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[Intervention Protocol]

Open release for carpal tunnel syndrome

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of conventional open techniques for carpal tunnel release compared to any other surgical intervention for the treatment of carpal tunnel syndrome. More specifically, to evaluate the relative impact of the open techniques in relieving symptoms, producing functional recovery (return to work and return to daily activities) and reducing complication rates compared to other surgical treatments.

BACKGROUND

Carpal tunnel syndrome (CTS) is the most common compressive neuropathy of the upper extremity. In the US, one person in 20 will suffer from CTS during his or her lifetime (Atroshi 1999). Women are most commonly affected (Bland 2005; Latinovic 2006). Most cases are diagnosed between the ages of 40 and 70 years (Latinovic 2006). In the UK, 90 men and 193 women are diagnosed with CTS per 100,000 visits to primary care departments (Latinovic 2006). The equivalent figures in the Netherlands in 2001 were 90 and 280 per 100,000 visits (Bongers 2007). Approximately 500,000 operations for CTS are performed every year in the US, at a cost of over USD 2 billion annually (Palmer 1995). According to US Department of Labor 2009 figures, sick leave of at least 30 days per year is recorded in around 45% of cases attributed to carpal tunnel syndrome, which suggests important insurance-related consequences (U.S. Department of Labor 2009).

Description of the condition

CTS is a median nerve neuropathy. The median nerve at the level of the wrist passes through an anatomical tunnel between the transverse carpal ligament and the carpal bones called the 'carpal tunnel'. Increased pressure on the median nerve inside the carpal tunnel is the trigger that leads to the symptoms of CTS. Sustained pressure on the nerve compromises its blood supply and leads to oedema, and this causes functional impairment and clinically evident symptoms (Fuchs 1991). CTS can be secondary when there is an obvious pathology that puts extrinsic pressure on the median nerve or that indirectly contributes to the median neuropathy - this usually occurs through metabolic pathways such as diabetes

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mellitus (Stevens 1992). The vast majority of cases, however, are considered idiopathic; that is, without an identified cause.

While CTS is generally believed to increase with age (Latinovic 2006), it can occur at any age and the diagnosis should not be discounted purely on these grounds (Bland 2005; www.carpal-tunnel.net). Several predisposing factors have been described, the most common of which are pregnancy, diabetes mellitus, hypothyroidism (or probably even hyperthyroidism) or other endocrine diseases (de Rijk 2007; Osterman 2012). Labour characteristics, such as jobs requiring repetitive hand work (e.g. secretary or typist) or vibrating tools, may also predispose to the onset of CTS (Jenkins 2013; Palmer 2007; Shiri 2009).

Paraesthesia and numbness in the area of sensory distribution of the distal median nerve, accompanied by pain, are the first symptoms of CTS. Symptoms are typically more apparent during the night and can disturb sleep. Pain may occur more proximally in the arm. Denervation of the thenar muscles may gradually cause atrophy and the patient eventually notices weakness. Sensory disability and weakness contribute to a growing inability to handle small objects (e.g. fastening buttons and handling keys, cups and forks).

Electrophysiological tests (nerve conduction studies) have been used as a documentation tool to confirm median nerve damage, locating the source of the dysfunction at the level of the carpal tunnel. Electrophysiological tests are used to support the clinical diagnosis of CTS and to distinguish CTS from other lesions of the more proximal peripheral or central nervous system that can mimic CTS and produce similar symptomatology (for example, brain tumours, multiple sclerosis or cervical disc hernia). The tests usually reveal a decreased conduction velocity and increased latency in the part of the median nerve located along the carpal tunnel (Jordan 2002).

Conservative treatment is recommended for the early stages of CTS. This consists of rest, splinting and anti-inflammatory medication, either orally or in the form of perineural corticosteroid injections (O'Connor 2012; Page 2012; Page 2012a; Page 2013; Piazzini 2007). The aim of conservative treatment is to lessen the presumed inflammation and oedema of the median nerve, reducing the pressure applied by the surrounding tissues in the carpal tunnel. However, there is currently unsatisfactory or limited evidence from double-blind randomised controlled trials for the use of non-steroidal anti-inflammatory drugs (NSAIDs) or other non-surgical treatment options for the treatment of CTS. If conservative or surgical treatments are ineffective, the chronic pressure on the median nerve leads to irreversible nerve damage and permanent muscle weakness (Gelberman 1988), even if surgery is performed at a later date. Surgical intervention is eventually recommended in 30% to 40% of people (Latinovic 2006; Wilson 2003).

Description of the intervention

Surgical treatment of CTS consists of dividing the transverse carpal ligament, with a subsequent decrease in pressure on the median nerve. There are several surgical techniques used to perform this release.

Conventional open release (open carpal tunnel release, OCTR) is the oldest and most frequently used technique. It starts with a skin incision just over the transverse ligament of the wrist, followed by incision of the underlying subcutaneous tissue. Finally, the surgeon directly approaches the transverse ligament and cuts it under direct vision. This is generally considered to be a safe surgical approach, allowing the surgeon to visualise and avoid damaging the major tissues at risk, namely the median nerve and its branches, and the ulnar artery (Scholten 2007).

In the past, additional interventions have been suggested in order to increase the efficacy of CTS surgical treatment. Epineurotomy or even internal neurolysis of the median nerve have been performed, but are not common and are not usually performed except for specific indications (Curtis 1973; Fissette 1979). Reconstruction of the transverse ligament has also been suggested but authors have not managed to demonstrate its superiority (Karlsson 1997).

However, the open technique is associated with relatively large surgical trauma. The complete incision of skin and subcutaneous tissue can increase postoperative morbidity. This may be associated with increased postoperative pain due to more extended damage to subcutaneous nerves than is necessary. Consequently, the procedure may prolong the time to return to work or to daily activities.

Minimally invasive procedures have been suggested for the treatment of CTS; such procedures are endoscopic or mini-open techniques. In both cases, the skin incisions are limited and usually not directly superficial to the transverse ligament (Cellocco 2009; Teh 2009; Wongsiri 2008). Special equipment is necessary in the endoscopic and in many of the mini-open approaches. These approaches have the theoretical advantage over OCTR of minimising surgical trauma, hence offering faster recovery (Vasiliadis 2009). However, indirect or limited vision of the tissues to be divided may result in a higher rate of injuries to other tissues, leading to a higher rate of complications. There is also a theoretical increase in the risk of incomplete dissection of the transverse ligament, which may lead to an inadequate decrease in pressure on the median nerve and thus to an increased rate of CTS recurrence.

How the intervention might work

All techniques work through the same mechanism: cutting of the transverse ligament, which reduces pressure on the median nerve within the carpal tunnel. Each technique (conventional open, mini-open or endoscopic) has its own limitations as described above. In brief, the conventional open technique is associated with increased damage to superficial adjacent tissues, whereas the mini-open or endoscopic techniques are conducted with limited vision, which can lead to incomplete ligament transection or damage to adjacent deep tissues.

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There is still controversy in the literature regarding the safety and effectiveness of OCTR compared to the new minimally invasive techniques (either endoscopic or mini-open).

Why it is important to do this review

CTS is very common. The conventional open release is still considered the gold standard for the treatment of CTS. It is important to assess the efficacy of standard OCTR, especially to compare the conventional open technique with the new mini-open techniques or with the endoscopic techniques available, and also to assess the effectiveness and safety of additional procedures like epineurotomy or transverse ligament reconstruction.
The current review will replace a previous Cochrane review (Scholten 2007). The relative effectiveness and safety of endoscopic techniques for carpal tunnel syndrome are subject of another Cochrane review (Vasiliadis 2014). The current review will follow the same protocol with a view to inclusion in an overview of reviews.

OBJECTIVES

To assess the effectiveness and safety of conventional open techniques for carpal tunnel release compared to any other surgical intervention for the treatment of carpal tunnel syndrome. More specifically, to evaluate the relative impact of the open techniques in relieving symptoms, producing functional recovery (return to work and return to daily activities) and reducing complication rates compared to other surgical treatments.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised controlled trial (RCT) or quasi-RCT comparing open carpal tunnel release (OCTR) with any other surgical intervention for the treatment of carpal tunnel syndrome (CTS). We will also include studies comparing different OCTR techniques with each other.

Types of participants

We will include studies with participants who have a clinical diagnosis of CTS with or without electrophysiological confirmation. We will accept the authors' definition of CTS and their views of what constituted electrophysiological confirmation.

Types of interventions

We will include studies comparing OCTR with any other surgical intervention for the treatment of CTS.
These could be endoscopic carpal tunnel release (ECTR), release with mini-open techniques (MOCTR) or OCTR techniques with concomitant interventions (such as lengthening of flexor retinaculum, internal neurolysis, epineurotomy or tenosynovectomy).

Types of outcome measures

These outcomes are not criteria for including studies in the review, but rather a list of the outcomes of interest within whichever studies are included.

Primary outcomes

1. Improvement of CTS symptoms as measured by the patient-reported Symptom Severity Score (SSS) (Levine 1993), or any other measure of improvement in pain, paraesthesiae or nocturnal paraesthesiae.
2. Functional status, measured with any validated instrument for measuring disability, e.g. the Functional Status Scale (FSS), a patient-reported questionnaire (Levine 1993).

Secondary outcomes

1. Questionnaires measuring overall improvement with ratings such as 'improved' or 'not improved'. We will include these measures if they evaluate global improvement across all symptoms.
2. Disability (measured with a validated instrument, e.g. the arm, shoulder and hand (DASH) questionnaire).
3. Grip strength.
4. Time to return to work or to resume activities of daily living (ADL).

Complications

1. Recurrence of CTS.
2. The rate of re-operations (at final follow-up).
3. Minor complications (e.g. pain or scar disorders), defined as the number of patients with at least one minor complication.
4. Major complications (e.g. nerve, vascular or tendon injuries), defined as the number of participants with at least one major complication.

We will consider both short-term (less than or equal to three months) and long-term (greater than three months) effects. If multiple time points are reported, then we will consider the latest (being less or equal to three months) as 'short-term'. We will consider the longest follow-up available, if greater than three months, as 'long-term' measurement.
We will extract data regarding the cost of interventions and present these in a narrative way.

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Search methods for identification of studies

Electronic searches

We will search the Cochrane Neuromuscular Disease Group Specialised Register, the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. The MEDLINE search strategy is presented in Appendix 1.

We will also conduct a search of the US National Institutes for Health Clinical Trials Registry, ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) for ongoing studies. We will search all databases from their inception to the present. We will impose no restriction on language of publication.

We will search DARE, NHSEED and HTA for information of relevance to the Discussion.

Searching other resources

We will search reference lists of all primary studies and review articles for additional references. For techniques where special instrumentation is required we will search relevant manufacturers' websites for trial information. We will also contact trial authors.

We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (HSV, MES) will independently screen titles and abstracts of all studies identified by the above-mentioned strategies and exclude studies that obviously do not meet the inclusion criteria. The same two review authors (HSV, MES) will independently screen the full text of the study reports of the remaining studies. They will identify studies for inclusion and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third author (IS).

We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (HSV, MES) will independently extract data from included studies using a data extraction form for study characteristics and outcome data. Data extraction forms will include information on methods, participants, interventions and outcomes. Notes will also be included reporting information on funding, baseline differences and notable conflicts of interest of trial authors. We will resolve any disagreement through discussion or, if required, we will consult a third author (IS).

One review author (MES) will transfer data into Review Manager (RevMan) (RevMan 2012). A second author (HSV) will check the outcome data entries.

Assessment of risk of bias in included studies

Two review authors (HSV, MES) will independently assess the risk of bias for each trial using The Cochrane Collaboration 'Risk of bias' tool, described in the *Cochrane Handbook for Systematic Reviews and Interventions* (Higgins 2011).

We will assess the adequacy of sequence generation, allocation concealment and blinding (of participants, personnel and outcome assessors). We will make judgements about the possible impact of incomplete outcome data, selective outcome reporting and other sources of bias. We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. The bias items that we will adapt to the context of our review are presented in more detail below.

The criteria for judging the risk of bias in each study are given in detail in table 8.5.c of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Blinding

We will assess blinding of participants and personnel, and blinding of outcome assessors separately.

It is not possible to blind either the surgeons or the participants to the operation performed, therefore we will assess all studies as at 'high risk of bias' for the item 'blinding of participants and personnel', unless otherwise reported by the authors. However, the outcome assessor could be blinded (e.g. for assessing grip strength).

Incomplete outcome data

We will collect the number of and reasons for exclusions. We will report differences in attrition between intervention groups and also report whether the trial authors have conducted intention-to-treat (ITT) analysis.

The judgement will be 'low risk of bias' when there were no missing values in the outcome data, when the amount and reasons for missing values are not likely to affect the outcome or appropriate imputations to achieve ITT analysis are performed. When the

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extent of missing outcome data and the reasons for missing data are likely to have affected the outcome, then the judgement will be 'high risk of bias'. We will use 'unclear risk of bias' when the trial authors do not report enough information about the amount and reasons for attrition.

Selective reporting

We will evaluate the possibility of selective reporting. We will base our judgements primarily on comparing the study protocols (if we are able to identify them) with the published report. We will search in www.clinicaltrials.gov and the WHO trials portal (www.who.int/ictrp/en/) to identify protocols for the included studies. In the absence of the protocols we will evaluate whether the trial authors present all expected outcomes and whether there is agreement between the methods section and the results.

Other bias

We will consider two additional sources of bias.

The trial sponsors (usually manufacturers of the instrumentation needed in ECTR) might bias the results. The judgement will be 'high risk of bias' in the presence of a commercial sponsor and 'low' when there is a statement that the trial had not received any funding from a party with a vested interest; otherwise the judgement will be 'unclear'.

Given that trials are anticipated to be of small sample size, the presence of baseline differences might impact on the results. We will classify as 'high risk of bias' a study with baseline imbalance in important participant characteristics or the measured outcome. If these differences at baseline are not clinically relevant, we will classify the study as being at 'low risk of bias'. We will reserve the judgement 'unclear risk of bias' for studies with insufficient information to form a judgement.

Measures of treatment effect

For dichotomous outcomes, we will calculate the risk ratio (RR) with 95% confidence interval (95% CI).

For continuous outcomes measured with the same scale we will calculate the mean difference (MD) and 95% CI. When studies have used different scales for the same outcome, we will calculate the standardised mean difference. We will collect results based on change scores only if final values are not available.

Unit of analysis issues

Bilateral CTS and surgical treatment of both hands are common. If trial authors report results for the first hand only, we will use these results to bypass the problem of dependency.

In the case of bilateral involvement where the authors analyse and present data for hands rather than for participants, we will extract effect sizes that account for the dependency of observations (such as effects calculated with generalised estimating equations or methods for cluster-randomised trials). Studies may apply a cross-over type of design in which randomisation takes place for the first hand and the second hand is operated with the alternative technique. In such cases we will extract outcomes taking into account the paired nature of the data by seeking information on paired statistics and estimate standard errors as described in Section 16.4.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When the correlation coefficient is not provided to derive the appropriate adjusted estimate we will employ a correlation of 0.5 for the standard analysis and we will use two extreme values of 0.1 and 0.9 in a sensitivity analysis.

When we are not able to obtain adjusted estimates and in trials where both hands are operated upon in only a subset of the participants and it is unclear whether randomisation took place for hands or participants, we will collect crude estimates of effect based on outcomes pertaining to hands along with the number of randomised participants who contributed information from both hands to evaluate the degree of dependence in the outcomes. We will then perform sensitivity analyses to evaluate the extent to which the conclusions of the meta-analysis might be altered by failure to account for bilateral hand involvement in individual trials.

In case of studies with more than two eligible intervention groups, we will divide the sample size and event rate of the OCTR group by two so that the participants randomised to OCTR are not double-counted.

Dealing with missing data

With the purpose of including all participants randomised to any intervention, we will make every effort to extract data according to the ITT principle; that is, to analyse participants as randomised. When outcome data are not available for some participants, we will include the data as reported and record the analysis method (e.g. whether results pertain to per-protocol or available case analysis) and note the lack of ITT as a risk of bias.

Assessment of heterogeneity

We will evaluate the presence of clinical heterogeneity by comparing the participants' characteristics and the methodology across studies (see Data synthesis). We will assess statistical heterogeneity by visual inspection of the forest plots along with consideration of the test for heterogeneity and the I^2 statistic. If we identify enough studies per comparison, we will examine possible sources of heterogeneity by means of subgroup analysis or meta-regression analysis.

Assessment of reporting biases

For outcomes with at least 10 studies, we will draw contour-enhanced funnel plots to assess the association between study size

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and effect size. Where appropriate, we will use contour-enhanced funnel plots to distinguish between reporting bias and other causes of asymmetry (Peters 2008).

Data synthesis

We will combine results from studies that are sufficiently similar with respect to participant characteristics (e.g. age, sex, grip strength) and methodology followed (length of follow-up, diagnostic criteria etc.) using a random-effects model. If multiple trial arms are reported in a single trial, we will include only the relevant arms. Synthesis will take place accounting for the different interventions being compared; that is, we will synthesise open versus mini-open studies separately from open versus endoscopic studies.

'Summary of findings' table

We will include the outcomes major complications, re-operations, Symptom Severity Score (SSS), Functional Status Scale (FSS), grip strength and time to return to work in a 'Summary of findings' table according to GRADE methodology (Schünemann 2008).
For dichotomous outcomes (re-operations and major complications) we will calculate the assumed risk from the control intervention of the included RCTs by simply merging samples, as we do not expect important variations and we anticipate a small number of studies.

Subgroup analysis and investigation of heterogeneity

For outcomes and comparisons with a sufficient number of studies we will undertake a subgroup analysis considering the open technique used (with or without concomitant procedures, such as neurolysis or transverse ligament reconstruction).
To assess small study effects and the appropriateness of the random-effects model we will also calculate summary estimates according to the fixed-effect model and compare the results with those from the random-effects model. If small studies appear to differ from larger ones and if the number of included studies permits, we will perform meta-regression using the study variance as an explanatory variable. To investigate small study effects we will also use cumulative meta-analysis (where studies are ordered from the most to least precise), as described in Borenstein 2009.

Sensitivity analysis

We will conduct sensitivity analysis to assess the robustness of the results. We will exclude studies according to the following characteristics.

1. High/unclear risk of bias for incomplete outcome data.
2. Inappropriate adjustment for bilateral involvement.
3. High/unclear risk of bias for allocation concealment.
4. Studies with electrophysiologically confirmed CTS/not confirmed or unclear

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to October Week 3 2013>
Search strategy:

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1 randomized controlled trial.pt. (388233)
2 controlled clinical trial.pt. (89763)
3 randomized.ab. (285800)
4 placebo.ab. (156314)
5 drug therapy.fs. (1761599)
6 randomly.ab. (198582)
7 trial.ab. (300943)
8 groups.ab. (1271374)
9 or/1-8 (3287235)
10 exp animals/ not humans.sh. (4051824)
11 9 not 10 (2799041)
12 Carpal Tunnel Syndrome.tw. or Carpal Tunnel Syndrome/ (7893)
13 ((nerve entrapment or nerve compression or entrapment neuropath$) and carpal).mp. (1044)
14 12 or 13 (8001)

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15 octr.mp. (35)
16 (open adj3 release).mp. (586)
17 (open adj3 techni$).mp. (5242)
18 or/15-17 (5810)
19 11 and 14 and 18 (105)

CONTRIBUTIONS OF AUTHORS

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Screening search results:HSV, MES, IS

Organising retrieval of papers: HSV, MES, RS

Screening retrieved papers against inclusion criteria: HSV, MES, IS

Appraising quality of papers: HSV, MES, IS

Abstracting data from papers: HSV, MES

Writing to authors of papers for additional information: HSV

Providing additional data about papers: RS

Obtaining and screening data on unpublished studies: HSV

Data management for the review: HSV, GS

Entering data into RevMan 5: HSV

Analysis of data: HSV, GS, RS, IS

Interpretation of data: HSV, GS, IS, RS

Writing the review: HSV, GS

Performing previous work that was the foundation of the present study: RS, HSV

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Statistical analysis: HSV, GS

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IS is consulting medical director for Cirque de Soleil and receives grants from the Canadian Institutes of Health Research. These financial relationships were unrelated to the work on this manuscript and did not have an influence on any decisions.

MES: none known

RS: none known

HV received travel support from a manufacturer of instrumentation for mini-open and endoscopic release to attend an orthopaedic conference. Additionally, he is the Principal Investigator in an ongoing RCT comparing ECTR versus mini-open release.

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