Surgery versus corticosteroid injection for carpal tunnel syndrome (DISTRICTS): an open-label, multicentre, randomised controlled trial

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Summary

Background Surgery and corticosteroid injections are established treatments for carpal tunnel syndrome, but the optimal treatment strategy remains unclear. This study aimed to compare starting treatment with surgery versus starting with a corticosteroid injection.

Methods We conducted an open-label, randomised controlled trial across 31 hospitals in the Netherlands. Eligible patients, diagnosed with carpal tunnel syndrome for at least 6 weeks and confirmed by electrophysiological or sonographic testing, were randomly assigned (1:1) to start treatment with either surgery or an injection via a web-based system. Randomisation was stratified by unilateral or bilateral symptoms, carpal tunnel syndrome with or without concomitant disease as risk factor, and previous ipsilateral injections. If needed, additional treatments were allowed, such as additional injections or surgery. The primary outcome, assessed in the intention-to-treat population, was the proportion of patients who were recovered (defined as a score of less than eight points on the six-item carpal tunnel syndrome scale) at 18 months. The trial was preregistered with the ISRCTN Registry (ISRCTN13164336) and is now completed.

Findings From Nov 7, 2017, to Nov 4, 2021, 934 participants (545 female and 389 male participants) were included. 468 were randomised to the surgery group and 466 to the injection group. At 18 months, 805 (86%) of 934 participants had primary outcome data. In the surgery group, 243 (61%) of 401 participants had recovered, significantly higher than the 180 (45%) of 404 participants recovered in the injection group (relative risk 1·36; 95% CI 1·19–1·56; p<0·0001). One or more adverse event occurred in 376 (86%) of 436 participants in the surgery group and in 384 (85%) of 453 participants in the injection group. One participant in the surgery group was hospitalised due to complications. No treatment-related deaths were reported.

Interpretation In patients with carpal tunnel syndrome, initiating treatment with surgery offers a higher chance of recovery after 18 months compared with starting with a corticosteroid injection, even with the possibility of additional interventions.

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Introduction

Carpal tunnel syndrome is the most prevalent entrapment neuropathy. The compression of the median nerve at the wrist can cause tingling, numbness, pain, and weakness in the hand.[1,2] The prevalence of carpal tunnel syndrome is estimated at 0·6–5·8% and is highest after the age of about 45 years.[3–5] Carpal tunnel syndrome is more common in women than in men. Bilateral presentation is common, and when the dominant hand is affected, carpal tunnel syndrome can have a greater effect on daily functioning.[5]

A wide variety of treatments is advocated.[5,6] Although there is insufficient evidence to conclude whether splinting benefits people with carpal tunnel syndrome,[7] surgical release of the transverse carpal ligament and injection of corticosteroids near the median nerve in the wrist are both effective treatments.[8–13] Surgery is typically a one-time procedure. A corticosteroid injection is relatively quick and easy to administer and if an injection proves ineffective or symptoms reappear, an individual can opt for another injection or proceed to surgery. Multiple studies have shown no relationship between steroid dose and clinical outcomes in patients receiving injection for carpal tunnel syndrome.[6] Although both approaches are used in clinical practice, the optimal approach (ie, whether to initiate treatment with surgery or corticosteroid injection) remains uncertain.[14,15] The absence of comparative knowledge regarding the best treatment strategy for carpal tunnel syndrome is also reflected in considerable practice variation in the treatment of carpal tunnel syndrome

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See Online for appendix

Research in context

Evidence before this study

Surgical release of the transverse carpal ligament and an injection of corticosteroids near the median nerve in the wrist are both effective treatments for carpal tunnel syndrome. Often, the treatment starts with a steroid injection because it is considered less invasive and easy to do. However, there is also a substantial group of clinicians who refer patients directly for surgery, believing that injections offer only temporary relief and thus delay more effective surgical treatment. To determine which treatment is more effective in adults with carpal tunnel syndrome, we searched databases for randomised controlled trials from database inceptions to Feb 3, 2015, with search terms covering carpal tunnel and corticosteroid injections and surgery (for the full search strategy and terms see the appendix p 43). Three randomised controlled trials were identified that compared surgical treatment directly to one or two steroid injections for carpal tunnel syndrome. The quality of these single-centre studies was moderate and sample sizes were small. The two trials with a follow-up shorter than 6 months indicated that surgery might be more beneficial. The only trial with a follow-up of more than 6 months indicated that injection was initially more beneficial but this was not found at the 2-year follow-up, with participants who had additional surgery in the injection group excluded from analysis. Informal updates of the search aligned with a recently published Cochrane review (which covered literature up to November, 2022), showing insufficient evidence on the most effective treatment strategy with long-term follow-up for carpal tunnel syndrome to end the unwanted treatment variation in medical practice.

Added value of this study

This study is the first adequately powered randomised controlled trial comparing the effectiveness of starting with surgery versus starting with injections for carpal tunnel syndrome with a long-term follow-up of 18 months. We found that starting treatment for carpal tunnel syndrome with surgery had a greater chance of recovery at 18 months than starting with injections, even with the option of additional treatments. Furthermore, the survival analysis showed that the median time to recovery in the surgery group was around half that in the injection group. We also found better outcomes in the surgery group than in the injection group regarding upper-limb functioning, the participant's global perception of recovery, and the participant's satisfaction with the results of treatment. From 6 weeks to 9 months, more participants in the surgery group had palmar pain than in the injection group; thereafter, the proportion of participants with palmar pain were similar in both groups. The results for the proportion of participants with limitations due to palmar pain showed the same pattern. Physician-reported adverse events were scarce. Participant-reported adverse events were similar between both treatment strategies, except for more wound or skin problems requiring treatment in the surgery group and more often reported changed sensation in the hand in the injection group.

Implications of all the available evidence

This is the first study that shows that initial surgery is more effective than initial corticosteroid injection, with a higher and earlier chance for long-term recovery and relatively few adverse events. In clinical practice, patients can be advised convincingly that early surgery is more beneficial in the long term.

worldwide.[16,17] Based on the relatively scarce data available on long-term recovery rates for treatment of carpal tunnel syndrome and strategies that can include combinations of different types of treatment, we hypothesised that starting with surgery could be more effective than starting with injection.[9,10,12] The Dutch Injection versus Surgery Trial in Carpal Tunnel Syndrome (DISTRICTS) was designed to compare the effectiveness of a treatment strategy starting with surgery to a treatment strategy starting with a corticosteroid injection, with additional treatments allowed in both strategies if needed. The study also focused on the cost-effectiveness and cost–utility of carpal tunnel syndrome treatment. The results of these economic analyses will be published separately.

For the **protocol** see https://www.isrctn.com/editorial/retrieveFile/3c249669-e3f9-429ca63a-2303d3a2dfd8/33817

Methods

Study design

In this investigator-initiated, multicentre, open-label, randomised controlled trial, patients were recruited from 31 hospitals in the Netherlands. The trial design was published previously.[18] The protocol was approved by the ethics committee at the Amsterdam University Medical Center (2017_171) and is available online. The trial was done in accordance with the Principles of the Declaration of Helsinki. Trial monitoring and data management were done in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. There was no industry involvement in the trial. The trial was designed and overseen by a steering committee (appendix p 3). The trial was preregistered with the ISRCTN registry on July 13, 2017 (ISRCTN13164336) and is now completed.

Patients

Patients were eligible for enrolment if they had clinically suspected carpal tunnel syndrome, which was confirmed by electrophysiological or sonographic testing and for which surgery and injection were both potential treatment options. Symptoms had to be present for at

least 6 weeks and treatment should have been possible within 6 weeks after inclusion. In case a patient had bilateral carpal tunnel syndrome, the hand with the most severe symptoms was included. If the symptoms in both hands were equally severe, the dominant hand was included. Patients were excluded if they had previous surgery for carpal tunnel syndrome on the ipsilateral wrist or an injection for carpal tunnel syndrome in the ipsilateral wrist less than a year ago. A complete list of the inclusion and exclusion criteria is provided in the appendix (p 6).

Patients were recruited from neurology outpatient clinics. These clinics are often organised as centralised centres with a streamlined care process designed to deliver efficient and standardised diagnosis and treatment for carpal tunnel syndrome patients. All participants gave written informed consent.

Randomisation and masking

After baseline assessment, participants were randomly assigned in a 1:1 ratio by the local clinician through a centralised web-based application (ALEA Clinical software, FormsVison) to the surgery group or the injection group. Randomisation was stratified according to unilateral or bilateral carpal tunnel syndrome, carpal tunnel syndrome with a concomitant disease as risk factor (yes or no), and a history of previous ipsilateral carpal tunnel syndrome injections (yes or no) through variable permuted blocks with block sizes of two, four, six, and eight. The allocated treatment was open label, with neither participants nor investigators masked to group allocation.

Procedures

For the surgery group, participating centres continued to refer the patients to their surgeon of choice, whether this be a plastic surgeon, neurosurgeon, orthopaedic surgeon, or another surgeon. Surgeons could use any surgical technique for decompression of the carpal tunnel applied in common clinical practice. For the injection group, each participating centre was allowed to use their choice of brand and dose of corticosteroids, with or without local anaesthetic. If needed, the initial treatment (ie, surgery or injection) could be followed by any additional treatments, such as injections, surgery, or any other treatment (eg, splint or physiotherapy), at the discretion of the patient and treating physician. Protocol deviations were either deviations from the eligibility criteria or failure to administer the allocated initial treatment (ie, surgery or a corticosteroid injection) within 6 weeks of randomisation. Baseline data collection was done by local investigators and follow-up self-report questionnaires were collected centrally at 6 weeks and at 3, 6, 9, 12, 15, and 18 months. Sex data were self-reported by participants, consisting of the options male or female. Upon inclusion, each participant received a personalised study card indicating the hand included in the study. At each follow-up questionnaire, participants filled in which hand had received the study treatment (ie, left or right) and responded to the questions for that hand.

Outcomes

The primary outcome was the proportion of participants recovered at 18 months after randomisation. Recovery was defined as having no or mild symptoms; that is, a score of less than eight points on the six-item carpal tunnel symptoms scale (CTS-6).[19] The CTS-6 score is a disease-specific scale that measures symptoms for a typical 24-h period during the past 2 weeks. The sum score ranges from six (best) to 30 (worst). As part of a prespecified subgroup analysis, we defined subgroups to evaluate the primary treatment effect (appendix p 8).

Secondary outcomes were time to recovery during 18-month follow-up, time-specific proportion of participants with a CTS-6 sum score of less than eight at each timepoint, symptom severity measured with the CTS-6 sum score at all timepoints, upper limb functioning at 18 months (measured with QuickDASH),[20] severity of pain in the scar or proximal palm and pain-related activity limitation (according to the palmar pain scale) at all timepoints,[21] participants' global perception of recovery and participants' satisfaction (measured with seven-point Likert-type items) at 18 months, number and type of additional treatments during 18-month follow-up, and adverse events reported by physicians during injection or surgery and by participants during 18-month follow-up. For the time to recovery outcome, recovery was defined as the first outcome measurement after the last self-reported intervention for carpal tunnel syndrome (eg, additional injection, surgery, or splint) with a CTS-6 sum score of less than eight if this outcome measurement was followed by a CTS-6 sum score of less than eight at the next outcome measurement or if it was the 18-month outcome measurement. The QuickDASH is an 11-item measure of upper limb functioning;[20] the score ranges from 0 (no disability) to 100 (most severe disability). The palmar pain scale consists of two items that inquire about severity of pain in the scar or proximal palm or both (with six options: 0, 20, 40, 60, 80, or 100; 0 is no pain and 100 very severe pain) and degree of activity limitation because of pain (five options: 0, 25, 50, 75, 100; 0 is no limitation and 100 very severe limitations).[21] Presence of palmar pain in scar or proximal palm and related activity limitation was defined as a palmar pain score of greater than 0. The options for participants' global perception of recovery on the seven-point Likert-type items were 1 (much worse), 2 (worse), 3 (a little worse), 4 (similar), 5 (a little improved), 6 (improved), and 7 (vastly improved). Options for participants' satisfaction on the seven-point Likert-type items were 1 (very dissatisfied), 2 (dissatisfied), 3 (a little dissatisfied), 4 (similar), 5 (a little satisfied), 6 (satisfied), and 7 (very satisfied). At baseline (because injections were often administered shortly after randomisation) and

immediately after surgery, health-care providers were asked about possible adverse events through an open-ended question on a form. During each follow-up assessment, participants were asked about adverse events in a questionnaire. The questionnaire included a list of possible adverse events, such as pain, tingling, loss of strength, and wound issues, which participants could tick if applicable, and an open-ended question about any additional adverse events.

Statistical analysis

There are scarce data available regarding the recovery rate in carpal tunnel syndrome with treatment strategies that can include combinations of different types of treatment. The long-term effectiveness (12 months) of surgery has been estimated to be approximately 75%[9,10] and the long-term effectiveness (12 months) of one to three injections was 38–61%.[9,10,12] We assumed a 60% recovery rate at 18 months in the injection group and considered a 10% difference in recovery rate the minimum clinically important difference between the two groups. A Fisher's exact test with a 0·05 two-sided significance level would have 80% power to detect the difference between a proportion of 0·70 recovery in the surgery group and 0·60 recovery in the injection group when the sample size in each group is 376 patients (752 patients in total). Anticipating a 20% attrition rate, we planned to include 470 participants per trial group.

Statistical analyses were prespecified in the statistical analysis plan (appendix pp 21–42) before the end of data collection. Data were analysed in the intention-to-treat population. The main analysis was the comparison between the two trial groups at 18 months. First, the difference between the groups in proportion of participants who recovered was analysed with Fisher's exact test, in accordance with sample size considerations. Effect size was expressed as a relative risk with its corresponding 95% CI. Sensitivity analyses included modelling the odds of recovery at 18 months with a logistic regression model, including trial group and the three stratification variables as linear predictors, with effect size expressed as adjusted odd's ratio with 95% CI. Additionally, we used model-based multiple imputation, as-treated analysis, and an alternative definition of recovery (ie, fewer than nine points on the overall CTS-6 and fewer than three points on any individual item of the CTS-6) to evaluate the robustness of the results and to address the issue of missing data. Data were assumed to be missing at random. In a model-based imputation that used predictive mean matching, we included variables related to missingness, three stratification variables, and the allocated treatment group. 14 datasets (equal to the percentage of missing cases for the primary endpoint[22]) were generated with 50 iterations. Convergence plots for each imputed variable were evaluated, and the pooled effects and SEs were computed in accordance with Rubin's rules. For the as-treated analysis, participants were categorised according to the actual first treatment they received. The as-treated population included all participants who met the following three criteria: provided informed consent, received surgery or a corticosteroid injection within 6 weeks of randomisation, and provided data for the primary endpoint for the correct hand after 18 months of follow-up.

For secondary outcomes, formal statistical tests to examine differences between the trial groups were not done. Time to recovery was estimated by Kaplan–Meier analysis and median times to recovery (with corresponding 95% CIs) are reported per trial group. Participants were excluded from the Kaplan–Meier analysis if their CTS-6 score was missing or if it was unknown whether they had received additional treatment for carpal tunnel syndrome. No censoring was applied for additional treatments. For each timepoint, the proportions of participants who recovered per trial group are presented as point estimates with 95% CI, using the binomial approach and applying normal distribution, and their proportional differences are expressed as relative risks with 95% CI. Symptom severity at all timepoints was analysed with a linear mixed-effect model with trial group as a fixed-effect and the timepoint as a categorical variable. Dependency among repeated measures per patient was accommodated by a first-order autoregressive covariance structure, selected from candidate covariance models on the basis of Akaike's information criterion with restricted maximum likelihood estimation. Differences in symptom severity between the surgery and injection group are presented as estimated mean differences with 95% CIs for each timepoint during the 18-month follow-up. The effect on upper limb functioning at 18 months (via QuickDASH), participants' global perception, and participants' satisfaction are presented as mean differences with 95% CIs. The effect on scores on the palmar pain scale are presented as relative risks with 95% CIs for each timepoint. The subgroup analyses assessed the relative risks of recovery in the surgery versus the injection group after 18 months follow-up. Additional treatments and adverse events during the 18 months of follow-up were summarised as proportions and presented with their corresponding 95% CIs. We also calculated risk differences with 95% CIs for the occurrence of adverse events and assessed relative differences with the χ^2 test, or when frequencies were less than five, Fisher's exact test. It is important to note that the study was powered to detect statistically significant differences for the primary outcome, not for adverse events. A two-sided p value of less than 0·05 was considered statistically significant.

All statistical analyses were done in SPSS (version 28). We did not use additional modules or programming.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants were recruited between Nov 7, 2017, and Nov 4, 2021. Seven of 941 participants were excluded because written informed consent could not be retrieved (two from the surgery group and five from the injection group). The diagnosis of carpal tunnel syndrome was supported in 623 (67%) of the 934 participants based on electrophysiology, in 175 (19%) based on ultrasonography, and in 136 (15%) based on both electrophysiology and ultrasonography (with at least one of the modalities showing findings supportive for carpal tunnel syndrome). Of the 934 participants, 468 were randomised to the surgery group and 466 to the injection group (figure 1; appendix pp 9–10). In the surgery group, 430 (92%) participants underwent surgery, and the median time from randomisation to surgery was 4·0 weeks (IQR 2·1–7·0 weeks). In the injection group, 465 (>99%) participants received the injection immediately after randomisation, whereas one participant had surgery instead of an injection. More information on the type of surgery, the specialisations of the surgeons, type of corticosteroid injections, and the use of local anaesthetics can be found in the appendix (p 20). Details on other treatments during the 18-month follow-up are also reported (figure 1; appendix pp 14–15). Data for the primary outcome in the intention-to-treat population were available for 805 (86%) of 934 participants at 18 months post-randomisation. The two trial groups were well balanced with respect to demographic and clinical characteristics (table 1).

The primary outcome had a significant difference in the proportion of participants who were recovered at 18 months (p<0·0001; table 2). In the surgery group, 243 (61%) of 401 participants with primary outcome data had recovered at 18 months and in the injection group 180 (45%) of 404 participants had recovered (relative risk 1·36; 95% CI 1·19–1·56).

The survival analysis showed a median time to recovery of 9·0 months (95% CI 7·7–10·3) in the surgery group and 18·0 months (16·0–20·0) in the injection group (figure 2A). At 6 weeks, more participants had a score of less than eight on the CTS-6 sum score in the injection group than in the surgery group, but from 3 months onwards, the proportion of participants with a CTS-6 sum score of less than eight was higher in the surgery group than in the injection group (figure 2B; appendix p 16). The analysis of between-group differences in symptom severity over time showed that, at 6 weeks, symptoms had improved more in the injection group, but from 3 months onwards this pattern was reversed, with symptoms being less severe in the surgery group (figure 2C). At 18 months, the point estimates and 95% CIs showed a better outcome in the surgery group than in the injection group regarding upper-limb functioning measured with the QuickDASH, the patient's global perception of recovery, and the patient's satisfaction with the results of treatment (table 2). At

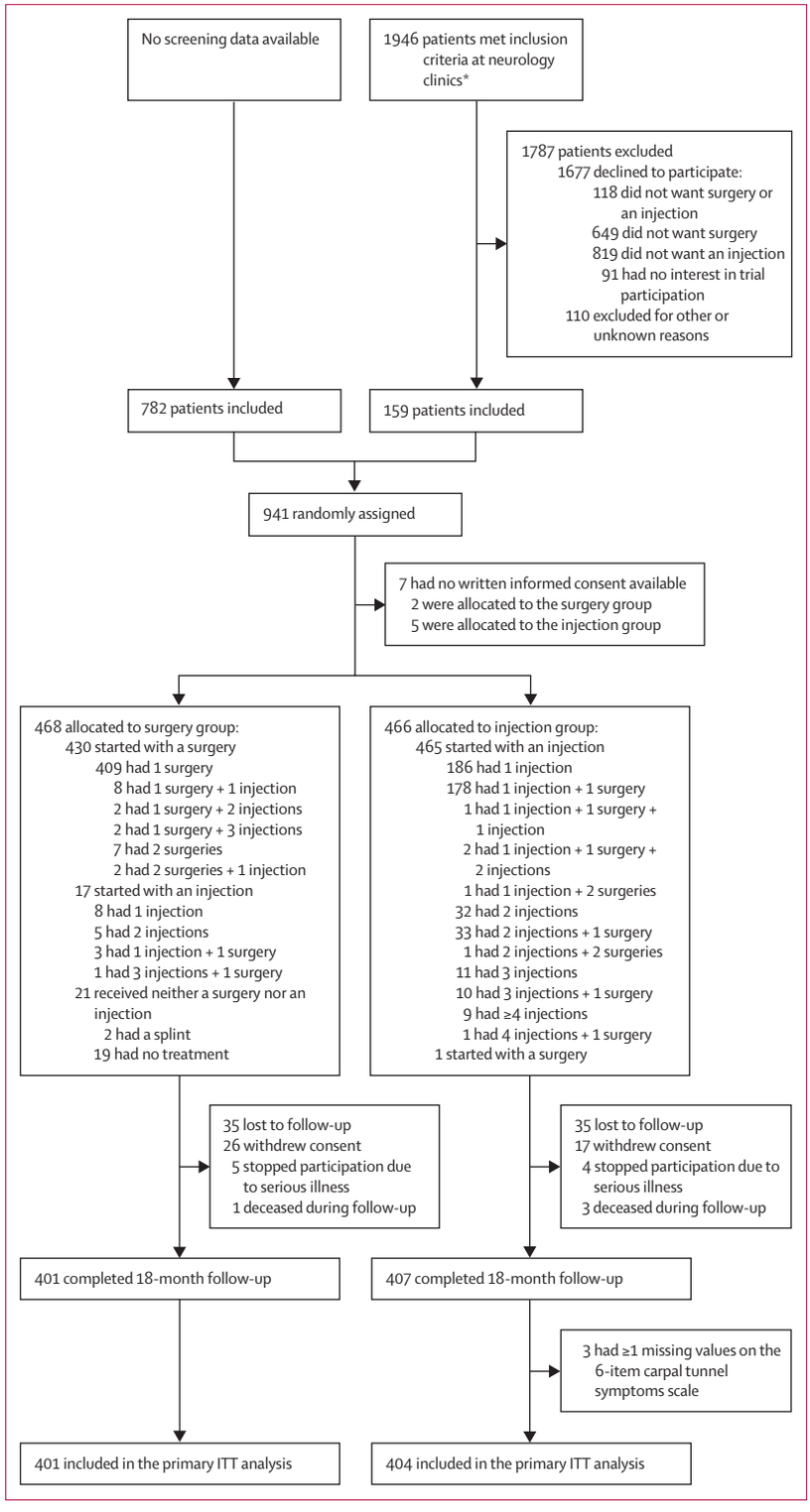

Figure 1: **Trial profile**
ITT=intention-to-treat. *Due to logistical complexity, screening data were not completely registered. Eight recruiting hospitals registered patients with carpal tunnel syndrome that visited centralised outpatient clinics, a streamlined care process designed to deliver efficient and standardised diagnosis and treatment for patients, during their inclusion time period.

	Surgery group, n=468	Injection group, n=466
Sex		
Female	269 (57%)	276 (59%)
Male	199 (43%)	190 (41%)
Age, years*	59·0 (51·0–69·0)	58·0 (48·3–71·0)
BMI, kg/m²*	27·5 (24·9–31·6)	27·7 (25·2–31·3)
Unilateral or bilateral CTS		
Unilateral	175 (37%)	178 (38%)
Bilateral	293 (63%)	288 (62%)
Dominant side more severely affected*		
Yes	290 (62%)	286 (61%)
No	173 (37%)	176 (38%)
Duration of CTS symptoms, months*	8·0 (4·0–24·0)	9·0 (5·0–23·3)
CTS symptoms, in terms of a sensation of pins and needles (with or without pain) and numbness in median nerve innervated area of the hand		
Yes	467 (100%)	466 (100%)
No	1 (<1%)	0 (0%)
CTS symptoms at night, which wake the patient		
Yes	416 (89%)	416 (89%)
No	52 (11%)	50 (11%)
Worsening of CTS symptoms during specific hand or wrist movements*		
Yes	411 (88%)	414 (89%)
No	56 (12%)	52 (11%)
Neurological examination*		
Sensory disturbances	236 (50%)	244 (52%)
Paresis	87 (19%)	90 (19%)
Atrophy	80 (17%)	87 (19%)
Concomitant disease as risk factor for CTS		
Diabetes	48 (10%)	44 (9%)
Rheumatoid arthritis	17 (4%)	16 (3%)
Thyroid disease	30 (6%)	26 (6%)
Renal failure requiring dialysis	2 (<1%)	1 (<1%)
Anatomical abnormality at the carpal tunnel†	3 (1%)	2 (<1%)
Ipsilateral CTS injections >1 year ago	18 (4%)	19 (4%)
CTS symptom severity (CTS-6 sum score)*‡	19·0 (16·0–22·0)	18·0 (15·0–21·0)
Upper limb functioning (QuickDASH)*§	43·2 (27·3–56·8)	40·9 (27·3–56·8)

Data are n (%) or median (IQR). CTS=carpal tunnel syndrome. *Data not available for all randomised participants (between two and eight participants missing per group). †Abnormality that could have induced changes in structures at the level of the carpal tunnel (eg, space-occupying lesion or status after trauma or surgery). ‡The CTS-6 score is a disease-specific six-item scale that measures symptoms for a typical 24-h period during the past 2 weeks; the sum score ranges from six (best) to 30 (worst). §The QuickDASH is an 11-item measure of upper limb functioning. The score ranges from 0 (no disability) to 100 (most severe disability).

Table 1: **Demographical and baseline clinical characteristics**

18 months, 325 (82%) of 395 participants in the surgery group compared with 247 (61%) of 406 participants in the injection group reported improvement or vast improvement of symptoms and 314 (79%) of 396 participants in the surgery group compared with 248 (61%) of 406 participants in the injection group were satisfied or very satisfied with their treatments (appendix p 11).

From 6 weeks to 9 months, more participants in the surgery group had palmar pain than did those in the injection group, thereafter the proportions of participants with palmar pain were similar in both groups (figure 2D). The results for the proportion of participants with limitations due to palmar pain showed the same pattern (appendix pp 12, 16).

The results of the subgroup analyses were similar across all subgroups except for participants in whom the difference in distal latency between the median nerve and ulnar nerve was equal to or less than 0·4 ms (figure 3). However, the number of participants in this subgroup was low, resulting in a wide CI.

Physician-reported adverse events were scarce. Participant-reported adverse events were similar between both treatment strategies, except for more wound or skin problems requiring treatment in the surgery group and more reports of changed sensation of the hand in the

	Surgery group	Injection group	Mean difference (95% CI)	p value
Primary outcome after 18 months				
Recovered	243/401 (61%)	180/404 (45%)	1·36 (1·19 to 1·56)*	<0·0001
Secondary outcomes after 18 months				
QuickDASH score	12·45 (10·78 to 14·11)	19·80 (17·76 to 21·84)	−7·35 (−9·99 to −4·72)	..
Participants' global perception of recovery†	6·21 (6·08 to 6·34)	5·43 (5·25 to 5·60)	0·78 (0·57 to 1·00)	..
Participants' satisfaction†	5·94 (5·80 to 6·11)	5·33 (5·16 to 5·51)	0·61 (0·37 to 0·84)	..
Interventions‡				
Surgeries	443	230	..	..
Injections	44	617	..	..

Data are n, n/N (%) or mean (95% CI), unless otherwise specified. p values are from χ^2 tests. *Data are relative risk (95% CI). †Participants' global perception of recovery and participants' satisfaction were measured with seven-point Likert-type items of 1 (much worse), 2 (worse), 3 (a little worse), 4 (similar), 5 (a little improved), 6 (improved), or 7 (vastly improved) and 1 (very dissatisfied), 2 (dissatisfied), 3 (a little dissatisfied), 4 (similar), 5 (a little satisfied), 6 (satisfied), and 7 (very satisfied). ‡Some participants had more than one of each intervention (figure 1).

Table 2: **Outcomes**

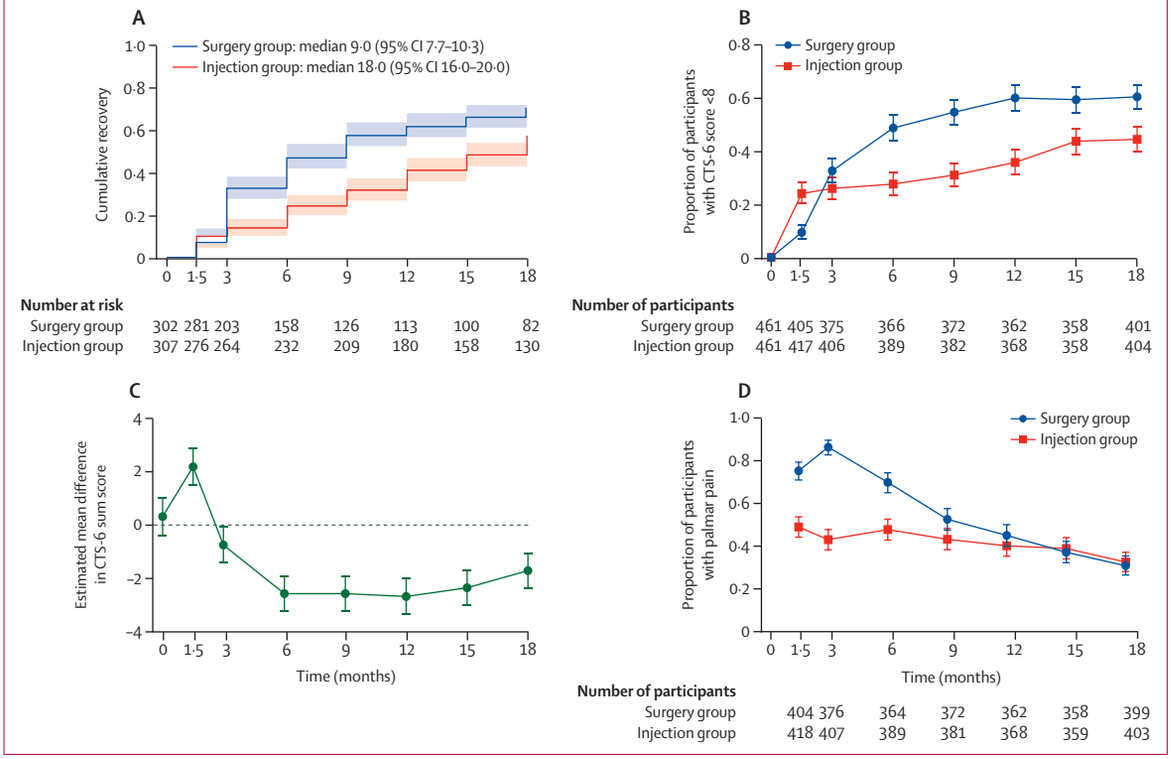

Figure 2: **Graphs of four of the secondary outcomes**

(A) Inverse Kaplan–Meier curves estimating the cumulative time to recovery during 18 months of follow-up. The median time to recovery was 9·0 months (95% CI 7·7–10·3) in the surgery group and 18·0 months (16·0–20·0) in the injection group. Time to recovery was defined as the first timepoint after the last self-reported carpal tunnel syndrome intervention (eg, additional injection, surgery, or splint) with a CTS-6 sum score of less than eight if this timepoint was followed by a CTS-6 sum score of less than eight at the next available timepoint or if this was the last available timepoint. (B) The proportion (with 95% CIs) of participants with a CTS-6 sum score of less than eight per timepoint in the surgery group and in the injection group. (C) The estimated mean difference of the CTS-6 sum score, generated with a linear mixed model, for the two trial groups. (D) The proportion (with 95% CIs) of participants with scar or proximal palm pain (or both) in the surgery group and in the injection group during 18 months of follow-up.

injection group (table 3; appendix p 17). One or more patient-reported adverse event occurred in 376 (86%) of 436 participants in the surgery group and in 384 (85%) of 453 participants in the injection group. One participant in the surgery group was hospitalised due to complications. No treatment-related deaths were reported.

The results of the sensitivity analyses of the primary outcome (ie, the logistic regression model including the

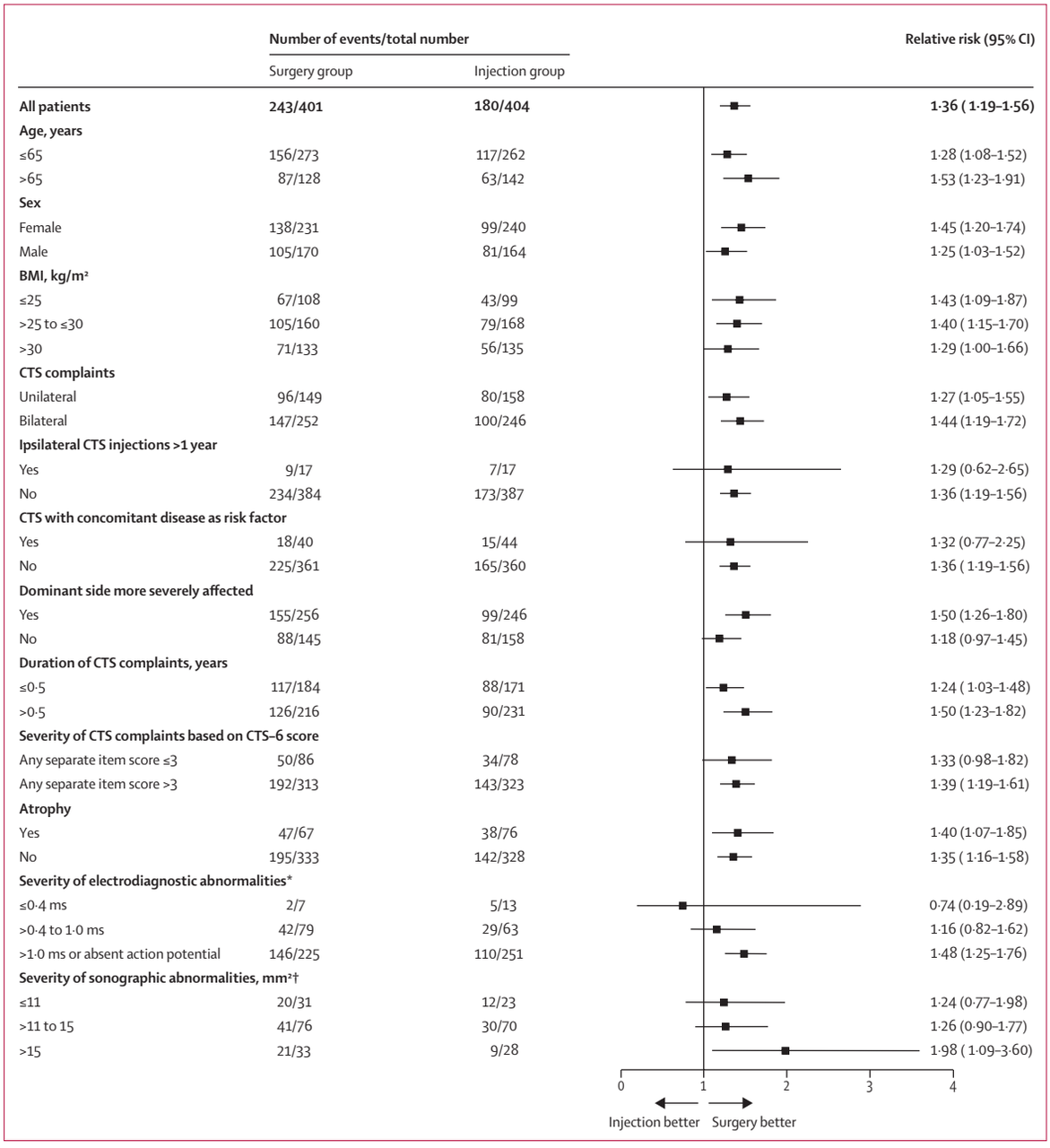

Figure 3: **Rate of recovery in subgroups as part of the prespecified subgroup analysis**
Relative risks and 95% CIs show the effect within each subgroup. CTS=carpal tunnel syndrome. CTS-6=six-item carpal tunnel symptoms scale. *The distal sensory latency difference of the 4th finger between the median and the ulnar nerve in milliseconds was recorded, with a greater difference or absence of a median sensory nerve action potential indicating more severe electrodiagnostic abnormalities. †The median nerve cross-sectional area in mm^2 was recorded, with a higher cross-sectional area indicating more severe sonographic abnormalities.

three stratification variables, the model-based multiple imputation, the as-treated analysis, and the analysis using an alternative definition of recovery) all showed patterns that were in line with the primary analysis (appendix pp 18–19).

In the surgery group, 228 (57%) of 401 participants had recovered at 18 months without requiring additional injections or surgery. Additionally, seven participants (2%) in this group recovered with the aid of additional injections or surgery. In the injection group, 54 (13%) of 404 participants had recovered at 18 months without needing further injections or surgery. 11 (3%) participants in this group recovered with the use of additional injections alone. 228 (49%) of 465 participants in the injection group also underwent surgery during follow-up; based on the available recovery data of 204 of these

	Surgery group	Injection group	Risk difference (95% CI)	p value*
Adverse events during surgery†				
Nerve injury	0/441	1/226 (<1%)	0·00 (–0·01 to 0·01)	0·56
Tendon injury	0/441	0/226	0·00 (0·00 to 0·00)	1·00
Haematoma	0/441	2/226 (<1%)	–0·01 (–0·02 to 0·00)	0·12
Pain	1/441 (<1%)	2/226 (<1%)	–0·01 (–0·02 to 0·01)	0·27
Adverse events during injection‡				
Nerve injury	NA	0/465	..	..
Tendon injury	NA	0/465	..	..
Haematoma	NA	1/465 (<1%)	..	..
Pain	NA	2/465 (<1%)	..	..
Adverse events during follow-up				
Wound or skin problem requiring treatment§	60/435 (14%)	30/453 (7%)	0·07 (0·03 to 0·11)	0·0004
Pain in the hand, wrist, or scar¶	273/435 (63%)	291/453 (64%)	–0·01 (–0·08 to 0·05)	0·65
Changed sensation in the hand	287/435 (66%)	326/453 (72%)	–0·06 (–0·12 to 0·00)	0·05
Diminished strength of the hand	287/435 (66%)	289/453 (64%)	0·02 (–0·04 to 0·08)	0·50
Decreased dexterity of the hand	264/435 (61%)	259/453 (57%)	0·04 (–0·03 to 0·10)	0·29
Allergic reaction	1/436 (<1%)	0/453	0·00 (–0·00 to 0·01)	0·49
Sleep and mood complaints	1/436 (<1%)	2/453 (<1%)	–0·00 (–0·01 to 0·01)	0·51
Increased complaints or treatment at contralateral side	18/436 (4%)	11/453 (2%)	0·02 (–0·01 to 0·04)	0·15
Admitted to hospital for other reasons	46/436 (11%)	45/453 (10%)	–0·05 (–0·10 to 0·01)	0·14
Other adverse events (not related)	153/436 (35%)	159/453 (35%)	–0·00 (–0·06 to 0·06)	1·00

Data are n/N, unless otherwise indicated. NA=not available. *p values are from χ^2 tests and, for cases with fewer than five observations, Fisher's exact test. †The number of surgeries includes 11 revision surgeries; nine for the surgery group and two for the injection group. For two participants in the surgery group and for four participants in the injection group, adverse events during surgery were not reported because no surgery report was available. ‡Only available for injection group for the initial injection. §One participant in the surgery group was hospitalised due to a serious wound infection. ¶Reported separately from the palmar pain scale.

Table 3: **Physician-reported adverse events during surgery or injection and participant-reported adverse events during follow-up**

participants, 115 participants (56%) recovered after the additional surgery.

Discussion

Participants starting treatment with surgery for carpal tunnel syndrome had a 16 percentage point increased chance of recovery after 18 months compared with those who started with corticosteroid injection. Approximately half of the participants allocated to the injection group underwent additional surgery within the 18-month period. Of the patients randomised to start treatment with an injection, only 16% had recovered after 18 months without the need of surgery during follow-up. In contrast, 57% of those randomised to initial surgery had recovered after 18 months without the need for additional treatment.

Despite the allowance of additional treatments in both strategies, a large difference exists between the strategies even after 18 months. The survival analysis showed a median time to recovery of 9 months in the surgery group and 18 months in the injection group.

The rates of surgery we report after injection are similar to that found in previous literature.[12,13,23] In a study in which patients were followed up for up to 5 years after initial treatment with a corticosteroid injection, 80–90% of the patients underwent surgery within 16 months of the initial injection.[23]

Palmar pain, an adverse effect of surgery for carpal tunnel syndrome, was assessed with the palmar pain scale.[21] This scale was dichotomised into the presence or absence of symptoms indicative of palmar pain, irrespective of severity. During the first 6 months, palmar pain appeared more prevalent in the surgery group. However, after this period, the prevalence of palmar pain became similar between the groups. At 6 weeks approximately half of the participants in the injection group had a score higher than 0 on the palmar pain scale, despite only 15 participants having undergone surgery by that point. This observation suggests that the dichotomisation of the scale might be missing some specificity. Wound and skin problems requiring treatment occurred twice as frequently in the surgery group, reflecting the disparity in the number of surgical procedures between treatment groups, indicating that this adverse event occurs in 15–20% of procedures. The more frequently reported altered sensation in the hand in the injection group might not be directly related to treatment, but could possibly indicate the return or exacerbation of symptoms related to carpal tunnel syndrome.

We used a concise, validated, self-reported primary outcome measure that evaluates symptom severity—a crucial factor in both seeking and assessing treatment

effectiveness. The use of self-reported questionnaires eliminated the need for hospital visits dedicated solely to the study, reducing the time demands on clinicians and helping to maintain a high patient retention rate throughout the extended follow-up period. Additionally, we used strict recovery criteria based on the CTS-6 sum score, complemented by a sensitivity analysis with more lenient criteria, and assessed the patient's global perception of recovery at 18 months. Although recovery rates appeared low based on our strict criteria, around 80% of patients in the surgery group reported improvement, compared with 60% in the injection group, consistent with findings reported in the literature.[8–11,24,25] The study deliberately remained as close to clinical practice as possible. This design accounted for the variety in surgery methods as well as type and number of injections. Many participants received multiple injections during the study period, reflecting that there is no consensus about the optimal treatment strategy. During the past couple of years, the use of ultrasound to increase preciseness of injections has been advocated, but this was not evaluated separately in our study.[26]

One limitation of our study is that it was not masked for the initial treatment, as knowledge of the first treatment was essential for the participants to select subsequent treatments. Ethical considerations prevented the use of sham surgeries to mask participants. Additionally, the endpoint assessment was not masked. However, since carpal tunnel syndrome primarily presents with symptoms such as tingling, pain, and numbness, masking the assessment of the primary outcome would probably offer little methodological advantage. Another challenge was the incomplete registration of eligible patients and reasons for non-participation, which was successful in only a few centres. In the Netherlands, many neurology clinics have specialised, streamlined pathways for carpal tunnel syndrome care, making it logistically difficult to incorporate this registration. However, given the large sample sizes from the centres that did register all eligible patients, we believe the available data still provide useful insights into patient selection: it is striking that many patients declined both initial surgery and injections, indicating they had strong preferences regarding their preferred initial treatment. This finding implies that when implementing the study results in clinical practice, it is equally important to provide patients with appropriate information about the study findings.

Another limitation of the study is that race or ethnicity data were not collected. Three-quarters of the Dutch population consists of people with a native background, meaning they were born in the Netherlands, as were both of their parents. The remainder of the population has a diverse background. Finally, the choice of follow-up duration was arbitrary. We aimed for the longest possible follow-up to ensure that any additional treatments could be properly applied, while also trying to avoid a situation in which many patients would prematurely withdraw due to the length of the follow-up and the number of measurement points.

In conclusion, our research shows that patients who begin treatment for carpal tunnel syndrome with surgery have a higher likelihood of recovery after 18 months than those who start with a corticosteroid injection, even when additional treatments are available.

Contributors

RMAdB, CV, DvdB, CAJMdB, TWHA, and LHV contributed to trial conceptualisation and funding acquisition. RMAdB, CV, AMH, WACP, CAJMdB, and JAB contributed to the formal analysis and verified the underlying data reported in the manuscript. WACP, AMH, RMAdB, and CV wrote the first draft of the report. All authors had full access to all the data in the study, contributed to manuscript review and editing, and accept responsibility for the decision to submit for publication.

Declaration of interests

EV is a member of the board of the Dutch Neurology Society. DvdB reports payments from ZonMw, European Research Council, and ItsME Foundation to their institution, outside of the submitted work. All other authors declare no competing interests.

Data sharing

De-identified datasets will be available upon request, 2 years after publication of the study results (during which time we will do additional planned analyses). Emails should be sent to the corresponding author, stating the fields required and purpose of the request (ideally with a protocol but, at a minimum, with a research plan). The data dictionary can also be made available. The statistical analysis plan is provided in the appendix. Requests will be considered on a case-by-case basis and requestors will be asked to complete a data sharing agreement with the sponsor before data transfer. Data will be retained for 15 years after the close of the study.

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