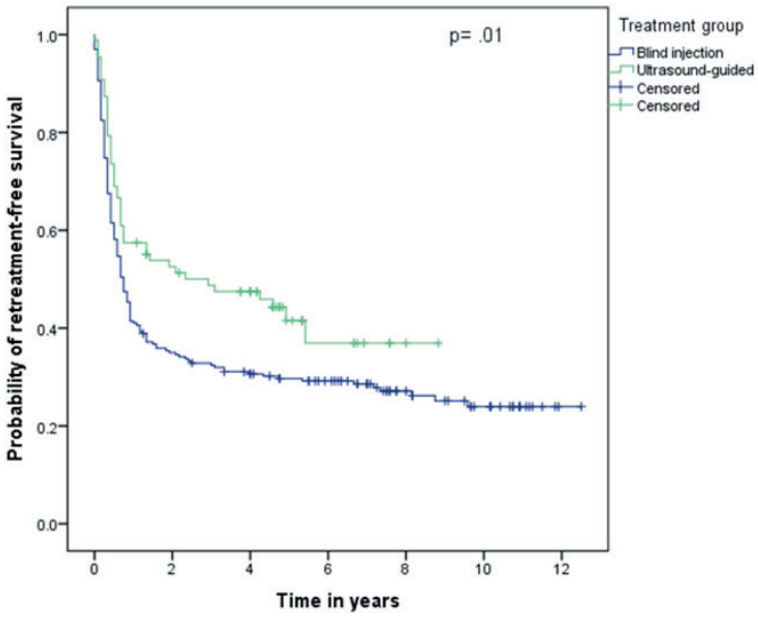

Figure 2. Kaplan-Meier curves.

Subgroup analysis

Since the majority of the ultrasound-guided injections was performed by a physical medicine and rehabilitation (PMR) physician (Table 2), we realized that specialty of physician might be a confounder in our cohort. Therefore, we also compared the blind and ultrasound-guided injections performed by only the PMR physicians. This subgroup consisted of 60 ultrasound-guided injections and 124 blind injection cases. We found a comparable adjusted odds-ratio of 0.48 (95% CI, 0.23 – 1.00), although not significant in this smaller sample.

Table 2. Proportion of ultrasound-guided and blind injections subdivided by specialty of physician in matched dataset.

Physician specialty	Blind injection (%)	Ultrasound-guided injection (%)
Orthopedic surgery	37	3
Plastic surgery	3	0
Physical medicine and rehabilitation	53	69
Family medicine	1	0
Rheumatology	5	26
Internal medicine	0.4	0
Radiology	0	1

DISCUSSION

The purpose of this study was to assess the efficacy of ultrasound-guided injections compared to blind injections in the treatment of CTS. Our findings, based on a large population-based cohort, indicate that ultrasound-guided injections are more effective in comparison to blind injections. We found that the retreatment-free survival between blind and ultrasound-guided injections was significantly different, in favor of the ultrasound-guided group. In addition, the odds of 'failure' of injection within one year were 55% reduced in the ultrasound-guided group relative to the blind injection group.

Our finding of an improved effectiveness of injections when they are performed under ultrasound-guidance is in line with the results of previous studies. A trial on 46 patients with CTS, randomized to either an ultrasound-guidance or blind injections found significantly more improvement of symptoms on Boston Carpal Tunnel Questionnaire (BCTQ) at 12 weeks follow-up in favor of the ultrasound-guided group[11]. In addition, a study on 75 cases of 44 patients with CTS receiving an injection using either one of two different ultrasound-guided approaches or a blind injection found not only a significantly greater improvement in symptoms in one of the ultrasound-guided

groups, but also a larger decrease in cross-sectional area of the median nerve and greater improvement in nerve conduction[12]. In the present study, we confirm that the previously reported improvement of short term symptoms can also reduce the number of reinjections or surgery.

While our outcomes are only defined in terms of therapeutic success, there are additional potential benefits of ultrasound guidance. Ultrasound guidance can potentially lead to a decreased risk of median nerve and surrounding tissue damage[6,10,25]. In addition, a randomized controlled study on the cost-effectiveness of ultrasound-guided injections found reduced costs for responders in the ultrasound-guided group relative to the blind injection group, due to a reduction in costs of reinjection or referral to surgery[13]. Moreover, ultrasound does not only provide real-time visualization of the needle tip, it also provides high-resolution images of all the structures within the carpal tunnel and can therefore contribute to the diagnosis[26].

Some limitations of our study should be considered. Amongst clinicians there is not only little consensus with regard to the value of ultrasound guidance of injections into the carpal tunnel, but also with regard to almost all aspects of therapeutic injections in carpal tunnel syndrome, including volume of injection and type and concentration of steroid. This was also reflected in our dataset and resulted in exclusion of a subset of the cases. Although we were able to adjust for the remaining differences in treatment characteristics, a standardized type and volume of the corticosteroid would have been preferable. Another limitation of our study is the exclusion of about 7% of potential cases because the patients had not authorized the use of their medical records for research[14]. In addition, a limitation of the study design is the lack of blinding. As a result, the use of ultrasound-guidance may have affected the patients' perception of injection effect, especially as objective measures such as post injection electrodiagnostic testing were not available for analysis.

A strength of the present study is the use of propensity score matching to account for imbalances in observed variables. However, this method cannot account for possible hidden confounding factors.
The suggested higher efficacy of ultrasound-guided injections may depend on the experience of the physician and we cannot rule out that specialty of physician was a confounder. In addition, the physicians in our cohort used different techniques for both types of interventions. Different techniques of ultrasound guidance in carpal tunnel injections have been described[12,27,28] and since the study by Lee et al. suggests that one technique may be more efficient than the other, this may have influenced the outcome.

The present study suggests that ultrasound-guided injections are more effective compared to blind injections in the treatment of carpal tunnel syndrome. This outcome warrants further study, for example in a well-designed randomized trial with a well-defined type of steroid and injection volume, using a standardized technique.

ACKNOWLEDGEMENTS

This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676. The project was additionally supported by NIH/NCRR Colorado CTSI Grant Number UL1 RR025780 and Mayo Foundation.

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11

ULTRASOUND-GUIDED HYDRODISSECTION DECREASES GLIDING RESISTANCE OF THE MEDIAN NERVE WITHIN THE CARPAL TUNNEL

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Muscle Nerve. 2018 Jan;57(1):25-32.

ABSTRACT

Purpose

To assess alterations in median nerve biomechanics within the carpal tunnel resulting from ultrasound-guided hydrodissection in a cadaveric model.

Methods

Twelve fresh frozen human cadaver hands were used. Median nerve gliding resistance was measured at baseline and post-hydrodissection, by pulling the nerve proximally and then returning it to the origin. Six specimens were treated with hydrodissection, and 6 were used as controls.

Results

In the hydrodissection group there was a significant reduction in mean peak gliding resistance of 92.9 ± 34.8 mN between baseline and immediately post-hydrodissection (21.4% ± 10.5%, p= .001). No significant reduction between baseline and the second cycle occurred in the control group: 9.6 ± 29.8 mN (0.4% ± 5.3%, p= .467).

Conclusion

Hydrodissection can decrease the gliding resistance of the median nerve within the carpal tunnel, at least in wrists unaffected by carpal tunnel syndrome. A clinical trial of hydrodissection seems justified.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, with a reported annual incidence per 100,000 persons ranging from 324 to 524 among women and 135 to 303 among men[1-4]. Although the precise pathoetiology of idiopathic CTS remains undefined, the syndrome is characterized by increased pressure in the carpal tunnel, with consequent median nerve compression. The most common and effective treatment methods for CTS are corticosteroid injections and surgical decompression[5,6]. Corticosteroid injections often provide temporary relief, but approximately half of injected patients require further treatment within one year[5,7,8].

Previous research has shown that the subsynovial connective tissue (SSCT) surrounding the tendons in the carpal tunnel is thickened and fibrotic in CTS patients compared to normal individuals[9-12], and this thickening appears to result in reduced motion of the median nerve within the carpal tunnel[13-16]. While the relationship between fibrosis and neuropathy is still unknown, this reduction of mobility can prevent the nerve from moving aside as the tendons move anteriorly during strong grip or pinch[17]. This situation may compress the median nerve during gripping, thus contributing to development or progression of CTS. In addition, fixation can lead to traction neuropathy during hand activity as the tendons move along the nerve within the tunnel [18]. Consequently, freeing the median nerve from any motion restriction might restore the dynamic balance in relative motion between the median nerve and the surrounding tissues, thus reducing CTS symptoms[19,20].

Ultrasound-guided hydrodissection has recently been proposed to treat nerve entrapment[21-23]. The potential utility of hydrodissection in CTS is based on the theory that nerve entrapment is exacerbated by median nerve fixation to surrounding tissues such as the transverse carpal ligament (TCL). This fixation, which is often seen at the time of surgery, appears to correlate with the reduction in nerve motion visualized by ultrasound imaging[13-15]. Hydrodissection uses an ultrasound-guided injection of sterile saline to create a perineural fluid plane between the nerve and surrounding tissues and consequently improve the nerve mobility. Advantages of hydrodissection are that it can be performed using only sterile saline solution or a similar physiologically compatible fluid, and the injection can be done in the office. In addition, hydrodissection is performed under ultrasound-guidance, lessening chances of median nerve injury compared to a blind injection.

Several reports have anecdotally noted the use of hydrodissection to treat CTS[21-23], but have not formally investigated whether the nerve is mobilized by this technique.

Consequently, the aim of this study was to assess alterations in the biomechanics of the median nerve environment resulting from the hydrodissection procedure in an unembalmed cadaveric model. Our hypothesis was that gliding resistance of the median nerve would be decreased after ultrasound-guided hydrodissection, presumably due to disruption of fibrous connections between the median nerve and surrounding tissue. In addition, we performed cyclic testing to assess whether the potential effect of hydrodissection was permanent or changed over time, as SSCT fibers weakened or stretched by hydrodissection might be more likely to break with continuous cycling.

METHODS

Experimental Set Up

Twelve fresh frozen human cadaveric hands were obtained from our institution's anatomical bequest program for use in this experiment, with approval from our institutional biospecimen committee. Specimens were screened for a history of CTS, rheumatoid arthritis or traumatic injuries of the ipsilateral arm. We used cadaveric hands from donors unaffected by CTS, because the SSCT is expected to be less fibrous and therefore should be easier to dissect with the sterile saline injections. Hands were amputated approximately 13 cm proximal to the wrist joint. All soft tissue was removed 6 cm distal to the amputation site, in order to expose the proximal ends of the ulna and radius. The wrist was fixed in a neutral position with a customized external fixator, and the proximal ends of the ulna and the radius were locked into a clamp.

All digits were fixed in extension with 1.5-mm diameter K-wires. The median nerve and tendons in closest proximity to the median nerve in a neutral wrist position, namely the flexor pollicis longus (FPL), the flexor digitorum profundus of the index finger (FDP2) and the flexor digitorum superficialis of the index, middle and ring finger (FDS2 - FDS4) were exposed 2.5 cm proximal to the proximal wrist crease. Soft tissue in contact with the median nerve was removed to eliminate friction between the structures. The TCL was left intact (Figure 1A). Each tendon was connected proximally to a 50 gram weight suspended over a pulley to maintain tension. The three common palmar digital nerves, motor branch of the median nerve and the anastomotic branch to the ulnar nerve were divided distally and were sutured together. Before dividing the digital branches (Figure 1B), these and the underlying tendon were marked at the level of the proximal part of the metacarpal bones, using a 6.0 Prolene suture, in order to define the neutral position for the median nerve (Figure 1C). The sutured median nerve bundle was connected distally to a 50 gram weight suspended over a pulley to maintain tension. The proximal end of the median nerve was connected to a stepper-motor driven mechanical actuator

controlled by a microcontroller (Arcus Technologies) and instrumented with a load cell (Transducer Techniques, Temecula, CA) (Figure 2). A similar experimental concept and apparatus has been used in previous studies from this laboratory to measure gliding resistance which indicated that when testing the same condition similar force-displacement curves were found repeatedly[24-26].

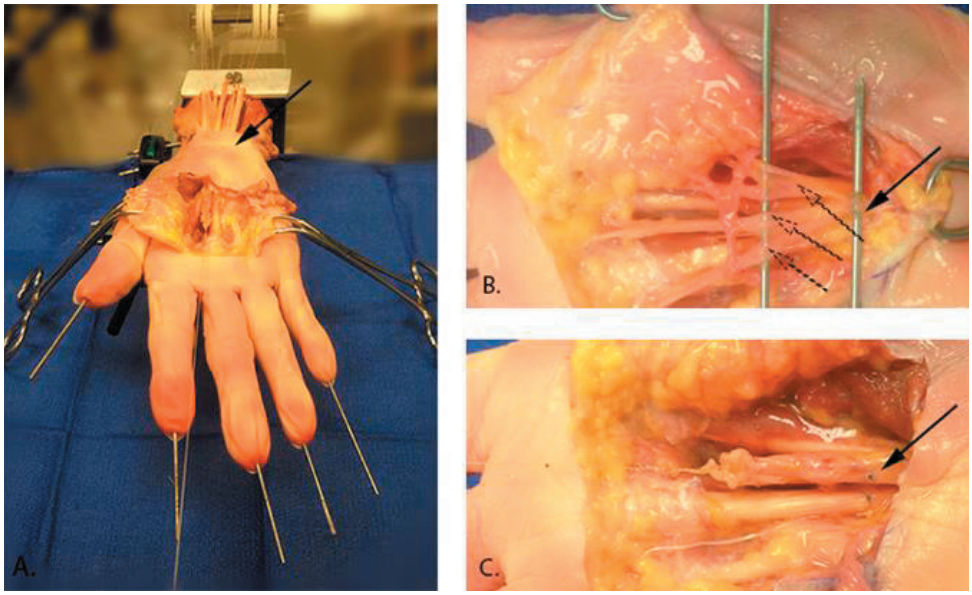

Figure 1. A) Median nerve and tendons in closest proximity to the median nerve exposed 2.5 cm proximal to the proximal wrist crease (arrow). Median nerve exposed distal to the carpal tunnel outlet, approximately 5cm distal to the proximal wrist crease depending on hand size. **B)** Three palmar digital branches (dotted arrows) and motor branch (solid arrow) of the median nerve identified. **C)** Branches of the median nerve sutured together: the neutral position of the nerve identified by markers at the same level of the nerve and underlying FDS3 tendon (arrow).

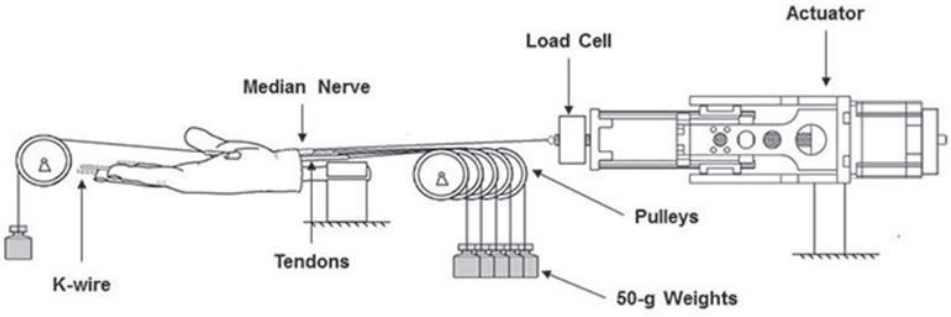

Figure 2. Experimental set up.

Prior to formal testing one preconditioning cycle was performed to ensure that any force reduction post treatment resulted from the hydrodissection, and not from the mechanical effect of the excursion/stretching. The median nerve was pulled proximally at a rate of 1 mm/s for a distance of 6 mm, which is within the physiological range of median nerve excursion with full finger motion[27-29], and then returned to the neutral position. Following a 30 minute delay to allow viscoelastic recovery, the baseline median nerve gliding resistance was assessed by pulling the nerve using the same parameters. Subsequent to the hydrodissection procedure, the median nerve gliding resistance was measured again. To measure the potential effect of hydrodissection over time, the nerve was subsequently pulled for 1000 repetitive cycles post-hydrodissection at the same velocity and amplitude as described above. Six specimens were treated with ultrasound-guided hydrodissection using the ulnar approach and 6 specimens were used as a control group -testing the gliding resistance of the median nerve using the same experimental set up, without performing hydrodissection (Figure 3).

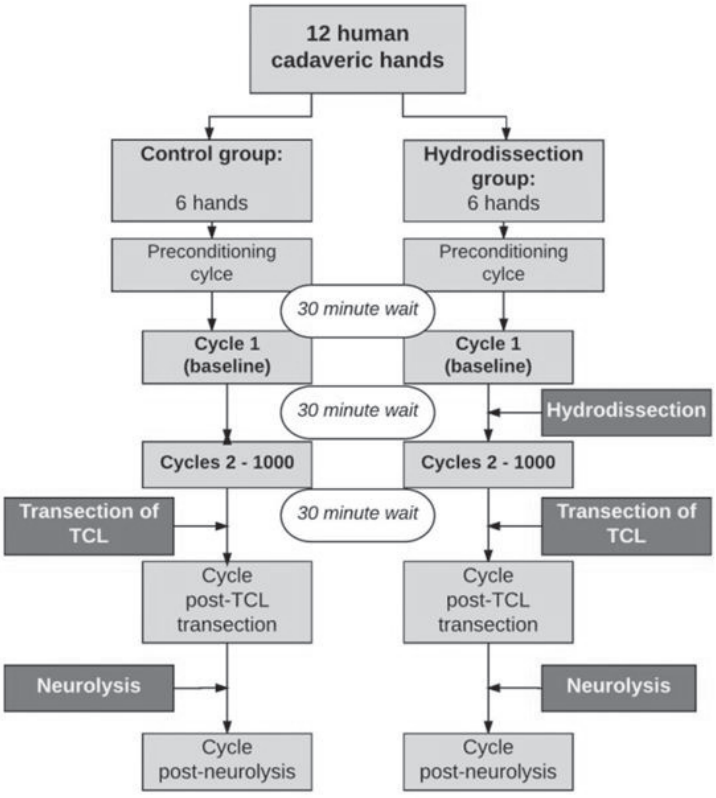

Figure 3. Flow chart describing testing sequence.

Subsequently, in both groups the carpal tunnel was opened by transecting the TCL and the gliding resistance of the median nerve was measured. Finally, the gliding resistance was measured after neurolysis of the median nerve. With this final step, we aimed to investigate if fibrous connections that could not be dissected with hydrodissection can be dissected surgically, which then would result in an even lower gliding resistance. Force and displacement data were collected at a sample rate of 50 Hz during excursions.

Hydrodissection Technique

A Philips iE33 ultrasound machine (Philips Electronics, Best, The Netherlands) with an L15-7io MHz linear array transducer was used to guide the hydrodissection. We used the ulnar approach for performing hydrodissection as described previously by Smith et al.[30]. The ultrasound transducer was placed transversely along the proximal wrist crease (carpal tunnel inlet). First, the median nerve and the pisiform (on the ulnar side) were identified. Under ultrasound guidance, a 27 gauge needle was inserted into the skin on the ulnar side of the palmaris longus at the level of the wrist crease along a trajectory approximately parallel to the transducer footprint. Subsequently, the needle penetrated the TCL on the ulnar side of the carpal tunnel and under real time visualization the needle was directed to the superficial ulnar side of the median nerve. Then, the first injectate was delivered and the median nerve was hydrodissected from the undersurface of the TCL while advancing the needle between the superficial aspect of the median nerve and the overlying TCL (Figure 4A, supplemental video 1). After complete separation of the nerve and TCL was sonographically confirmed along the length of the carpal tunnel, the needle was withdrawn to the ulnar side of the median nerve and redirected to its deep surface. The remainder of the injectate was delivered, separating the nerve from the underlying SSCT and tendons (Figure 4B, supplemental video 2), once again confirming with ultrasound complete hydrodissection along the deep surface of the median nerve throughout the carpal tunnel within the TCL region (supplemental video 3). All hydrodissections were performed with a total volume of 5 mL of saline based on clinical experience and a pilot study of one cadaveric specimen demonstrating complete median nerve hydrodissection throughout the carpal tunnel with this volume. We then waited for 30 minutes to allow the saline to disperse within the wrist, before testing the median nerve gliding resistance again.

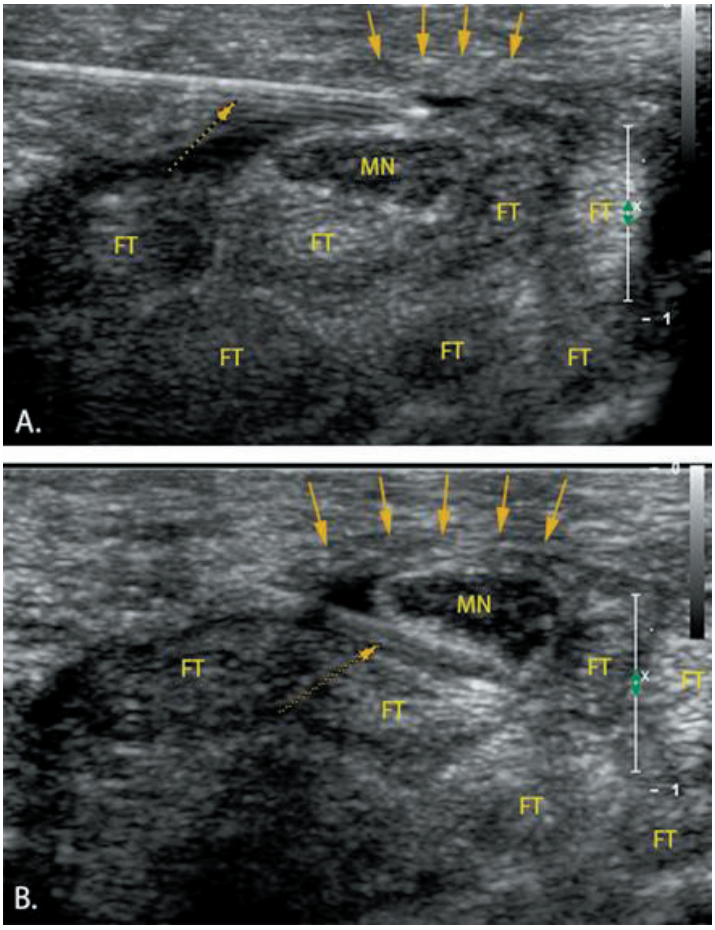

Figure 4. Transverse ultrasound image of the carpal tunnel. Left=ulnar. A 27-gauge needle (dotted arrow) penetrated the TCL (down pointing arrows) on the ulnar side of the carpal tunnel **A)** freeing the median nerve (MN) from the transverse carpal ligament **B)** separating the nerve from the underlying subsynovial connective tissue and flexor tendons (FT).

Data Analysis

The peak gliding resistance and total energy for each cycle were calculated as described in previous studies evaluating the characteristics of the SSCT[31,32]. Peak gliding resistance was the difference between the maximum force and the minimum force observed within each specific cycle and the energy absorption was the area under the curve of the resistance load-excursion curve, up to the maximum displacement. Peak gliding resistance of the median nerve and energy absorption were analyzed at baseline, at the second cycle and subsequently at intervals of 50 cycles up to cycle 1000, post-TCL

transection and post-neurolysis. A custom MATLAB (version 2016a, MathWorks, Natick, MA) program was developed to analyze the repetitive force-excursion data, providing the peak gliding resistance and energy absorption for the selected cycles.

Statistical Analysis

Summary statistics are shown as mean ± standard deviation. Peak gliding resistance and energy absorption of the baseline conditions were compared to the same parameters obtained after hydrodissection using a paired t-test. The same test was applied to the control group in order to assess whether there was a significant difference between baseline measurement and the second cycle. Independent t-test was used to compare the gliding resistance and the energy absorption of the selected cycles between the two groups. P-values less than 0.05 were considered significant. Statistical analyses were performed using the Statistical Package for Social Science (SPSS) software (version 22.0, Chicago, IL, USA) and R version 3.2.3.

RESULTS

The hydrodissection and the control groups did not differ significantly in terms of age, gender or baseline peak gliding resistance and energy absorption. Mean age at death was 73 ± 12.3 years in the hydrodissection group and 73 ± 21.3 years in the control group ($p = .961$). There were 2 female and 4 male specimens in each group. Mean baseline peak gliding resistance was 584.9 ± 419.8 mN in the hydrodissection group and 452.9 ± 189.9 mN in the control group ($p = .499$). Mean baseline energy absorption was 1.8 ± 1.1 mJ in the hydrodissection group and 1.6 ± 0.5 mJ in the control group ($p = .674$).
In the hydrodissection group, we found a decrease in mean peak gliding resistance of 92.9 ± 34.8 mN between baseline and immediately post-hydrodissection and a decrease in mean energy absorption of 0.3 ± 0.2 mJ. In the control group a reduction in mean peak gliding resistance of 9.6 ± 29.8 mN occurred between baseline and cycle 2 and a reduction in mean energy absorption of 0.03 ± 0.15 mJ (Figure 5). The mean percentage difference in peak gliding resistance between baseline and post-hydrodissection was 21.4% ± 10.5%. The mean percentage difference between baseline and second cycle in the control group was 0.4% ± 5.3%.
There was no significant difference in mean peak gliding resistance between the preconditioning cycle and baseline cycle in the hydrodissection group ($p = .161$), indicating that a perturbation alone is not enough to disrupt the equilibrium.

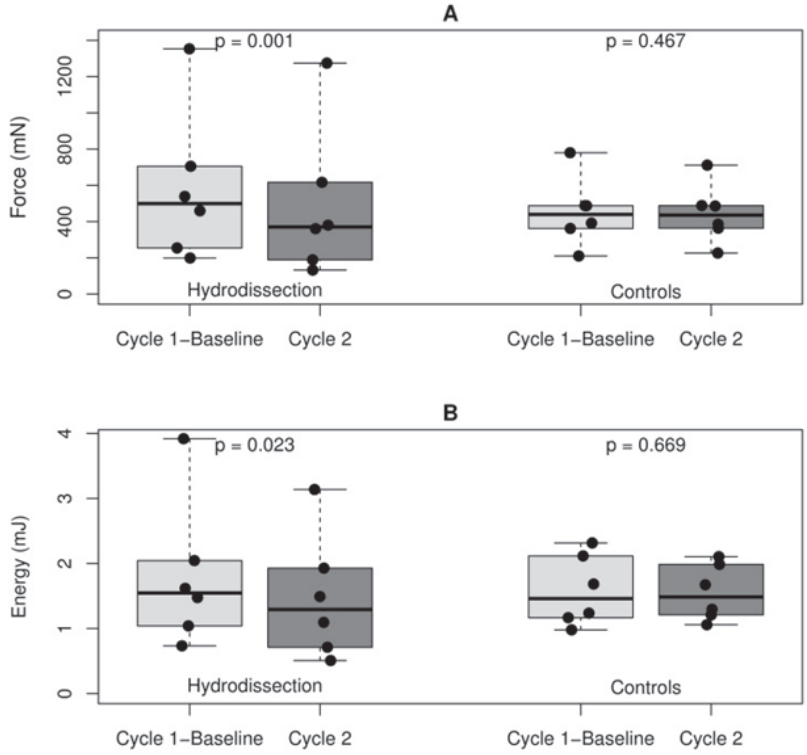

Figure 5. Difference in **A**) peak gliding resistance and **B**) energy absorption between baseline (cycle 1) and second cycle for both groups. The boxplots show the distribution of peak gliding resistance and energy absorption for the two groups. The boxes represent the 25th, 50th, and 75th percentiles. The whiskers show the range and points represent the data values.

Repetitive Motion Testing

The peak gliding resistance slightly decreased over 1000 repetitive cycles (difference between cycle 1 and cycle 1000) in both the hydrodissection and the control groups. However these changes were not statistically significantly different for either group (hydrodissection group p = .139, control group p = .276) or between groups (p = .615) (Figure 6A). In addition, there was no statistically significant difference in energy absorption over 1000 repetitive cycles in either group (hydrodissection group p = .056, control group p = .310). Greater reduction in energy absorption was found in the hydrodissection group during 1000 cycles compared to the control. However the difference between the two groups was not statistically significant (p = .308) (Figure 6B). Transection of the TCL resulted in a decrease of 26.3% ± 10.9% and 33.8% ± 8.5% in peak gliding resistance compared to the previous cycle, for the hydrodissection group and the control group respectively (hydrodissection group p = .100, control group p < .001,

between groups p = .210). The greatest decrease in peak gliding resistance was found after neurolysis of the median nerve: a 69.1% ± 9.2% decrease in the hydrodissection group and a 81.0% ± 7.0% decrease in the control group compared to the previous cycle, resulting in a peak gliding resistance of 48.0 ± 26.9 mN and 77.0 ± 23.9 mN respectively (hydrodissection group p = .010, control group p = .002, between groups p = .523).

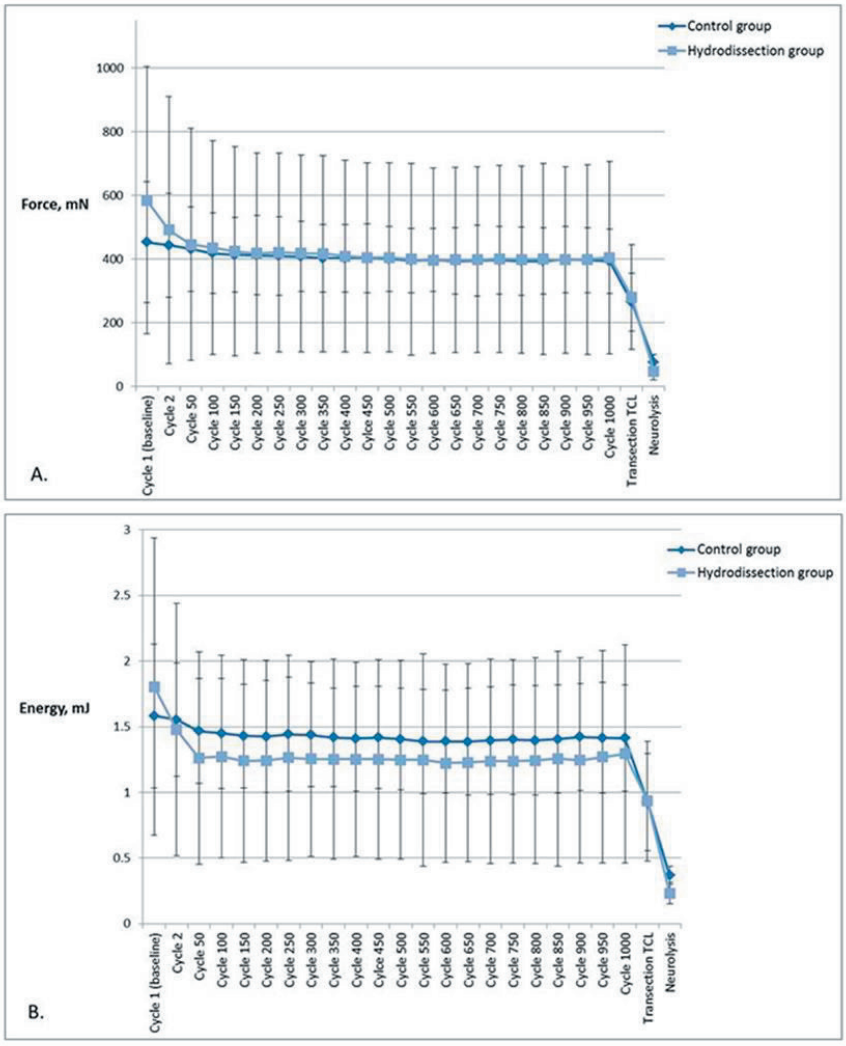

Figure 6. **A)** Mean peak gliding resistance at baseline, during repetitive motion testing, post-TCL transection and post-neurolysis of the median nerve. Error bars represent standard deviations. **B)** Energy absorption at baseline, during repetitive motion testing, post-TCL transection and post-neurolysis of the median nerve. Error bars represent one standard deviation.

DISCUSSION

Based on this cadaveric study we can conclude that ultrasound-guided hydrodissection can decrease the peak gliding resistance of the median nerve within the carpal tunnel, at least in wrists unaffected by CTS. Although the precise mechanism by which hydrodissection may reduce median nerve peak gliding resistance cannot be determined within the context of the current study, it is plausible that hydrodissection mechanically mobilizes the median nerve relative to the surrounding carpal tunnel structures. The most common histological finding in CTS is non-inflammatory fibrosis of SSCT surrounding the tendons in the carpal tunnel[9,12,33]. Several studies suggest that fibrosis leads to decreased motion of the median nerve within the carpal tunnel[13-15]. Freeing the median nerve from the TCL and surrounding tendons by dissecting the SSCT might result in restoration of the normal kinematics within the carpal tunnel, thereby reducing symptoms.

Our repetitive data indicate that the effects of hydrodissection may be long lasting and not entirely dependent on the persistence of a fluid bolus, which might have provided lubrication. Thus, the repetitive motion data suggest that there was no apparent additive effect of repetitive gliding and that there was no loss of hydrodissection effect over time, at least over 1000 repetitive cycles. TCL transection and neurolysis reduced the gliding resistance. Examining the effect of TCL transection and neurolysis validated our model, since we expected the gliding resistance to decrease.

Few studies have investigated the clinical effect of ultrasound-guided hydrodissection in patients with CTS. DeLea et al. treated 12 patients with scleroderma in the hand with ultrasound-guided hydrodissection (using 3 mL of 1% lidocaine) of entrapped structures within the carpal tunnel followed by a corticosteroid injection of 80 mg triamcinolone and included 14 patients with rheumatoid arthritis (RA) related CTS as a control group. They found that the treatment reduced the pain scores by 47% from baseline at two weeks in RA-related CTS and by 67% from baseline in scleroderma subjects[22]. Malone et al. treated 44 wrists in 34 patients with CTS using hydrodissection of the median nerve and fenestration of the flexor retinaculum[21]. The median nerve was separated from the deep surface of the flexor retinaculum, using 9 cc of sterile saline, 1cc of 1% lidocaine and 1cc of 40mg/ml triamcinolone acetonide. Subsequently, a series of 150 fenestrations of the flexor retinaculum was made, using a 20 gauge needle tip. In 39 wrists the symptoms improved and in 5 wrists open carpal tunnel release was required after an average of 32 weeks. In addition, a prospective study on 75 cases of 44 patients with CTS receiving an injection of a 2 mL anesthetic-corticosteroid mixture using either one of two different ultrasound-guided approaches or a blind injection found

a significantly greater improvement in symptoms using the in-plane ulnar approach with hydrodissection compared to the out-plane ulnar ultrasound-guided approach without hydrodissection or the blind injection group at twelve weeks[23]. In addition to the clinical improvement, a larger decrease in cross-sectional area of the median nerve and greater improvement in nerve conduction study were found with the in-plane ulnar approach compared to the out-plane approach and blind injection. A limitation of all of these clinical studies is that due to the study designs, the differential contributions of hydrodissection, injected steroid, lidocaine, or fenestration of the flexor retinaculum could not be determined.

Some limitations of our study should be considered. First, we have tested specimens unaffected by CTS only, which is the best case scenario since the SSCT will likely be fibrous and therefore more difficult to dissect in specimens with a history of CTS. In addition, the shape of the median nerve can be altered in patients with CTS and this might have an effect on the kinematics within the carpal tunnel[15]. Conversely, it might be easier to mechanically see the effect of the treatment in specimens affected by CTS. This study could be repeated in specimens obtained from donors with clinical CTS. Second, a sham experiment, in which we just inserted a needle without injecting saline, was not performed. Although we do not expect a significant change in gliding resistance and energy absorption from just inserting the needle, this possibility has not been explored. Third, the groups had a slightly different gliding resistance at baseline and the standard deviations for all the measurements were relatively wide. This variation was probably due to normal inter-individual biological variability. Fourth, clinicians should exercise appropriate caution when extrapolating our cadaveric results to clinical populations. Although we have used fresh frozen specimens, it is possible the biomechanical and morphological properties of the median nerve and surrounding SSCT may be affected by the freezing and thawing[34]. In addition, the results of hydrodissection may be influenced in vivo by differing hydrostatic pressure conditions compared to those found in cadavers. Fifth, the experimental set up is artificial since we tested isolated median nerve motion relative to the immobilized structures around it in the longitudinal plane only. In vivo, these structures may all be moving relative to each other in both the longitudinal and transverse plane during functional activities. In our model, only the median nerve moved.

The strength of this study is that it provides information about the kinematic properties within the carpal tunnel. This information may contribute to a better understanding of the mechanism of action of hydrodissection. Clinical studies have already suggested that ultrasound-guided hydrodissection can reduce symptoms in patients with CTS as

described above. However, this clinical improvement might be due to a placebo effect. With this study we have shown that the perineural fluid plane created by hydrodissection and visualized by ultrasound actually leads to altered forces within the carpal tunnel.

In conclusion, this study shows that ultrasound-guided hydrodissection can decrease the peak gliding resistance of the median nerve. The next step would be to assess whether the use of hydrodissection leads to improved nerve mobility, greater reduction in symptoms, or decreased recurrence rate in comparison with regular ultrasound-guided injections, with and without an anesthetic corticosteroid mixture. A clinical trial of ultrasound-guided hydrodissection seems justified.

ACKNOWLEDGEMENTS

This study was funded by a grant from NIH/NIAMS (RO1 AR62613).
We thank Dr. H. Liu and Dr. T.H. Yang for assistance with preparation of the specimens, and Dr. K.N. An for his valuable comments on data interpretation.

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12

GENERAL DISCUSSION

In this chapter, which contains three paragraphs, the main findings of the thesis are discussed. Firstly, we focus on the conventional treatment options for carpal tunnel syndrome (CTS). Since there is only support for the short-term effect of steroid injections[1,2], the role of local injections for CTS remains under discussion. We therefore assessed the long-term effect of corticosteroid injections in CTS. In addition, for both corticosteroid injections and surgery it remains challenging to predict treatment outcome. Using a large population-based cohort from Olmsted County, MN, USA, and a large dataset from Xpert Clinic, the Netherlands, we identified prognostic factors for treatment outcome after a corticosteroid injection and carpal tunnel release (CTR), respectively. The results of these studies are discussed in the first paragraph.
The second paragraph focuses on ultrasound in CTS. The Mayo Clinic, Rochester, MN, is conducting a clinical trial on ultrasound in CTS: *'Dynamic ultrasound to enhance understanding of CTS (DUCATS) study'*. The main aim of the clinical trial is to identify ultrasound parameters that can serve as predictors for treatment outcome in CTS. The ultimate goal is to provide more tailored treatment for specific patients with CTS. However, prior to analyzing the study data, the method of analyses had to be optimized. In this paragraph we discuss a new technique to analyze dynamic ultrasound data in the longitudinal plane. Furthermore, the prognostic potential of both static and dynamic ultrasound assessments for surgical outcome are discussed.
Lastly, in the third paragraph, the effectiveness of ultrasound-guided injections and additionally, hydrodissection (a new technique to treat nerve entrapment) are discussed. Each paragraph finishes with recommendations for future research.

1. TREATMENT OUTCOMES OF CTS

1.1.1. Treatment guideline

Although generally there is concordance between different clinical practice guidelines for CTS (injection and/or splinting as a first option if clinically indicated and subsequently surgery if needed), there is no consensus on the optimal treatment algorithm in terms of, for example, maximum number of subsequent corticosteroid injections, time-window between interventions and timing of surgery. Some studies even suggest proceeding directly to surgery, without attempting an injection, to reduce costs[3-5]. Additionally, some surgeons consider the value of steroid injection for CTS to be of diagnostic benefit only[6]. Thus, there remains uncertainty in treating this seemingly straightforward condition and regional variations in care are a reflection of this uncertainty[7]. In this thesis, we explored factors that influence treatment outcome in CTS.

1.1.2. The role of corticosteroid injections

Since there is only support for the effectiveness of corticosteroid injections in the short-term, we performed a retrospective analysis of the effectiveness of steroid injection for CTS using a cohort from Olmsted County with a median follow-up of 7.4 years (**chapter 2**). We found that approximately one third of the patients did not have subsequent treatment after a single corticosteroid injection. Due to the nature of our data, our outcome measure (patient-received additional treatment) was only a proxy for the underlying clinical question regarding patient experience of symptoms. Therefore, further studies with more targeted outcomes such as the Boston Carpal Tunnel Questionnaire (BCTQ) are needed to assess that question. Still, our study indicates that there is a therapeutic role for corticosteroid injections in CTS and we therefore think that a steroid injection should be a serious consideration in CTS. On the other hand, since there is not much literature on the natural history of CTS, we cannot tell whether these patients did not receive further treatment because the injection decreased the symptoms or because the patients elected for some other reason not to receive subsequent treatment.

Milone et al. performed a cost-minimizing analysis to identify the least costly strategy for CTS treatment utilizing reported success rates including, amongst others, our study from **chapter 2**.[8] They concluded that initial management with steroid injections minimizes the direct payer costs. However, besides cost-effectiveness, many other factors play a role in deciding on the type of treatment for CTS and, although important, costs-effectiveness may not be the most relevant factor. In addition, based on our study in **chapter 2** we cannot state that all patients with CTS should have an injection first. As described, within the same time frame many patients diagnosed with CTS underwent surgery without a preceding injection. In general, these were patients with a more severe disease as measured by electrodiagnostic testing (EDS). This may be appropriate for patients with severe CTS, including patients with thenar atrophy and decreased sensibility. Around 75% of the patients in our cohort with a severe EDS result eventually underwent surgery. There were an insufficient number of patients who received a second injection (5%) to assess the effect of repeated injections. However, we found that the proportion that eventually proceeded to surgery after a second injection was similar to the rate of failure after the first injection (62.7% versus 62.8%).

Our data suggest that a single injection may reduce the rate of subsequent surgery for many years. If symptoms persist, surgery can follow promptly. If the injection controls the symptoms, though, based on our data it may be reasonable to await the return of symptoms, rather than assuming that all patients will have a recurrence of symptoms within a few weeks to months, and therefore routinely offering surgery.

1.2.1 Prediction of treatment outcome

Corticosteroid injection

Ideally, we will be able to reduce patient burden by predicting who will respond to a corticosteroid injection. In **chapter 2** we described prognostic factors for subsequent treatment after a single injection for CTS. Our data suggested that patients with more severe EDS results were more likely to experience injection failure. Rheumatoid arthritis was found to be significantly associated with a decreased likelihood of injection failure for both any retreatment and for carpal tunnel release. This might be explained by a different underlying pathophysiology of rheumatoid arthritis associated CTS compared to idiopathic CTS; an inflammatory condition versus non-inflammatory fibrosis in idiopathic CTS. Other risk factors that were examined, namely age, sex, a history of diabetes mellitus and diagnosis of peripheral neuropathy or cervical radiculopathy were not significantly associated with treatment failure.

In **chapter 3** we looked further into injection volume and found a significant association between higher injectate volume and reduced rate of subsequent treatment within one year after the initial injection. Interestingly, the effective dose of steroid was not significantly associated with subsequent treatment. Our result therefore indicates that the mechanism of action of an injection in CTS might not solely depend on the effect of a corticosteroid. Additionally, the exact mechanism of action of corticosteroid injections in CTS is not fully understood. Different types of steroids have been clinically used; triamcinolone, betamethasone and methylprednisolone have been most frequently described[2,9]. The general thought is that the steroid leads to reduced inflammation and swelling of the median nerve and tendons within the carpal tunnel and consequently reduces the pressure. However, there is also support for the effect of local anesthetics in CTS[10]. Lidocaine has been shown to have a potential as an anti-inflammatory agent and might therefore contribute to the treatment effect of injections in CTS, since steroids are commonly mixed with lidocaine[11,12]. Karadas et al. assessed the effectiveness of triamcinolone acetonide versus procaine hydrochloride (HCl) injections in the management of carpal tunnel syndrome[10]. They found that procaine HCl injections were as effective as steroid injections, in terms of improved symptoms and functions on the BCTQ and improved EDS results. Since 96% of the injections in our study consisted of a mix of steroid combined with 1% lidocaine, we could not assess the effect of the anesthetic unfortunately. Furthermore, another potential mechanism of action is the mechanical effect of the volume of the injectate creating a perineural fluid plane. This mechanism is known as hydrodissection; a novel technique to treat nerve entrapment[13]. The potential of this technique will be discussed in paragraph 3.

Although greater injectate volume is associated with decreased likelihood of failure, we could not determine the optimal injection volume (mean (SD) volume used in

our study: 3.7 mL (1.2)). In addition, while trends in the observed data were reported, we would be hesitant to extrapolate effects in volumes beyond the range of values present; it is possible that the relationship of injectate volume to failure of treatment might show a different trend in higher volumes. Further research is necessary to define the optimal volume of a corticosteroid injection in CTS. A prospective study with a low and high volume injection group, using a validated outcome measure, would be ideal. Additionally, further research is necessary to identify those patients who could benefit from an injection, to provide more individually tailored treatment.

1.2.2 Prediction of treatment outcome

Carpal tunnel release

Although carpal tunnel release is considered the most effective treatment option for CTS, it is challenging to predict the outcome of carpal tunnel surgery. CTR is usually considered if there are clinical signs of median nerve denervation or symptoms persist despite trying corticosteroid injections and splinting[14,15]. As described in **chapter 4**, symptoms usually reduce after surgery for CTS. However, it remains difficult to predict how effective a CTR is for each individual patient. In **chapter 4** we showed that a low score on the BCTQ at intake was associated with less symptom improvement. Additionally, a co-diagnosis of a trigger finger, ulnar nerve neuropathy, trapeziometacarpal joint arthrosis, and instability or arthrosis of the wrist were associated with a smaller improvement in the BCTQ domains at 6 months after surgery. These results can help understand the capabilities of a CTR in terms of symptom relief for different subgroups and consequently provide information for the management of patient expectations. Additionally, the variables only accounted for 35-42% of the variance on the BCTQ in our multivariable regression models. Therefore, there must be other factors contributing to variance in treatment outcome. Mental health[16,17] and pre-operative expectations[18-20] can both influence patient reported outcomes. For example, Ring et al. reported a significant correlation between the Disabilities of the Arm, Shoulder and Hand (DASH) score and depression in patients with CTS[16]. In addition, several studies in the field of orthopedics described a significant association between higher treatment-specific expectations and better treatment outcomes[18-20]. Including these variables might contribute to a more precise prediction of treatment outcome after a CTR. Physicians can influence patient expectations and consequently treatment outcome by carefully informing the patient. Furthermore, treatment outcome could have been influenced by other factors, such as surgeon experience. Several studies have shown that higher-volume surgeons achieve better results for a specific procedure[21-23].

In **chapter 5** we focused on surgeon volume and treatment outcome after CTR. As described, we did not find a volume-outcome relationship. However, our cohort involved

highly specialized hand surgeons operating in high volume centers only. Therefore, we can only conclude that 'practice does not make perfect' in specialized hand surgeons performing CTR. Whether this is also the case for other specialists, fellows or residents performing a CTR, should be further investigated. In addition, in the case of CTS, having an experienced physician make the correct diagnosis might have greater influence on outcome than the performance of the procedure. Since CTR is considered a relatively simple procedure, part of the worse outcomes might be due to misdiagnosis rather than a suboptimal execution of the procedure. Conditions which can be mistaken for CTS are for example musculotendinous strain, cervical radiculopathy, ulnar neuropathy or thoracic outlet syndrome[24,25]. A more experienced physician might be more likely to differentiate between these conditions.

Recommendations for future research

We evaluated conventional treatment options and found that both a corticosteroid injection and CTR should be considered in the treatment of CTS patients.

In the literature, several prognostic factors for treatment outcome after corticosteroid injections for CTS have been identified. However, most of the studies included only a subset of these variables. Due to the low proportion of overlapping prognostic factors between studies, it would be difficult to pool the data of the different studies in other to perform a meta-analysis. In addition, the definition of success varied between studies. Need for additional treatment and the recurrence of symptoms are most frequently used outcome measures. Future studies should ideally use patient reported outcomes in order to measure the effect of the intervention from the patients' perspective.

In addition, clinical trials can only assess whether interventions are effective on average whereas a prediction model can be used to estimate treatment outcome for an individual patient. Therefore, large multivariable studies including all identified prognostic factors using targeted patient reported outcomes are necessary. Ideally, patient reported experience measures (PREMS) will be added to these models, since it is known that better experience with healthcare delivery is associated with better patient-reported outcomes in, for example, Dupuytren's disease[26]. In addition, since there is evidence for the association between psychological factors, such as patients expectations[20] and depression[16] and patient reported outcomes, pre-treatment psychological factors should be added to such a prediction model as well.

Up till now, there is no consensus on the effectiveness of a second or subsequent injection. However, our study on long-term follow-up of steroid injections indicated a similar success rate for the second compared to the first injection. This result justifies a comparison between long-term treatment with corticosteroid injections and CTR.

Several studies have also identified prognostic factors for surgical outcome. However,

most of these studies just considered only a subset of the variables as well. The same applies as for treatment outcome after a corticosteroid injection: large multivariable studies including all identified prognostic factors including PREMS and psychological factors, using targeted patient reported outcomes with sufficient follow-up are necessary.

Currently, little is known about the natural history of CTS. It would also be helpful to identify prognostic factors for improvement in symptoms in a cohort of patients who received a wait-and-see approach to identify who might not require an intervention.

In addition, since the exact pathophysiology of CTS is still unknown and there are probably still 'unknown unknowns' that influence treatment outcome in CTS, basic research is required in order to fully understand and consequently treat and prevent this syndrome.

To summarize, we suggest focusing on building prediction models with targeted outcome measures including psychological variables as mental health and patient expectations to be able to select the most appropriate treatment for each patient.

2. ULTRASONOGRAPHIC ASSESSMENT OF CTS

Ultrasound imaging provides accurate visualization of structures within the carpal tunnel and can consequently support the diagnosis of CTS. The most recent Dutch guideline for CTS even suggests to perform ultrasound examination, if available, as a first diagnostic tool[15]. However, up until now, there is only support for the diagnostic value of static images of the carpal tunnel. The development of high-resolution, high-frequency ultrasound transducers allows us to perform dynamic ultrasound scanning of the carpal tunnel. In the longitudinal plane we were mainly interested in the shear index between the flexor digitorum superficialis tendon of the middle finger (FDS3) and surrounding subsynovial connective tissue (SSCT), since previous studies have shown that the relative motion between FDS3 and SSCT in patients with CTS is different compared to controls[27,28]. In the transverse plane we were interested in both the morphology of the median nerve and the mobility of the nerve during motion of the hand and wrist as potential predictors of treatment outcome.

2.1 Ultrasonographic assessment in the longitudinal plane

To be able to accurately measure longitudinal motion of structures within the carpal tunnel without the use of anatomical landmarks, we proposed and validated an improved ultrasound speckle tracking algorithm using Singular Value Decomposition (SVD) in a cadaver study as described in **chapter 6**. We showed that the relative displacement errors of the tendon for the improved speckle tracking was significantly lower compared

to the original algorithm and commercial tracking. Although the shear index of the tendon and SSCT was the main variable of interest, we could not assess the validity of the motion measurements of the SSCT. Because the SSCT is a multilayered structure of approximately 0.8 mm thick[29], unfortunately, it is challenging to create a ground truth measurement. Nevertheless, after optimizing the algorithm for several parameters (**chapter 7**) we tested the reliability of the algorithm using in-vivo data of CTS patients and controls. The reliability of measurements of the FDS3 tendon, SSCT and shear index were assessed, as described in **chapter 8**. Mean intraclass-correlations (ICC) of tendon displacement varied between 0.88-0.98 in the CTS patients. SSCT tracking showed lower reliability values compared to tendon tracking but the results were still considered fair to good (ICC 0.74-0.81). As we now have a customized technique to reliably measure the motion of the tendon and SSCT within the carpal tunnel, the next step would be to use the algorithm in a clinical study and assess whether there is an association between these ultrasound parameters, especially shear index, and patient reported outcome. The parameter(s) may ultimately serve as a predictor of treatment outcome.

2.2 Ultrasonographic assessment in the transverse plane

In addition to longitudinal measurements, we focused on ultrasound measurements in a transverse plane. We explored the differences in nerve morphology and dynamics after CTR using ultrasound and assessed the association with patient-reported outcomes as described in **chapter 9.** We found that the median nerve area and perimeter decreased significantly after surgery. However, these changes were not associated with the change in clinical outcome. It has been shown that pressure within the carpal tunnel decreases directly after CTR[30], indicating that perineural edema caused by compression can reduce shortly after surgery. Nevertheless, currently it is unknown if and when changes to the fibrotic SSCT also occur after surgery. We found that excursion in the dorsal direction during wrist flexion increased after surgery, providing evidence that the nerve regains mobility in that direction. In addition, higher overall nerve mobility after surgery during finger flexion was associated with symptom relief. However, the nerve mobility at baseline was not associated with clinical outcome. Furthermore, we could not define a nerve movement threshold that captured a subpopulation that represents either good clinical outcomes or less excellent outcomes. The only baseline ultrasound parameter that was associated with clinical outcome was the cross sectional nerve area: larger cross sectional area was associated with more functional improvement. However, this variable was not associated with symptom relief. Previous studies have shown conflicting results on the predictive value of the median nerve cross sectional area, as both negative[31,32] and positive[33,34] associations between nerve area and outcomes have been found. In addition, there are also studies that found no association between median nerve area

and clinical outcome[35,36]. These conflicting findings might be due to timing of the assessments and differences in ultrasound protocols. Bland et al. concluded that one ultrasound parameter alone is unlikely to support treatment counseling for individual patients in CTS[35]. Our test-retest data from healthy volunteers indicated that there was a physiological variation in the mobility of the median nerve during finger and wrist movements. Therefore, it would be interesting to add ultrasound data of a sagittal view (longitudinal plane), since structures within the carpal tunnel move in a 3D-plane.

Recommendations for future research

As described in the first paragraph, some prognostic factors of treatment outcome in CTS have been identified. However, it remains challenging to predict treatment outcome. We hypothesized that ultrasound parameters can serve as predictors of treatment outcome. However, our clinical study showed that although the mobility of the median nerve increased after CTR, there is limited potential to use baseline ultrasound parameters for the prediction of surgical outcome. Other dynamic ultrasound parameters, such as shear index between FDS3 and the SSCT, that were not yet included in our study, might correlate with treatment outcome. Therefore we recommend assessing whether there is an association between the longitudinal ultrasound parameters and treatment outcome. Although longitudinal imaging could provide more information on SSCT dynamics, one should keep in mind that the SSCT is a relatively small structure with lower reliability values compared to tendon tracking. Right now, it seems difficult to use dynamic ultrasound in order to make a difference in understanding the pathophysiology of CTS and consequently to predict treatment outcomes. However, recent higher frequency ultrasound machines may provide increasing possibilities for imaging analyses and options for studying smaller structures such as the SSCT and for example the epineurium of the median nerve.

In addition, conservative treatment including splinting and corticosteroid injections should be topic of similar studies. The surgical outcome in our study was generally good. Clinical outcomes after a corticosteroid injection could have a greater variability. Therefore, there might be a role for ultrasound as a predictor for treatment outcome after an injection.

Because we cannot provide the optimal treatment algorithm for CTS, new ultrasound techniques, such as ultrasonographic elastography[37], which has the potential to serve as a predictor, deserve further investigation. Elastography provides information on the elasticity of tissue. Both strain[38,39] and shear wave[37] elastography have been studied in the context of CTS. Strain elastography applies compressive force to tissue and measures stiffness (semi-quantitative measure), whereas shear wave is a quantitative measurement of elasticity of tissue based on the velocity of shear waves (in stiffer tissue,

the shear waves travel faster). It has been shown that the median nerve is stiffer in CTS patients compared to healthy controls[37,38]. Whether there is an association between stiffness of the median nerve and clinical outcome needs to be further investigated.
To summarize, up until now, dynamic ultrasound seems to have limited potential in predicting surgical outcome in CTS. Whether this is also the case for conservative treatment options such as splinting and corticosteroid injections should be further investigated. In addition, since we still cannot provide the optimal treatment algorithm for CTS, new ultrasound techniques should be topic of future studies.

3. ULTRASOUND GUIDANCE IN THE TREATMENT OF CTS

3.1. Effectiveness of ultrasound-guided injections

Besides serving as a diagnostic tool, ultrasound can also be used to guide therapeutic injections.
In **chapter 10** we described the effectiveness of ultrasound-guided injections compared to blind injections in the treatment of CTS. We found reduced odds of retreatment within one year for ultrasound-guided injections compared to blind injections. However, our study lacked a validated outcome measure, such as the symptom and function domains of the BCTQ. In addition, ultrasound guidance might have served as a placebo. Despite the limitations of our study, it was the first longitudinal study on ultrasound guidance in carpal tunnel injections and the results justified a clinical trial.
A recent systematic review and meta-analysis on the effectiveness of ultrasound-guided compared to anatomically-guided local corticosteroid included three randomized controlled trials (RCTs), involving a total of 181 analyzed hands[40]. The review suggested that ultrasound-guided injection was more effective than anatomically-guided injection in reducing symptom severity at 12 weeks post-injection. Nonetheless, the pooled data did not show significant differences in functional status or electrodiagnostic improvements between the two techniques. A limitation of all three included RCTs was lack of blinding. Just like our study, ultrasound guidance could have resulted in greater symptom severity improvement due to a placebo effect. Recently, Chen et al. performed a clinical trial that was not included in the described systematic review[41]. A strength of their study was that they used sham ultrasound-guidance so that patients remained blind to their allocation throughout the trial. They found that the ultrasound-guided injection group showed greater improvements in the Semmes-Weinstein Monofilament test, sensory nerve conduction velocity, and digit-4 comparison study (median-to-ulnar sensory nerve distal latency difference measured at the ring finger). However, contrary to what the systematic review concluded, Chen et. al did not find a difference in symptom severity between the two groups. Nevertheless, with 22 wrists included in

the ultrasound group and 17 in the blind injection group, their statistical power might have been too low. A trial including more patients should confirm the results.
Based on the current data we cannot conclude whether ultrasound should be used routinely to guide injections in CTS. Further research including larger sample sizes is necessary. Additionally, other potential beneficial effects of ultrasound should be taken into consideration. For example, ultrasound guidance can potentially lead to a decreased risk of median nerve and surrounding tissue damage. In addition, cost-effectiveness should be assessed. Makhlouf et al. found a reduction in costs for responders in the ultrasound-guided group relative to the blind injection group in CTS as there lies a reduction in costs of additional treatment[42]. Whether the routine use of ultrasound guidance leads to an overall cost reduction should be further investigated.

3.2. Ultrasound-guided hydrodissection

While some reports have anecdotally described the use of ultrasound-guided hydrodissection[43-45], the underlying mechanism of action has not been investigated. In **chapter 11** we described a cadaveric study in which we have shown that ultrasound-guided hydrodissection decreases gliding resistance within the carpal tunnel. However, it is too early to draw conclusions about this new technique. Firstly, our experiment did not include arms with CTS and due to the set-up the study cannot be extrapolated to the clinic directly. Nevertheless, our cadaveric study showed support for the theoretical mechanism of action of hydrodissection and therefore a clinical study assessing the effectiveness of hydrodissection seems justified. To support the thought that hydrodissection can break adhesions, a study in which ultrasound-guided hydrodissection with saline has superior effect to injecting saline just proximal from the carpal tunnel is necessary. In addition, the clinical safety of ultrasound-guided hydrodissection should be investigated. Furthermore, case selection might be important. Patients with more severe CTS might be more likely to benefit from hydrodissection. A randomized controlled trial with subject blinding, is necessary to assess whether ultrasound-guidance, with or without hydrodissection, is more effective compared to a blind injection in CTS. In addition, the optimal injection volume should be established.

Recommendations for future research

Although ultrasound-guided injections and additionally, hydrodissection have shown potential, we should be hesitant about implementing these new techniques. Based on our findings, we recommend performing well-designed randomized controlled trials prior to clinical implementation, since there is not enough support for the effectiveness of ultrasound-guided injections in reducing symptoms compared to blind injections and the clinical use of hydrodissection has not been investigated well.

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SUMMARY

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy, with a prevalence of 1-4% of the population. Although CTS is a mononeuropathy that only affects a small part of the median nerve, it is a serious health problem that can result in decreased quality of life due to sleep disturbance and can interfere with one's ability to work. The aims of this thesis were 1) to explore factors that influence treatment outcome in CTS, 2) to assess the prognostic role of ultrasound and 3) to assess its value to guide interventions in the treatment of CTS.

PART I: TREATMENT OUTCOMES OF CTS

Recommended treatment options for CTS include splinting, local steroid injection and carpal tunnel release (CTR). Most guidelines recommend splinting or a corticosteroid injection before proceeding to surgery, if axonal loss or denervation of the median nerve innervated muscles are absent. Nevertheless, the role of injections remains controversial since there is only strong evidence for short-term benefits. In addition, up till now, it remains difficult to predict treatment outcome for a patient with CTS. In **chapter 2** we evaluated the reintervention rate after a corticosteroid injection for CTS in a population based cohort and prognostic indicators for subsequent treatment were identified. In the sample of 774 affected hands, with a median follow-up period of 7.4 years, reintervention was performed in 68% of cases (N=525) with eventual CTR in 63% of cases (N=485). The presence of rheumatoid arthritis was associated with both reduced rate of any retreatment (hazard ratio 0.627, 95% confidence interval: 0.404-0.97) and reduced rate of surgery (hazard ratio 0.493, 95% confidence interval: 0.292-0.83). Since 32% of the patients did not receive subsequent treatment after a single injection, the study indicated that there is a therapeutic role for corticosteroid injections in the treatment of CTS. In **chapter 3** we looked further into the association between corticosteroid injection volume and the rate of subsequent intervention in CTS since the optimal volume of corticosteroid injections for the treatment of CTS has not yet been established. In this study, 856 affected hands in 651 patients were included. We found that 65% of the treated hands received subsequent treatment within 1 year. Larger injectate volume was significantly associated with reduced rate of treatment failure within one year. Severe electrodiagnostic results were associated with increased rate of failure.

The ability to determine the prognosis after CTR can help manage patient expectations and may consequently improve treatment satisfaction. In **chapter 4** we described predictors for symptom relief after CTR and the contribution of these factors in predicting the amount of symptom relief. A cohort of 1049 patients who underwent CTR at one of eleven outpatient hand clinic locations (Xpert Clinic, the Netherlands) completed online

questionnaires at intake, three and six months postoperatively. The primary outcome measure was the amount of symptom relief on the Boston Carpal Tunnel Questionnaire (BCTQ)-score. A low score on the BCTQ at intake, a co-diagnosis of a trigger finger, ulnar nerve neuropathy, trapeziometacarpal joint arthrosis, and instability or arthrosis of the wrist were associated with smaller improvements in the BCTQ domains after a CTR at six months postoperatively. These factors accounted for only 35-42% of the variance on the BCTQ domains, indicating that other non-examined variables play a role.

There is growing evidence that more experienced surgeons have better patient outcomes following a variety of surgical procedures. In **chapter 5** we assessed whether there is an association between surgeon volume and patient outcomes following open CTR. The study was based on 1345 patients, operated on by seventeen hand surgeons working in high volume centers. Median (interquartile range) annual surgeon volume was 75 (50 - 149) CTRs. We found that all hand surgeons had similar patient outcomes at six months after surgery and that their annual volume did not influence patient outcome.

PART II: ULTRASONOGRAPHIC ASSESSMENT OF CTS

There is expanding evidence for the added value of ultrasound in managing CTS. Thus far, most research focused on the cross sectional area of the median nerve. Nevertheless, additional to static transverse imaging, longitudinal and dynamic assessment of structures within the carpal tunnel have also gained interest. In CTS patients, fibrosis of subsynovial connective tissue (SSCT) may result in altered dynamics of the structures within the carpal tunnel. Assessing these alterations might influence the clinical diagnosis process and support treatment choice.

Longitudinal motion analysis on ultrasound images using ultrasound speckle tracking allows studying the (relative) motion of tendons. Nonetheless, formerly developed tendon displacement quantification algorithms tend to suffer from underestimation due to stationary background. To increase the robustness of the previously developed customized speckle tracking algorithm, we investigated a novel technique to reduce the effect of clutter and noise as described in **chapter 6.** Singular Value Decomposition filtering was used to suppress clutter and potentially improve the speckle tracking. The accuracy of our improved speckle tracking method was validated against a ground truth and compared to the accuracy of the original algorithm and to a standard commercial tissue tracking tool. For this comparison, the ground truth displacements were generated by analyzing the ultrasound recordings of six human cadaver arms. Inserted metal markers within the tendons were tracked and served as the ground truth. The mean relative displacement error with respect to the ground truth for the improved method was 12 ± 16.9%, which was significantly lower than for the original

speckle tracking (19.7 ± 20.8%) and the commercial tool (25.8 ± 18.4%). This study demonstrated that SVD filtering improves tendon tracking.

Since it is known that even the improved algorithm is sensitive to different ultrasound settings, various parameters involved in the algorithm were optimized for best tracking accuracy using one human cadaver arm as described in **chapter 7**. Parameters such as frame difference, number of kernels and kernel size in the region of interest and filtering parameters were optimized. The ground truth was again generated by tracking a metal marker inserted in the tendon. An overall minimum relative error of 3.2 ± 2.3% was observed using the improved algorithm compared to 7.4 ± 4.8% using the original method.

After validating our new speckle tracking technique in **chapter 6** and **7**, its reliability was tested in **chapter 8**. Ultrasound images of the third superficial flexor tendon and surrounding SSCT from sixteen healthy volunteers and twenty-two CTS patients were acquired during flexion-extension of the middle finger. The clips were analyzed using our improved speckle tracking algorithm. Both the tendon and the SSCT were tracked. Subsequently, a shear index (relative motion between tendon and SSCT) was calculated. Mean intra-class correlation coefficients (ICCs) varied between 0.73-0.95 in the control group and 0.66-0.98 in CTS patients. Tendon tracking (mean ICC range: 0.82-0.95) showed higher reliability values compared to the SSCT tracking (mean ICC range: 0.70-0.93) and the shear index (mean ICC range: 0.66-0.87). Values between the control and CTS groups were comparable. We concluded that SVD enhanced speckle tracking can reliably be used to analyze (relative) longitudinal SSCT displacement.

In **chapter 9** we explored differences in nerve dynamics after CTR and assessed the association with patient-reported outcome. Ultrasound and clinical data were collected before and three months following CTR. Both static ultrasound measurements and nerve mobility measurements during finger and wrist flexion in the transverse plane were acquired. Our primary outcomes were changes in the symptom severity and functional status scales of the BCTQ. A total of 85 patients were included in the study. Median nerve area (-1.3 mm^2) and perimeter (-0.6 mm) decreased significantly after surgery. Displacement in dorsal direction during wrist flexion increased (0.54 mm). An increase in radio-ulnar displacement and higher overall nerve mobility after surgery during finger flexion was associated with symptom relief. A larger cross sectional nerve area at baseline was significantly associated with more functional improvement, but not with symptomatic relief. None of the baseline nerve mobility parameters showed an association with clinical outcome. In addition, we could not define a nerve movement threshold that evidently captured a subpopulation that represents either good or no symptomatic improvement.

PART III: ULTRASOUND GUIDANCE IN THE TREATMENT OF CTS

The third part of this thesis focused on the role of ultrasound in the guidance of interventions in CTS. Firstly, the effectiveness of ultrasound-guided injections was compared with blind injections in **chapter 10.** The study evaluated residents of Olmsted County, MN, USA, treated with a corticosteroid injection for CTS. The proportion of patients requiring retreatment; either a second injection or CTR, as well as the duration of retreatment-free survival between blind and ultrasound-guided injections were compared after controlling for confounding by indication with the use of propensity score matching. In the matched dataset consisting of 234 hands treated with a blind injection and 87 ultrasound-guided injection cases, 57% of the blind injection and 41% of the ultrasound-guided injection group had 'failure' of treatment within one year. Analysis of retreatment-free survival showed an adjusted hazard of retreatment in favor of the ultrasound-guided group (hazard ratio 0.59, 95% confidence interval: 0.37 - 0.93). Additionally, binary logistic analysis indicated that ultrasound guidance was associated with 55% reduced odds of retreatment within one year compared to blind injections (adjusted odds ratio 0.45; 95% confidence interval: 0.24 - 0.83). Thus, we concluded that ultrasound-guided injections are more effective compared to blind injections in the treatment of CTS.

Different techniques of ultrasound guidance in carpal tunnel injections have been described. Recently, ultrasound-guided hydrodissection has been proposed to treat (median) nerve entrapment. In **chapter 11** we assessed alterations in the biomechanics of the median nerve environment resulting from ultrasound-guided hydrodissection in a cadaveric model. Twelve human cadaver hands were used of which 6 were treated with hydrodissection and 6 were used as controls. In the hydrodissection group there was a significant reduction in mean peak gliding resistance of 21.4% ± 10.5% between baseline and post-hydrodissection. We did not find a reduction in mean peak gliding resistance between baseline and the second cycle in the control group. The results indicate that hydrodissection can decrease the gliding resistance of the median nerve within the carpal tunnel in cadaveric wrists unaffected by CTS. We therefore concluded that a clinical trial of hydrodissection is justified.

The final **chapter** (**12**) provided a general discussion including future research perspectives. Tunnel vision in CTS research should be avoided, since it remains difficult to predict treatment outcome and there is need for better understanding of formerly unknown prognostic variables such as psychological factors and patient expectations. Future studies will ultimately develop a multivariable model to help guide decision-making in the management of CTS. The added value of tunnel vision using ultrasound (both statically and dynamically acquired in different views) in such a model should be

further investigated. In addition, we provided evidence for the usefulness of ultrasound in the guidance of interventions in CTS, which should be further investigated in a well-designed clinical trial.

14

NEDERLANDSE SAMENVATTING

Carpaletunnelsyndroom (CTS) is de meest voorkomende perifere neuropathie met een prevalentie van 1-4%. Alhoewel CTS een mononeuropathie is die alleen een klein deel van de nervus medianus betreft, is het een serieus gezondheidsprobleem dat kan resulteren in een verminderde kwaliteit van leven door verstoring van de slaap en het interfereren met het vermogen om te kunnen werken. Het doel van dit proefschrift was om factoren die de behandelingsuitkomst van CTS beïnvloeden, te onderzoeken. Daarnaast werden zowel de prognostische waarde van echografisch onderzoek als de rol van echografie bij de geleiding van interventies in de behandeling van CTS onderzocht.

DEEL I: BEHANDELINGSUITKOMST VAN CTS

Zowel conservatieve therapie (spalk immobilisatie en corticosteroïd-injectie) als release van de carpale tunnel (CTR) zijn aanbevolen behandelingsopties voor CTS. Alhoewel axonale degeneratie of denervatie van de door nervus medianus geïnnerveerde spieren chirurgie rechtvaardigden, raden de meeste richtlijnen conservatieve therapie aan alvorens chirurgisch in te grijpen. Echter, de rol van injecties in de behandeling van CTS is controversieel, omdat er alleen sterk bewijs voor het kortetermijneffect is. Bovendien is het tot op heden lastig om de behandelingsuitkomst voor een patiënt met CTS te voorspellen.

In **hoofdstuk 2** werd het aantal herinterventies na een corticosteroïd-injectie voor CTS geëvalueerd en werden voorspellende factoren voor aanvullende behandeling geïdentificeerd. In de sample van 774 aangedane handen, met een mediane follow-up van 7.4 jaar, werd in 68% van de gevallen een herinterventie uitgevoerd en resulteerde 63% in een CTR. Het hebben van reumatoïde artritis was geassocieerd met een verminderd aantal totale herinterventies (hazard ratio 0.627, confidence interval: 0.404-0.97]) en een verminderd aantal CTR's (hazard ratio 0.493, confidence interval: 0.292-0.83). Aangezien 32% van de patiënten geen aanvullende behandeling kreeg na de initiële injectie, suggereert de studie dat er een therapeutische rol is voor corticosteroïd-injecties in de behandeling van CTS.

In **hoofdstuk 3** onderzochten we de associatie tussen het volume van de corticosteroïd-injectie en het aantal herinterventies, omdat het optimale volume van een steroïdinjectie in de behandeling van CTS nog niet is vastgesteld. In deze studie werden 856 aangedane handen in 651 patiënten geïncludeerd. In deze sample had 65% een aanvullende behandeling binnen één jaar. Een hoger volume injectie was geassocieerd met een afgenomen aantal herinterventies binnen één jaar. Een 'slechte' electrodiagnostische studie was geassocieerd met een toegenomen aantal herinterventies.

Het vermogen om de prognose na een CTR in te schatten, kan helpen om verwachtingen van patiënten te sturen en zou kunnen leiden tot een hogere patiënttevredenheid.

In **hoofdstuk 4** werden voorspellers van symptoomverlichting na een CTR en de bijdrage van deze factoren in het voorspellen van de mate van symptoomverlichting beschreven. Een cohort van 1049 patiënten die een CTR ondergingen in een van de elf handklinieken (Xpert Clinics, Nederland) vulden online vragenlijsten in op intake, drie en zes maanden postoperatief. De mate van symptoomverlichting op de Boston Carpal Tunnel Questionnaire (BCTQ)-score was de primaire uitkomstmaat. Een lage score op de BCTQ op intake, een co-diagnose van trigger vinger, nervus ulnaris neuropathie, carpometacarpale-1 artrose en instabiliteit of artrose van de pols waren geassocieerd met een kleinere verbetering in de BCTQ-domeinen na zes maanden postoperatief. Deze factoren verklaarden 35-42% van de variantie in de behandelingsuitkomst tussen patiënten. Dit suggereert dat andere factoren die hier niet zijn onderzocht, een rol spelen.
Er is toenemend bewijs dat meer ervaren chirurgen betere behandelingsresultaten hebben binnen een verscheidenheid aan procedures. In **hoofdstuk 5** is onderzocht of er een associatie is tussen chirurgisch volume en behandelingsuitkomst op zes maanden na een CTR. De studie was gebaseerd op 1345 patiënten, geopereerd door zeventien handchirurgen die allen werken in hoog-volume klinieken. Het mediane (interquartile range) jaarlijks chirurgisch volume was 75 (50 – 149) CTR's. Alle handchirurgen hadden vergelijkbare behandelingsresultaten en hun jaarlijks chirurgisch volume beïnvloedde de behandelingsuitkomst niet.

DEEL II: ECHOGRAFISCH ONDERZOEK BIJ CTS

Er is toenemend bewijs voor de toegevoegde waarde van echografie in de diagnostiek van CTS. Het meeste onderzoek heeft zich hierbij op de oppervlakte van de dwarsdoorsnede van nervus medianus gericht. Echter, naast statische transversale beeldvorming zijn ook longitudinale en dynamische evaluatie van de structuren in de carpale tunnel meer in de aandacht komen te staan. In patiënten met CTS kan fibrose van het subsynoviale bindweefsel (SSCT) resulteren in een veranderde dynamiek van structuren in de carpale tunnel. Het meten van deze veranderingen kan mogelijk het diagnoseproces beïnvloeden en de keuze voor een bepaalde behandeling ondersteunen.
Door middel van longitudinale bewegingsanalyse met behulp van speckle tracking van echobeelden kan de (relatieve) excursie van pezen worden onderzocht. Echter, eerder ontwikkelde algoritmes om peesexcursie te kwantificeren worden beïnvloed door statische achtergrondsignalen. De peesexcursie kan hierdoor worden onderschat. Om de robuustheid van het originele speckle tracking algoritme te verbeteren, werd een nieuwe techniek die het effect van ruis en clutter kan verminderden onderzocht (**hoofdstuk 6**). *Singular Value Decomposition* filtering werd gebruikt om clutter te onderdrukken

en zodoende de speckle tracking resultaten te verbeteren. De nauwkeurigheid van de vernieuwde speckle tracking methode werd gevalideerd door middel van een vergelijking met een *ground truth*. De vernieuwde tracking werd tevens vergeleken met de nauwkeurigheid van het originele algoritme en met standaard commerciële weefsel-tracking software. De ground truth-excursies werden gegenereerd door het analyseren van de echobeelden van zes menselijke kadaverarmen. Metalen markers die in de pezen werden geplaatst, werden getrackt en dienden als de ground truth-meting. De gemiddelde relatieve meetfout in verhouding tot de 'ground truth' was 12 ± 16.9% voor de vernieuwde methode en significant lager dan voor het originele algoritme (19.7 ± 20.8%) en voor de commerciële tool (25.8 ± 18.4%). Deze studie laat zien dat Singular Value Decomposition filtering tracking van peesexcursies verbetert.

Aangezien het bekend is dat zelfs het vernieuwde algoritme gevoelig is voor verschillende echosettings, werden verscheidene parameters betrokken bij het algoritme geoptimaliseerd voor de meest nauwkeurige tracking. Hiervoor werd één menselijke kadaverarm gebruikt (**hoofdstuk 7**). Parameters zoals *frame difference*, aantal kernels en kernelgrootte in de *region of interest* en filtering parameters werden geoptimaliseerd. De 'ground truth' werd opnieuw gegenereerd door het tracken van een metalen marker in de pees. Een overall minimale relatieve meetfout van 3.2± 2.3% werd gevonden voor het vernieuwde algoritme vergeleken met 7.4± 4.8% voor de originele tracking methode.

Na het valideren van de verbeterde speckle tracking-techniek in **hoofdstuk 6** en **7**, werden de test-hertest en intra- en interbeoordeelaarsbetrouwbaarheid getoetst in **hoofdstuk 8**. Echobeelden van de oppervlakkige buigpees van de middelvinger en omliggende SSCT van 16 gezonde vrijwilligers en 22 CTS-patiënten werden opgenomen gedurende flexie-extensie van de middelvinger. De echobeelden werden geanalyseerd met behulp van het verbeterde speckle tracking-algoritme. Zowel de pees als de SSCT werden getrackt. Vervolgens werd een shear index (relatieve verplaatsing tussen de pees en de SSCT) berekend. De gemiddelde intra-class correlatie coëfficiënten (ICC's) varieerden tussen 0.73-0.95 in de controlegroep en 0.66-0.98 in CTS patiënten. Tracking van pezen (gemiddelde ICC range: 0.82-0.95) toonde een hogere betrouwbaarheid vergeleken met tracking van de SSCT (gemiddelde ICC range: 0.70-0.93) en shear index (gemiddelde ICC range: 0.66-0.87). De betrouwbaarheid tussen de controle en CTS-groep was vergelijkbaar. We concludeerden dat speckle tracking met Singular Value Decomposition betrouwbaar de (relatieve) longitudinale SSCT excursie kan analyseren.

In **hoofdstuk 9** werden de verschillen in dynamiek van de nervus medianus voor en na een CTR geëvalueerd en onderzochten we de associatie met *patient-reported outcomes*. Echobeelden en klinische data werden verzameld voor en drie maanden na chirurgie. Er werden zowel statische echobeelden opgenomen voor het evalueren van de morfologie

van de zenuw als dynamische beelden voor het in kaart brengen van zenuwmobiliteit gedurende de vinger- en polsflexie. De primaire uitkomstmaten waren veranderingen in de twee domeinen (symptomen en functionaliteit) van de BCTQ. In totaal werden er 85 patiënten geïncludeerd in de studie. De mediane oppervlakte van de zenuw (-1.3 mm^2) en de perimeter (-0.6 mm) verminderden significant na chirurgie. De excursie in de dorsale richting nam toe (0.54mm) tijdens polsflexie. Een toename van de excursie in de radio-ulnaire richting en een hogere *overall* zenuwmobiliteit na chirurgie tijdens vingerflexie waren geassocieerd met symptoomverlichting. Een grotere dwarsoppervlak van de zenuw was geassocieerd met meer functionele verbetering, maar niet met symptoomverlichting. Geen van de baseline zenuwmobiliteit-parameters toonde een associatie met patient reported outcome. Daarnaast konden we geen drempelwaarde van de zenuwexcursie definiëren op basis waarvan een subpopulatie kon worden onderscheiden die een goede dan wel een minder goede uitkomst representeerde.

DEEL III: ECHOGELEIDING IN DE BEHANDELING VAN CTS

Het derde deel van dit proefschrift richt zich op de rol van echogeleiding van interventies in CTS.

Eerst werd de effectiviteit van echogeleide injecties vergeleken met 'blinde' injecties in **hoofdstuk 10**. In de studie werden inwoners van Olmsted County, MN, VS, die waren behandeld met een corticosteroïd-injectie voor CTS geëvalueerd. Zowel het percentage van de patiënten dat een herinterventie onderging (dan wel een tweede injectie, dan wel een CTR) als de duur van het herinterventie-vrije interval tussen 'blinde' en echogeleide injecties, werden vergeleken na het controleren van *confounders* door het gebruik van propensity score matching. In de *matched* dataset van 234 handen behandeld met een 'blinde' injectie en 87 echogeleide injecties, had 57% van de 'blinde' injecties en 41% van de echogeleide injectiegroep een herinterventie binnen 1 jaar. Analyse van het herinterventie-vrije interval toonde een *adjusted hazard* van herinterventie in het voordeel van de echogeleide groep (hazard ratio 0.59, 95% confidence interval: 0.37 - 0.93). Daarnaast toonde binaire logistische regressie dat echogeleiding was geassocieerd met 55% verminderde kans op een herinterventie binnen één jaar vergeleken met 'blinde' injecties (adjusted odds ratio 0.45; 95% confidence interval: 0.24 - 0.83). We concludeerden dan ook dat echogeleide injecties effectiever zijn dan 'blinde' injecties in de behandeling van CTS.

Verschillende technieken van echogeleiding injecties in CTS zijn beschreven. Echogeleide hydrodissectie is een recent aangedragen techniek om zenuwbeknelling te behandelen.

In **hoofdstuk 11** werden veranderingen in de biomechanica van de nervus medianus als resultaat van echogeleide hydrodissectie onderzocht in een kadavermodel. Twaalf menselijke kadaverarmen werden gebruikt, waarvan zes werden behandeld met hydrodissectie en zes werden gebruikt als controles. In de hydrodissectiegroep was er een significante reductie in gemiddelde *peak gliding resistance* van 21.4% ± 10.5% tussen baseline en posthydrodissectie. We constateerden dat er geen reductie was van de gemiddelde peak gliding resistance tussen baseline en de tweede cyclus in de controlegroep. Dit resultaat suggereert dat hydrodissectie de gliding resistance van de nervus medianus in de carpale tunnel in een niet-aangedane kadaverpols kan verlagen. Op basis hiervan concludeerden wij dat een klinische trial voor het onderzoeken van het effect van hydrodissectie gerechtvaardigd is.

Het laatste **hoofdstuk** (**12**) is een algemene discussie en bevat toekomstige onderzoeksperspectieven.
Tunnelvisie in onderzoek naar CTS zou moeten worden vermeden, omdat het voorspellen van de behandelingsuitkomst moeilijk blijft en we eerder onbekende prognostische variabelen, zoals psychologische factoren en verwachtingen van de patiënt, eerst beter moeten begrijpen. Toekomstige studies zouden idealiter een multivariabel model ontwikkelen om besluitvorming in de management van CTS te kunnen ondersteunen. De toegevoegde waarde van tunnelvisie door middel van echografie (zowel statisch als dynamisch in verschillende vlakken) in zo'n model moet verder worden onderzocht. Daarnaast hebben we bewijs voor de potentie van echogeleide interventies in CTS aangedragen, welke verder moet worden onderzocht in een klinische trial.

A

APPENDICES

LIST OF PUBLICATIONS

3D Volumetric measurements of neurofibromatosis type-2 associated meningiomas: association between tumor location and growth rate.
Evers S, Verbaan D, Sanchez E, Peerdeman SM. World Neurosurg. 2015 Oct;84(4):1062-9

Effectiveness of ultrasound-guided compared to blind steroid injections in the treatment of carpal tunnel syndrome.
Evers S, Bryan AJ, Sanders TL, Selles RW, Gelfman R, Amadio PC. Arthritis Care Res (Hoboken). 2017 Jul;69(7):1060-1065

Corticosteroid injections for carpal tunnel syndrome: long-term follow-up in a population-based cohort.
Evers S, Bryan AJ, Sanders TL, Gunderson T, Gelfman R, Amadio PC. Plast Reconstr Surg. 2017 Aug;140(2):338-347

Improved tendon tracking using Singular Value Decomposition clutter suppression.
Bandaru RS, Evers S, Bosch JG, Thoreson AR, Selles RW, Amadio PC. Conference paper: 2017 IEEE International Ultrasonics Symposium (IUS)

Ultrasound-guided hydrodissection decreases gliding resistance of the median nerve within the carpal tunnel.
Evers S, Thoreson AR, Smith J, Zhao C, Amadio PC. Muscle Nerve. 2018 Jan;57(1):25-32

Influence of injection volume on rate of subsequent intervention in carpal tunnel syndrome over 1-year follow-up.
Evers S, Bryan AJ, Sanders TL, Gunderson T, Gelfman R, Amadio PC. April 2018. J Hand Surg Am. 2018 Jun;43(6):537-544

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Bandaru RS, Evers S, Bosch JG, Thoreson AR, Selles RW, Amadio PC. IEEE J Biomed Health Inform. 2019 Mar;23(2):817-824

Hand surgeons performing more open carpal tunnel releases do not show better patient outcomes.
Evers S, Jansen M, Slijper H, de Haas KP, Smit X, Hovius SER, Selles RW. June 2018. Plast Reconstr Surg. 2018 Jun;141(6):1439-1446

Predicting clinical outcome after surgical treatment in patients with carpal tunnel syndrome.
Jansen M, Evers S, Slijper H, de Haas KP, Smit X, JT Porsius, PC Amadio, Hovius SER, Selles RW. J Hand Surg Am. 2018 Dec;43(12):1098-1106

Reliability of ultrasound speckle tracking with Singular Value Decomposition for quantifying displacement in the carpal tunnel.
Schrier VJMM, Evers S, Bosch JG, Selles RW, Amadio PC. J Biomech. 2019 Mar 6;85:141-147

PHD PORTFOLIO

PhD student: Stefanie Evers
PhD period: 2015 – 2018
Promotor: Prof.dr. S.E.R. Hovius
Copromotor: Dr. R.W. Selles

1. PhD training	Year	Workload (ECTS/hours)
General courses		
Human Subject Protection training program, Mayo Clinic	2015	0.7 ECTS
Critical Thinking and Scientific Writing, Mayo Clinic Graduate School	2016	2 ECTS
Scientific Integrity, Erasmus MC	2018	0.3 ECTS
Specific courses and training		
Biostatistics for Clinicians, NIHES Erasmus MC	2015	0.7 ECTS
Diagnostic Research, NIHES Erasmus MC	2015	0.9 ECTS
Regression Analysis for Clinicians, NIHES Erasmus MC	2015	1.4 ECTS
Principles of Epidemiologic Data-analysis, NIHES Erasmus MC	2015	0.7 ECTS
Logistic Regression, Mayo Clinic Graduate School	2016	1 ECTS
Propensity Scoring Methods for Observational Health Services Research, Mayo Clinic Graduate School	2016	1 ECTS
Introduction to medical imaging, Mayo Clinic Graduate School	2017	2 ECTS
Microvascular Surgery Training, Mayo Clinic	2016	40 hours
Microsurgery, Erasmus MC SkillsLab	2018	50 hours
Seminars and workshops		
Research meetings and Hand Surgery grand rounds, Mayo Clinic	2015-2017	2 ECTS
Patrick J. Kelly Research day, Mayo Clinic	2016	10 hours
Workshop Nerve Reconstruction, Erasmus MC SkillsLab	2017	0.2 ECTS
Presentations at (inter)national conferences		
Oral presentations		
Federation of the European Societies for Surgery of the Hand, Eurohand 2017, Budapest	2017	20 hours
Pre- and postoperative dynamic ultrasound assessment of the median nerve in patients undergoing carpal tunnel release.		

Association between ultrasound assessment of median nerve deformation and excursion and clinical outcome after carpal tunnel release.		
Dutch Society for Plastic Surgery (NVPC), scientific meeting (fall)	2017	15 hours
Is there are a relationship between treatment outcome of carpal tunnel release and the number of procedures carried oud by the surgeon?		

Poster presentations

Orthopaedic Research Society-annual meeting, Orlando		10 hours
The efficacy of Ultrasound-Guided injections compared to blind injections in the treatment of carpal tunnel syndrome.		
American Association for Hand Surgery-annual meeting, Hawaii		10 hours
Corticosteroid injections for Carpal Tunnel Syndrome: long-term follow-up in a population-based cohort.		
Biomechanical assessment of ultrasound-guided hydrodissection on median nerve mobility in a cadaveric model.		
Orthopaedic Research Society-annual meeting, San Diego		10 hours
Sonographic measurements of the epineurium: comparison of the thickness of the epineurium in carpal tunnel syndrome patients and healthy controls.		

Attendance at (inter)national conferences

Mayo Orthopaedic Research Alumni Association (MORAA), Rochester, USA	2015	10 hours
Big hand event, UMC Utrecht	2017	10 hours
Oncoplastic breast surgery, Esser Course, Rotterdam	2017	10 hours

2. Teaching	Year	Workload (ECTS/hours)
Supervising students		
Master's student, Scientific Internship, Mayo Clinic *'Sonographic measurements of the epineural sheath of the median nerve: comparison between patients with carpal tunnel syndrome and healthy controls.'*	2016	84 hours
Bachelor's student, Honours Programme Clinical Technology, TU Delft *'Validity and reliability of ultrasound speckle tracking to quantify tendon displacement in the carpal tunnel.'*	2016-2017	84 hours
Minor students, Erasmus MC '*Prognostic factors predicting effectiveness of corticosteroid injections for carpal tunnel syndrome*.'	2016	15 hours
Skills		
Teaching ultrasound examination of the carpal tunnel, ultrasonographer at Mayo Clinic & Master's student at Erasmus MC	2016-2017	50 hours

CURRICULUM VITAE

Stefanie Evers was born in Zwolle, the Netherlands, on October 21st 1985. After graduating from Thorbecke Scholengemeenschap in 2003, she spent 1 year in Australia and then moved to Amsterdam to study Human Movement Sciences at the VU University. She obtained her bachelor's degree in Human Movement Sciences and got accepted into medical school in 2008.

Her first research experience was gained at Boston Children's Hospital under the supervision of dr. J.R. Madsen, where she studied dynamics of hydrocephalus. She continued doing research at the department of Neurosurgery at the VU medical center, on meningiomas under the supervision of prof.dr. S.M. Peerdeman. In addition, she worked as a retrieval technician performing bone and tendon explantations at the foundation of Bio Implant Services in Leiden.

During her studies, she became convinced she wanted to become a plastic surgeon. In order to accomplish that, she started her career as a trainee at the department of General Surgery of the Spaarne Hospital, Hoofddorp in 2014. Her PhD-training started in 2015 under the supervision of prof.dr. S.E.R. Hovius and prof. P.C. Amadio at the Mayo Clinic in Rochester. In 2017 she returned to the Netherlands and worked as a trainee at the department of General Surgery (prof.dr. J.M. Hendriks) and subsequently at the department of Plastic Surgery of the Erasmus Medical Center (prof.dr. I.M.J. Mathijssen). After her traineeship, she was accepted for Plastic Surgery residency and subsequently started her residency at the department of General Surgery of the Franciscus Gasthuis & Vlietland Hospital in Rotterdam on the 1st of February 2019 (dr. T.A.M.L. Klem).

DANKWOORD

Dr. William Mayo zei het al: 'no one is big enough to be independent of others' en dat geldt ook voor de totstandkoming van dit proefschrift. Graag wil ik een aantal mensen in het bijzonder bedanken.

Mijn promotor, prof.dr. S.E.R. Hovius. Beste prof, veel dank voor uw vertrouwen in mij als promovendus. Dank voor uw adviezen en kritische blik tijdens het doornemen van de laatste stukken, maar ook voor het oefenen van mijn sollicitatiegesprek (rust, rust, rust). Ik heb het enorm gewaardeerd dat u daarvoor de tijd nam!

Mijn copromotor, dr. R.W. Selles. Beste Ruud, ik kan me nog goed herinneren dat ik de eerste keer mee kwam kijken bij een lab-meeting in het EMC. We hadden een raakvlak door ons beider achtergrond in de bewegingswetenschappen en een paar maanden later mocht ik solliciteren naar deze promotieplek. Dank voor de motiverende Skype-gesprekken en jouw pragmatische oplossingen als ik het even niet meer zag zitten aan de andere kant van de oceaan!

Dr. P.C. Amadio, dear Peter, thank you for giving me the opportunity to work at the Mayo Clinic as a research fellow on the DUCATS project. It has been an honor to work with you, a pioneer in the field of orthopedic research. Your passion for research and sharp intellect are unique and inspiring. I really appreciate your effort to come all the way from Minnesota to participate in the graduation committee!

Beste dr. J.G. Bosch, beste Hans, dank voor alle uren die jij hebt besteed aan het ontwikkelen en optimaliseren van ons speckle-tracking algoritme. Daarnaast veel dank dat jij in de leescommissie wilde plaatsnemen.

Overige leden van de commissie, prof.dr. J.H. Coert en prof.dr. B.W. Koes, veel dank voor het lezen en beoordelen van dit proefschrift. Dr. E.H.G. Oei en dr. E. Walbeehm, dank voor uw bereidheid om plaats te nemen in de grote commissie.

Colleagues from the Biomechanics lab, thank you for your support and collaboration during my time at the Mayo Clinic. Dr. K.N. An and dr. C. Zhao, your advice has been very much appreciated. Dr. A.R. Thoreson, dear Andy, thank you for your efforts in helping me set up experiments. Sandy and Ahron, you are the best manager and secretary.

Beste Carin, lieve C, dank voor jouw doortastendheid tijdens het indienen van alle formulieren. Van het begin tot het einde zag jij in ieder geval nog bomen door het bos.

Verena, Miguel en Raja, dank voor het samen schrijven en indienen van artikelen, zonder jullie was het nooit gelukt!

Veel dank aan alle andere co-auteurs voor het meedenken en jullie kritische blik.

Hand-wrist study group, thank you for your collaboration!

Manja en Esther, veel dank voor jullie geduld en tips tijdens de uurtjes microchirurgie in het SkillsLab.

Krijgers van de 15de, dank voor alle gezelligheid en koffies tijdens de laatste loodjes van mijn promotie-traject. 'De wetenschap wacht op niemand!'

Lieve Jet, dank voor jouw creativiteit en daarmee bijdrage aan het ontwerp van dit boekje. Kom maar op met de volgende klaverjasavond na jullie reis!

Chirurgen en arts-assistenten uit het Franciscus, wat was de skivakantie een mooi begin van mijn tijd bij de chirurgie! Ik kijk uit naar de rest van de vooropleiding.

Stafleden en arts-assistenten van de plastische chirurgie aan het EMC, dank voor de leerzame tijd als ANIOS bij jullie. Ik ben ontzettend blij om door en met jullie te worden opgeleid tot plastisch chirurg!

BIS'ers, met jullie heb ik de eerste snij-ervaring opgedaan. Wat is het mooi om nog steeds zo en nu en dan een biertje met elkaar te drinken.

Lieve vrienden, ik voel me bevoorrecht met zoveel fijne mensen om mij heen. Dispuutsgenootjes, wat kan ik genieten van onze borrels en etentjes! Oud-huisgenootjes van huize Kerkstraat, huize Rustenburg en huize 1ste C. Huygens, het is alweer even geleden dat wij onder één dak lief en leed deelden, maar de vriendschappen zijn voor het leven. Het boek is af; weer meer tijd voor jullie!

Modern family: Mike, Kayla, Eric, Nicole, Will and Sam, thank you for making Minnesota feel like home. I have such good memories of our time in the 'big' house and can't wait to have a reunion wherever on the globe.

Lieve Ka en Sharif, dank voor de zachte landing in Rotterdam!

Lieve Elisa, paranimf en collega in spe, we did it! Ik ben dankbaar dat wij onze tijd als onderzoeker aan de Mayo Clinic hebben gedeeld en wat hebben we daar veel uitgezocht: beste vliegtickets binnen de US, beste restaurants in Chicago, beste brunch in Rochester, etc., etc. Ik kijk uit naar nog meer trips met jou, maar ook naar de cursussen en congressen die we samen gaan bezoeken. Ik ben trots op jou!

Lieve Mir, paranimf, wat is het bijzonder dat onze levens zo parallel lopen. Het was geruststellend dat jij in 2017 promoveerde, want dat betekende dat het met mij ook wel goed zou komen. Jij bent mijn held: van het voorbereiden op de decentrale selectie tot afronding van dit proefschrift, jij was er. Het bezoek van Saar en jou aan de US was hiervoor kenmerkend. Je bent naast een harde werker een levensgenieter en van jouw strakke planningen plukken wij de vruchten! Ik verheug me op al het moois dat wij, al dan niet samen met onze mannen, nog mee gaan maken. Te beginnen met Flachau 2.0!

Lieve Jo en Louk, dank voor jullie interesse in mijn promotie en opleiding. Weekendjes Nijmegen (met of zonder pilates) voelen als mini-vakanties!

Lieve oma, dank voor uw betrokkenheid en interesse in ons. Ik kan me geen scherpere oma voorstellen dan u; ik geloof zelfs dat u eerder Instagram had dan ik. Alhoewel het niet de spannende literatuur is die u normaal leest, kijk ik er wel naar uit om u dit boekje te geven.

Lieve oom Evert en tante Inge, dank voor jullie interesse, warmte, meedenken en het feit dat Lindy en ik altijd bij jullie terecht kunnen. Ik verheug me op alle Evers-events die nog komen gaan.

Lieve tante Nini, jij bent voor Lindy en mij een rots in de branding. Je bent dapper, een voorbeeld! Weekenden Zwolle voelen als thuiskomen.

Lieve Lin, dank voor jouw eeuwige vertrouwen. Ik ben ongelooflijk trots op jou en kan me geen betere zus wensen. Warme herinneringen heb ik aan jouw bezoek aan Minnesota. Ik kijk uit naar alle reisjes die wij nog samen gaan maken!

Tot slot, lieve Thomas, mijn dankwoord aan jou. Van Amsterdam tot Minnesota en van Brazilië tot Montreal, het maakt niet uit waar wij ons op de wereld bevinden, jij zorgt voor de muziekjes, quizjes, stabiliteit, je maakt mij aan het lachen en geeft mij het gevoel van geborgenheid. Het leven met jou is zoals een powerplay, samen kunnen wij alles aan! Ik verheug me op de toekomst met jou!