Study protocol

Splinting or surgery for carpal tunnel syndrome? Design of a randomized controlled trial
Annette AM Gerritsen *1, Rob JPM Scholten 2, Willem JJ Assendelft 3, Herman Kuiper 4, Henrica CW de Vet 5 and Lex M Bouter 6

Address: 1Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands, 2Dutch Cochrane Center/Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, 3Dutch College of General Practitioners, Utrecht, 4Department of Neurology, Flevoziekenhuis, Almere, The Netherlands, 5Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands and 6Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands

E-mail: Annette AM Gerritsen* - aam.gerritsen.emgo@med.vu.nl; Rob JPM Scholten - r.j.scholten@amc.uva.nl; Willem JJ Assendelft - renw@nhg.nl; Herman Kuiper - hkuiperg@worldonline.nl; Henrica CW de Vet - hew.de_vet.emgo@med.vu.nl; Lex M Bouter - lm.bouter.emgo@med.vu.nl

*Corresponding author

Abstract

**Background:** Carpal tunnel syndrome is a common disorder, which can be treated with surgery or conservative options. However, there is insufficient evidence and no consensus among physicians with regard to the preferred treatment for carpal tunnel syndrome. Therefore, a randomized controlled trial is conducted to compare the short- and long-term efficacy of surgery and splinting in patients with carpal tunnel syndrome. An attempt is also made to avoid the (methodological) limitations encountered in earlier trials on the efficacy of various treatment options for carpal tunnel syndrome.

**Methods:** Patients of 18 years and older, with clinically and electrophysiologically confirmed idiopathic carpal tunnel syndrome, are recruited by neurologists in 13 hospitals. Patients included in the study are randomly allocated to either open carpal tunnel release or wrist splinting during the night for at least 6 weeks. The primary outcomes are general improvement, waking up at night and severity of symptoms (main complaint, night and daytime pain, paraesthesia and hypoesthesia). Outcomes are assessed up to 18 months after randomization.

**Background**

CTS is a compression neuropathy of the median nerve at the wrist. Any condition that reduces the size of the carpal tunnel or increases the volume of its content may cause compression of the median nerve. In the majority of cases the cause of CTS is unknown, referred to as idiopathic CTS. However, there are numerous medical conditions associated with CTS, such as diabetes mellitus, thyroid disease, rheumatoid arthritis and pregnancy. [1] The prevalence of CTS in the Netherlands was found to be 0.6% in men and 9.2% in women (age 25–74 years). [2] The symptoms of CTS include pain, paraesthesias and hypoesthesias in the hand, in the area innervated by the median nerve, and often occur or worsen during the night or early morning, waking the patient up. Furthermore, there may also be loss of sensibility and strength,
causing difficulties in performing the activities of daily life and work. The clinical diagnosis of CTS can be confirmed by electrodiagnostic studies, which have been found to be highly sensitive (49% to 84%) and specific (95% or greater). [3] Clinical tests (e.g. assessing thenar atrophy, performing provocative tests, Semmes-Weinstein monofilament testing) have been shown to have little diagnostic value, but are nevertheless still widely used. [4]

For the treatment of CTS, several conservative and surgical options are available. The most commonly used conservative treatment options are wrist splinting, injection of corticosteroids into the carpal tunnel, non-steroidal anti-inflammatory drugs (NSAIDs), systemic steroids, pyridoxine (vitamin B6) and diuretics. [5,6] However, there is only limited evidence of the efficacy of any of these conservative treatment options. [7] The methodological limitations observed in RCTs on conservative treatment options were prognostic inequalities between the study groups at baseline, small sample sizes (all less than 25 patients per treatment group), unacceptably high drop-out/loss to follow-up rates and absence of a long-term follow-up measurement. No RCTs were found in which wrist splints were compared with other conservative treatment options, placebo or no treatment at all, but some non-randomized and uncontrolled studies concerning wrist splints have been published. [8–10] Also a study comparing the effects of night-only to full-time splint wear instructions has recently been published. [11]

Surgical treatment options consist of sectioning the transverse carpal ligament, resulting in an increased canal volume [12] and/or widening the bony carpal arch, [13] thereby reducing the pressure on the median nerve. [14] There are several surgical techniques available, but standard open carpal tunnel release (OCTR) seems to offer similar relief from CTS symptoms in the short and long-term, compared to OCTR with a new incision technique, OCTR adding epineurotomy or internal neurolysis, or endoscopic carpal tunnel release. [15] The most prevalent (methodological) shortcomings observed in RCTs on surgical techniques were the performance of only short-term outcome measurements or only long-term outcome measurements (not both), small sample sizes (half of the studies included less than 25 patients per treatment group) and inadequate data-presentation (e.g. p-values instead of measures of variability).

When reviewing the literature, only 1 small-scale RCT was found that compared conservative treatment (plaster-of-paris splinting for 1 month) with surgery (OCTR). [16] However, the trial provided no information on comparability of the groups at baseline, co-interventions, compliance with the therapy or blinding of the outcome assessor. Furthermore, only 1 follow-up measurement was performed after 1 year, showing that all 10 patients who were treated surgically had complete relief from symptoms while 2 out of 10 patients who were treated with a wrist splint had temporary relief.

There is no consensus with regard to the choice of initial treatment for CTS. The American Academy of Neurology advises non-invasive treatment first, i.e. wrist splints, modification of activities, NSAIDs or diuretics, and using invasive steroid injections or OCTR only if non-invasive treatment have turned out to be ineffective. [17] However, in the Netherlands 39% of the neurologists prefer OCTR as the initial treatment for CTS, 40% prefer conservative measures (26% wrist splints), and 21% have no preference. [6] In the United Kingdom, 47% of the rheumatologists frequently choose wrist splints and 53% choose surgery as the initial treatment for CTS. [5]

Advocates of early surgery refer to its safety and effectiveness in electrophysiologically confirmed cases with no underlying reversible disorder. [18] In addition, they point out that conservative therapy generally offers only temporary symptom relief, and that surgery is unnecessarily delayed, causing further damage to the median nerve. Advocates of initial conservative management of CTS, however, refer to the potential benefits and safety of conservative treatment options and the potential complications of surgery. [19]

In summary, there is no consensus on the preferred initial treatment for CTS, due to insufficient scientific evidence for the efficacy of conservative treatment options, and for the relative efficacy of these measures compared with surgery. Therefore it was decided to conduct a properly designed RCT, comparing splinting and early surgery, including a sufficient number of patients and an adequate follow-up.

The main objective of this randomized clinical trial is to determine the short and long-term efficacy of splinting compared with early surgery in relieving CTS symptoms. A second objective is to assess from a societal perspective the cost-effectiveness of these treatment options.

Methods
The study is designed as a multicenter RCT. The Medical Ethics Committees of the 13 participating hospitals approved the study protocol.

Study population
Patients with clinically suspected CTS referred to one of the participating neurologists, are eligible for participation in the study if they meet the selection criteria. Pa-
tients are included if they have pain, paraesthesias and/or hypothesias in the hand, in the area innervated by the median nerve. The clinical diagnosis of CTS has to be confirmed by electrodiagnostic studies, the methods of which are described below. Furthermore, patients have to be 18 years or older and able to complete written questionnaires (in Dutch). Patients are excluded from the study if: 1) they have already been treated with a wrist splint or have had previous carpal tunnel release; 2) they have a history of wrist or median nerve injury from trauma (e.g. contusion, fractures) or prior surgery on the wrist; 3) they have a history suggesting underlying causes of CTS, such as diabetes mellitus, thyroid disease, rheumatoid arthritis, chronic renal failure treated by haemodialysis, space-occupying lesions in the volar wrist area, anatomic abnormalities of the wrist or hand, pregnancy or lactation; 4) they have clinical signs or symptoms, or electrodiagnostic studies suggesting conditions that could mimic CTS or interfere with its validation, such as cervical radiculopathy, brachial plexopathy, thoracic outlet syndrome, pronator teres syndrome, ulnar neuropathy, polyneuropathy, Raynaud's disease or sympathetic dystrophy; 5) there is severe thenar muscle atrophy. These inclusion and exclusion criteria are designed to select a relatively homogeneous group of patients with idiopathic CTS, suitable for both splinting and surgery.

Patients who are eligible for participation are informed about the trial by the neurologist. If they show interest, they receive written information about the trial and an appointment is made with the research assistant, who explains again the aim of the study and the implications of participation. A research physiotherapist checks again on all inclusion and exclusion criteria. Patient who meet the selection criteria and are willing to participate must complete the informed consent procedure by signing an informed consent form.

Subsequently, an assessment is made of baseline values of outcome measures and potential prognostic indicators, such as age, gender, bilateral symptoms, dominant side most severely affected, duration of symptoms and preference of the patient for splinting or surgery. For all CTS patients who are not eligible or not interested in participating, the reasons for not non-participation are recorded by the neurologist or the research physiotherapist, together with data on age, gender, duration of symptoms and prescribed treatment.

**Electrodiagnostic confirmation of CTS**

According to the guidelines of the American Association of Electrodiagnostic Medicine,[3] the following protocol is adopted: [20] Skin temperature is measured prior to testing, and hands with a temperature of less than 32°C are warmed. [21] Both hands are tested. Sensory and motor nerve conduction is studied, using surface electrodes for stimulating and recording. Latencies are measured from the stimulus onset to the initial negative response, and amplitudes are measured from baseline to negative peak. The sensory nerve action potentials are recorded antidromically with ring electrodes around the proximal (active) and distal (reference) interphalangeal joints. The ground electrode is attached to the distal region of the wrist. Median nerve sensory conduction velocity (SNCV) is measured from the wrist to the index and ring fingers. Ulnar nerve sensory conduction is measured from the wrist to the ring finger. The distances between the median and ulnar stimulation sides at the wrist and the recording electrodes on the ring finger are equal. The compound muscle action potential is recorded from the thenar eminence with the active recording electrode placed over the abductor pollicis brevis (APB) muscle belly. The reference electrode is placed over the APB tendon. Median nerve distal motor latency (DML) is measured with stimulating and recording cathodes 7 cm apart. Median motor nerve conduction velocity is measured in the forearm. Supramaximal stimulation is delivered to the elbow and wrist.

The electrodiagnostic criteria used to confirm the clinical diagnosis of carpal tunnel syndrome are: 1) SNCV (index finger) ≤ 41.9 meters/second (m/s) in patients < 55 years or ≤ 37.3 m/s in patients ≥ 55 years, or distal sensory latency (DSL) (index finger) ≥ 3.5 milliseconds (ms)[22], or 2) median-ulnar DSL difference (ring finger) > 0.4 ms[23], or 3) DML ≥ 4.34 ms. [22]

**Treatment allocation**

Patients are randomly allocated to either splinting or surgery. If bilateral symptoms are present, the hand with the most severe symptoms, according to the patient, is treated. A randomization list is prepared for each participating hospital. Permutated blocks of 4 patients are made to ensure near-equal distribution of patients over the two treatment groups in each hospital (i.e. after every 4 patients the number of patients allocated to splinting is equal to the number of patients allocated to surgery). [24] The random sequence of the permuted blocks is generated by using random number tables. The principle investigator (AG), who is not involved in the selection of patients, prepared coded, sealed, opaque envelopes containing the treatment allocation. [25] After the baseline assessment, the next envelope for the hospital concerned is handed over to the patient by the research assistant, thus the research physiotherapist remains blinded for the allocation of treatment. After the patient has opened the envelope, appointments for the allocated treatment, either splinting or surgery, are made to ensure that the
treatment is started as soon as possible after randomization.

Blinding
Obviously, the patients cannot be blinded for the allocated treatment. Therefore, blinding of most of the outcome measurements is not possible, due to the fact that mainly self-reported outcomes are used. Similarly, the care-providers cannot be blinded, but they are not involved in the outcome measurements. However, the research physiotherapist who scores the overall severity of CTS complaints after history-taking and a physical examination is not informed about the allocated treatment. In order to optimize blinding, the patients are asked immediately before their visits not to reveal any information regarding their treatment to the research physiotherapist. Furthermore, before each examination the research assistant sticks a plaster over the wrist and palm of all patients to conceal a potential operation scar. The success of blinding is evaluated after each examination.

Treatments
For patients allocated to splinting, the research assistant makes an appointment with a plaster technician, an occupational therapist or a home-care store, depending on the usual procedures in the hospital. The splint immobilizes the wrist in a neutral position in order to avoid flexion or extension of the wrist, which increases carpal tunnel pressure. [26] Depending on the hospital procedures, it can be a custom-made splint (made of soft-cast) or a prefabricated splint (trademark Tricodur), which contains a metal strip that can be adjusted to immobilize the wrist in a neutral position. There are no standard prescription guidelines for wearing splints, but for this study the patients are instructed to wear the splint during the night for at least 6 weeks, and during the day only if they wish to. The reason for this is that symptoms are often worse at night and also because compliance at night is higher than during the day [13] probably because splinting can interfere with the activities of daily living. The period of 6 weeks is chosen mainly because this period is generally used in the participating hospitals. No other types of therapy are permitted during these 6 weeks, except twice daily 250–500 mg Naproxen prescribed by the neurologist for pain relief, if necessary. Patients are instructed to perform gentle range-of-motion exercises to prevent stiffness of the wrist and fingers. There are no work or activity restrictions for the patients. After 6 weeks the neurologist and patient together determine whether any further treatment (continuing with the splint, other conservative treatment options or surgery) is necessary.

For patients allocated to early surgery, the research assistant makes an appointment with a general surgeon, neurosurgeon, plastic surgeon or orthopedic surgeon, depending on the usual procedures in the hospital, for an outpatient OCTR to be performed within 4 weeks after randomization. Before surgery, no other types of treatments are permitted, except twice daily 250–500 mg Naproxen, prescribed by the neurologist or surgeon for pain relief, if necessary. Patients are operated or under regional anesthesia, using a pneumatic tourniquet, or under local anesthesia. The following protocol is adopted: A skin incision is made in the palm, in line with the middle finger, between the thenar and hypothenar eminences. The superficial palmar fascia and the transverse carpal ligament are divided longitudinally. Neither synovectomy nor neurolysis is performed. The skin is closed in one single layer. A pressure dressing is applied immediately after the operation and removed the next day. Stitches are removed after 2 weeks. The patient is instructed to perform post-operative active range-of-motion exercises and encouraged to use the hand as tolerated. No absolute period off sickness absenteeism is recommended.

Outcome assessment
Although there is no consensus on which outcome measures should be used for evaluating treatment effects in patients with CTS, outcomes related to symptoms are considered to be the most relevant for the patients. [27]

Primary outcome measures
1. General improvement, scored by the patient on a 6-point ordinal transition scale, ranging from 'completely recovered' to 'much worse'. [28] To calculate success rates, this scale is dichotomized as 'improved' (completely recovered or much improved) and 'not improved' (slightly improved, no change, slightly worse, much worse). If patients indicate that the symptoms have improved, the date of improvement is recorded, to enable the calculation of time (from randomization) to recovery.

2. The number of nights that the patient awoke, due to the symptoms, during the past week.

3. The severity of the most important symptoms. At baseline, assisted by the research physiotherapist the patients selects the complaint that he or she considers to be the most important, e.g. paraesthesias when holding the telephone. [29] A list of possible complaints is offered to provide suggestions, but the patient is also allowed to select a complaint that is not on the list. The severity of this main complaint, pain, paraesthesias and hypoesthesias at night and during the day, during the past week are scored by the patient on an 11-point numerical rating scale, ranging from 0 'no symptoms' to 10 'very severe symptoms'.
Secondary outcome measures

1. The patients are asked to indicate their level of satisfaction with the results of the treatment(s) they received on an 11-point numerical rating scale, ranging from 0 'very unsatisfied' to 10 'completely satisfied'. [30]

2. The patients record the use of pain medication for the symptoms during the past week (yes/no). The use of analgesics is considered to be an indication of the severity of pain.

3. The severity of symptoms and functional status are assessed by means of a self-administered questionnaire, containing two scales. [31] The Symptom Severity Scale consists of 11 questions about the severity, frequency and duration of symptoms (pain, paraesthesias and hyposthesias at night and during the day, weakness, difficulty with gripping small objects) experienced during the past 2 weeks. Items are rated from 1 (mildest) to 5 (most severe), and the overall symptom-severity score is calculated as the mean score of all 11 items. The Functional Status Scale consists of 8 items concerning difficulties in performing various activities (writing, buttoning, holding a book, grabbing the telephone, opening jars, performing household chores, carrying a grocery bag, bathing and dressing) during the past 2 weeks. The overall score for functional status is calculated as the mean of the individual scores on the 8 items ranging from 1 (no difficulty) to 5 (cannot perform activity at all). Items that are not applicable are not included in the calculation of the overall score. Therefore a response category (0) was added, indicating that an activity is never performed with the hand studied in the trial (e.g. writing). Both scales are reported to be reproducible, internally consistent, valid and responsive to clinical change. [31] This study uses the Dutch version of the questionnaire, which has already been used in an RCT on the surgical treatment of CTS. [30]

4. The overall severity of CTS complaints is judged by the research physiotherapist on an 11-point numerical rating scale, ranging from 0 'no complaints' to 10 'very severe complaints', after standardized history-taking and physical examination. [29] To minimize inter-observer variation the research physiotherapists are trained in performing the measurements in a standardized way. The history-taking includes type, timing and location of complaints, and difficulties with performing the activities of daily life, hobbies and sports during the past week. The physical examination includes: a) assessing thenar atrophy (graded as none, mild or severe, based on the bulk of the abductor pollicis brevis muscle); [32] b) performing provocative tests: Tinel's percussion test, Phalen's wrist flexion test, wrist extension test, and the combined wrist flexion and carpal compression test (scored positive if symptoms are produced or exaggerated); [33] c) manual muscle-testing of the abductor pollicis brevis and opponens pollicis (graded from 0 to 5, according to the criteria of the American Orthopedic Association); d) measuring maximum grip strength with a Jamar hand-held dynamometer and maximum tip and key pinch strength with a Jamar pinch gauge, both in kilograms, calculating the mean of 3 attempts; [34] and e) performing Semmes-Weinstein monofilament testing on the thenar eminence, index and middle finger (recording the lightest monofilament that a patient can feel). [33]

5. Results of electrodiagnostic studies. These studies are performed according to the previously described protocol that is used to confirm the clinical diagnosis of CTS.

Other outcome measures

1. Patients are asked to record any treatment that they have received (e.g. wrist splint, surgery, injection with corticosteroids). To measure compliance with wrist splinting, patients have to rate the mean number of nights and days per week that they have been wearing the splint. The treating physicians are also asked to record any treatment they have prescribed for the patient on a standard form.

2. Adverse effects that are ascribed to the therapy (e.g. stiffness of the wrist or fingers, wound infection, hematoma, painful scar) are recorded by the patient and by the treating physicians.

3. Direct and indirect costs will be evaluated with diaries that have to be kept up to date weekly by the patients. [35] Patients record their visits to health care providers, use of (prescribed) medication, household help and time lost from paid or unpaid work. The consequences of CTS complaints for paid or unpaid work are also evaluated by means of a personal interview by the research assistant, using the Health and Labor Questionnaire. [36] To compare the results of the cost-effectiveness analysis with other conditions, general health status is measured according to the standard Dutch versions of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) [37] and the EuroQol.[38]

4. To evaluate the success of blinding, the research physiotherapist is asked to guess the allocated treatment after each examination, and to state the level of certainty (0–10) and reasons for this assumption. [28]

In order to study short and long-term treatment effects, data are collected in the hospital at baseline and at 3, 6 and 12 months after randomization. Additional postal questionnaires are sent to the patients in the months that they do not visit the hospital (1, 2, 4, 5, 7, 8, 9, 10 and 11
months after randomization), and again 18 months after randomization. Table 1 gives an overview of the data-collection: see Additional file 1: [table 1 (biomedcentral_revised)]

When bilateral symptoms are present, some outcome measures (waking up at night, severity pain, paraesthesias and hypoesthesias at night and during the day, use of pain medication and treatment received) are also recorded for the hand not studied in the trial, at baseline and 3, 6, 12 and 18 months after randomization.

**Sample size**
A relative difference of 50% or more in median time to recovery is considered to be clinically relevant. This gives, for example, a median time to recovery of 3 months for surgery and 4.5 months for splinting. To detect this difference in a survival-analysis with a significance level (alpha) of 5% (2-sided) and a power (1-beta) of 80%, 85 patients per treatment group are needed. To ensure the inclusion of 190 patients, 13 hospitals are participating in the study.

**Statistical analysis**
To determine whether randomization has been successful, prognostic similarity between the treatment groups is assessed at baseline for potential prognostic indicators and baseline values of outcome measures.

The outcome measurements at 1 month, 3, 6, 12 and 18 months are considered to be the most important. Therefore, the groups are primarily compared at these points in time. Differences in success rates and use of pain medication between the treatment groups are calculated, together with 95% confidence intervals. Survival-analysis is used to calculate differences in median time to recovery. All other outcomes are analyzed as continuous variables, and differences between the baseline measurement and each follow-up measurement (change score) are calculated for each patient separately. Subsequently, differences in mean change scores between the treatment groups are calculated, together with 95% confidence intervals. Multivariate analyses are performed to examine the influence of differences between the groups at baseline. All the analyses are performed according to the intention-to-treat principle. [39] In addition, alternative analyses are conducted, comparing patients in the splint group who received additional surgery with patients in this group who did not receive this extra treatment.

Finally, exploratory analyses are conducted to investigate whether the treatment effect (success rate and mean improvement in severity of the main complaint) after 3 months varies in specific subgroups of patients: age ≤ 49 years versus > 49 years, male versus female, duration of symptoms ≤ 50 weeks versus > 50 weeks, non-dominant versus dominant side affected, unilateral versus bilateral CTS complaints, no previous episodes versus previous episodes of CTS complaints, preference for surgery versus splinting versus no preference, baseline severity of the main complaint ≤ 7 versus > 7. Using logistic regression for success rate and linear regression for severity of the main complaint, each prognostic indicator is checked for interaction with treatment. If the interaction term is significant, a stratified analysis will be performed.

All patients who withdraw from the study are included in the analysis until the time of withdrawal, after which the group mean (continues outcomes) is used to impute the missing data. Similarly, occasional missing values are substituted by group means. For all comparisons, a p-value of 0.05 or less is considered to indicate statistical significance (two-sided).

**Conclusions**
In this article the rationale and design of an RCT on the efficacy of splinting compared with early surgery for CTS is discussed. The objective of this study is to provide scientific evidence for the choice of the initial treatment for CTS. The intended size of the study population is sufficiently large to detect clinically important treatment differences, and the follow-up period is long enough to study both short and long-term effects. The design of this study might provide guidance for other (randomized) studies on CTS or neurological ailments in general. The results of this trial will be presented as soon as they are available.

**Competing interests**
None declared.

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