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Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome (Review)

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[Intervention Review]

Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome

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ABSTRACT

Background

This review is an update of a review first published in Issue 2, 2003, which was substantially updated in Issue 7, 2010. The concept that many neuropathic pain syndromes (traditionally this definition would include complex regional pain syndromes (CRPS)) are "sympathetically maintained pains" has historically led to treatments that interrupt the sympathetic nervous system. Chemical sympathectomies use alcohol or phenol injections to destroy ganglia of the sympathetic chain, while surgical ablation is performed by open removal or electrocoagulation of the sympathetic chain or by minimally invasive procedures using thermal or laser interruption.

Objectives

To review the evidence from randomised, double blind, controlled trials on the efficacy and safety of chemical and surgical sympathectomy for neuropathic pain, including complex regional pain syndrome. Sympathectomy may be compared with placebo (sham) or other active treatment, provided both participants and outcome assessors are blind to treatment group allocation.

Search methods

On 2 July 2013, we searched CENTRAL, MEDLINE, EMBASE, and the Oxford Pain Relief Database. We reviewed the bibliographies of all randomised trials identified and of review articles and also searched two clinical trial databases, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, to identify additional published or unpublished data. We screened references in the retrieved articles and literature reviews and contacted experts in the field of neuropathic pain.

Selection criteria

Randomised, double blind, placebo or active controlled studies assessing the effects of sympathectomy for neuropathic pain and CRPS.

Data collection and analysis

Two review authors independently assessed trial quality and validity, and extracted data. No pooled analysis of data was possible.

Main results

Only one study satisfied our inclusion criteria, comparing percutaneous radiofrequency thermal lumbar sympathectomy with lumbar sympathetic neurolysis using phenol in 20 participants with CRPS. There was no comparison of sympathectomy versus sham or placebo. No dichotomous pain outcomes were reported. Average baseline scores of 8-9/10 on several pain scales fell to about 4/10 initially (1 day) and remained at 3-5/10 over four months. There were no significant differences between groups, except for "unpleasant sensation", which was higher with radiofrequency ablation. One participant in the phenol group experienced post sympathectomy neuralgia, while two in the

radiofrequency group and one in the phenol group complained of paraesthesia during needle positioning**.** All participants had soreness at the injection site.

Authors' conclusions

The practice of surgical and chemical sympathectomy for neuropathic pain and CRPS is based on very little high quality evidence. Sympathectomy should be used cautiously in clinical practice, in carefully selected patients, and probably only after failure of other treatment options. In these circumstances, establishing a clinical register of sympathectomy may help to inform treatment options on an individual patient basis.

PLAIN LANGUAGE SUMMARY

Cervico-thoracic or lumbar sympathectomy for neuropathic pain

Chronic pain due to damaged nerves is called neuropathic pain and is common. Some people consider that certain types of neuropathic pain (reflex sympathetic dystrophy and causalgia, now known collectively as Complex Regional Pain Syndrome (CRPS)) are caused by the sympathetic nervous system. Sympathectomy is a destructive procedure that interrupts the sympathetic nervous system. Chemical sympathectomies use alcohol or phenol injections to destroy sympathetic nervous tissue (the so-called "sympathetic chain" of nerve ganglia). Surgical ablation can be performed by open removal or electrocoagulation (destruction of tissue with high-frequency electrical current) of the sympathetic chain, or by minimally invasive procedures using thermal or laser interruption. Nerve regeneration commonly occurs following both surgical or chemical ablation, but may take longer with surgical ablation.

This systematic review found only one small study (20 participants) of good methodological quality, which reported no significant difference between surgical and chemical sympathectomy for relieving neuropathic pain. Potentially serious complications of sympathectomy are well documented in the literature, and one (neuralgia) occurred in this study.

The practice of sympathectomy for treating neuropathic pain is based on very weak evidence. Furthermore, complications of the procedure may be significant.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Lumbar sympathectomy using radiofrequency lesioning compared with phenol ablation for complex regional pain syndrome

Patient or population: adults with complex regional pain syndrome type 1 (lower limb)

Settings: hospital

Intervention: sympathectomy using radiofrequency lesioning

Comparison: sympathectomy using phenol ablation

Outcome	Probable outcome with intervention	Probable outcome with comparator	NNT or NNH and/or relative effect (95% CI)	No of participants	Quality of the evidence (GRADE)	Comments
At least 50% reduction in pain or equivalent	No data	No data				
At least 30% reduction in pain	No data	No data				
Proportion below 30/100 mm on VAS	Group average pain score fell from 9/10 to 4.5/10 within < 7 days and remained fairly stable for 4 months	Group average pain score fell from 8/10 to 4/10 within < 7 days and remained fairly stable for 4 months	Not calculated	19	Very low	Low number of events. One participant excluded from efficacy analysis
Patient Global Impression of Change: much or very much improved	No data	No data				
Adverse event withdrawals	1 in 10	0 in 10	Not calculated	20	Very low	Low number of events
Serious adverse events	1 in 10	0 in 10	Not calculated	20	Very low	Low number of events
Death	None	None				

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

NNT: number needed to treat for an additional beneficial outcome: NNH: number needed to treat for an additional harmful outcome; RR: risk ratio; VAS: visual analogue scale

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Straube 2010), which itself updated an earlier review on 'Sympathectomy for neuropathic pain' (Mailis-Gagnon 2003). We changed the title to more accurately reflect the scope of the review.

Description of the condition

The 2011 International Association for the Study of Pain (IASP) definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011) based on an earlier consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, but is often followed by changes in the central nervous system (CNS) (Moisset 2007). This recent definition would not cover all disease entities included in a previous, rather broad IASP definition (Merskey 1994), and in particular, it would probably exclude CRPS type I from being categorised as neuropathic pain. We wanted to be as inclusive as possible in the scope of our review and therefore considered all conditions that fulfil the old or new definition of neuropathic pain. To be unambiguous, the title of this review explicitly mentions CRPS.

Neuropathic pain is complex (Apkarian 2011; Tracey 2011), and typical features can be found in patients with joint pain (Soni 2013). It tends to be chronic and may be present for months or years. Many people are significantly disabled by moderate or severe pain.

In primary care in the UK the incidences, per 100,000 person years' observation, have been reported as 28 (95% confidence interval [CI] 27 to 30) for postherpetic neuralgia, 27 (95% CI 26 to 29) for trigeminal neuralgia, 0.8 (95% CI 0.6 to 1.1) for phantom limb pain, and 21 (95% CI 20 to 22) for painful diabetic neuropathy (Hall 2008). A study in the Netherlands estimated the incidence of CRPS as 26 per 100,000 person years (95% CI 23 to 30) (de Mos 2007), while an earlier smaller study in the USA reported an incidence of 5.5 per 100,000 person years, but using somewhat different diagnostic criteria (Sandroni 2003). Another estimate is that 1500 to 2000 cases of CRPS are diagnosed in Europe annually (Happak 2012). Estimates vary between studies, often because of small numbers of cases. The incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while more recently, a study of facial pain in The Netherlands found incidences per 100,000 person years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009). A systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy, can be more common, with *prevalence* rates up to 400 per 100,000 person years (McQuay 2007), illustrating how common the condition was as well as its chronicity. The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), as high as 8% in the UK (Torrance 2006), and about 7% in a systematic review of studies published since 2000 (Moore 2013a). Some forms of neuropathic pain, such as diabetic neuropathy and post surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008).

Neuropathic pain is known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical and/or cognitive interventions. Conventional analgesics are usually not effective. Some patients may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, though evidence about benefits is uncertain (Derry 2012; Khaliq 2007). High concentration topical lidocaine may benefit some patients with postherpetic neuralgia (Derry 2013). Treatment is more usually by so-called unconventional analgesics such as antidepressants like duloxetine and amitriptyline (Lunn 2009; Moore 2012a; Sultan 2008) or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2011). An overview of treatment guidelines points out some general similarities, but also differences in approach (O'Connor 2009). The proportion of patients who achieve worthwhile pain relief (typically at least 50% pain intensity reduction (Moore 2013b)) is small, generally 10% to 25% more than with placebo, with numbers needed to treat to benefit (NNTs) usually between 4 and 10.

Chronic painful conditions comprise five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life and employment and increased health costs (Moore 2013a).

Description of the intervention

Background and history

The concept of a dysfunctional sympathetic nervous system contributing to neuropathic pain is not new. The term 'Sympathetically Maintained Pain' (SMP), defined as pain maintained by sympathetic efferent innervation or by circulating catecholamines, was originally coined by Roberts (Roberts 1986). Many neuropathic pain syndromes, particularly CRPS types I and II, are thought to be SMP. Historically, this has led to attempts to interrupt the sympathetic nervous system dating back at least 80 years (Spurling 1930). Temporary and non-destructive interruption can be performed through injections of local anaesthetics or botulinum toxin, while a longer-lasting, "destructive" interruption can be achieved chemically or surgically. Chemical sympathectomies use alcohol or phenol injections to destroy ganglia of the sympathetic chain, but this effect is temporary until regeneration of the sympathetic chain occurs, usually after three to six months (Jackson 2008). Surgical ablation can be performed by open removal or electrocoagulation of the sympathetic chain, or by minimally invasive procedures using stereotactic thermal or laser interruption. The effects may be longer-lasting, up to one year with radiofrequency ablation (Jackson 2008). This review will consider the evidence for chemical and surgical sympathectomy, but not for temporary non-destructive interventions such as local anaesthetics and botulinum toxin.

Shumacker reported in 1948 the dramatic cure of causalgia (now called CRPS) by either surgical sympathectomy or alcohol injection in 81% of 57 post-war cases (Shumacker 1948). However, long term follow-up of post-war cases is usually missing from this and other similarly old literature. Currently, the most common indications for chemical neurolysis of the stellate ganglion are: CRPS types I and II, post-herpetic neuralgia of the trigeminal nerve, vasospastic conditions, and cancer pain of the face, neck, and upper extremities (Dobrogowski 1995). The bulk of experience concerning lumbar chemical neurolysis comes from the treatment of occlusive vascular diseases, but this procedure is also performed to treat cancer pain, CRPS types I and II, post-discectomy syndrome, phantom limb pain,

herpes-zoster, and the early stages of post-herpetic neuralgia (Dobrogowski 1995). The overwhelming indication for surgical sympathectomy is primary hyperhidrosis, while other indications for much smaller populations are neuropathic pain, vascular ischaemia, and Raynaud's phenomenon (Furlan 2000).

In 1996, Nath and colleagues conducted a literature review of surgical sympathectomy for reflex sympathetic dystrophy/ CRPS (Nath 1996). They concluded that sympathectomy should be reserved for patients with severe CRPS refractory to other treatment modalities. The reported results of the intervention varied widely but seemed to show a trend that sympathectomy was somewhat effective. However, Kingery 1997 reviewed the literature of controlled clinical trials for peripheral neuropathic pain and CRPS, and found no placebo-controlled trials to evaluate either local anaesthetic blocks of sympathetic ganglia or surgical sympathectomy. More recently Jackson and Gaeta (Jackson 2008) reviewed neuroablation and again found the quality of the evidence poor, concluding that no one agent was demonstrably better than any other, and that for malignant pain "short-term pain relief may outweigh risk at end of life", but for chronic benign pain it should be a treatment of last resort after careful consideration. Cetas et al. (Cetas 2008), in reviewing destructive procedures for nonmalignant pain, found few studies with sufficiently rigorous methods to avoid known biases, and additional problems of small study size (risk of random chance), mixed or poorly defined diagnoses, and inadequate follow up. They concluded that "efficacy has not been well established based on contemporary standards", and that "new, prospective, standardised studies are required .... to advance the field".

Current practice

Surgical sympathectomy for neuropathic pain or CRPS seems to be performed only rarely by vascular surgeons; if a sympathectomy is needed, then the more common procedure would be a percutaneous trial of local anaesthetic followed by either repeat with local anaesthetic or radiofrequency nerve ablation (RF). An alternative approach would be, after a trial of a local anaesthetic block, to inject 5 to 7 mL of phenol 6% or 10% either alone or in combination with RF. However, the majority of interventionalists would reserve the use of phenol for terminal cases because of the risk of the phenol leaking, and associated problems; reports of neuritis are not uncommon and paralysis has been reported.

Sympathectomy is not a commonly performed procedure, whichever method is used. For neuropathic pain or CRPS an initial local anaesthetic block, possibly repeated, may be followed by either RF or spinal cord stimulation (SCS); use of phenol is uncommon. Surgical division is uncommon for neuropathic pain or CRPS. For cancer or ischaemic leg pain, local anaesthetic block followed by RF or phenol, or both, might be used. Details are likely to vary in different parts of the world.

Computerised tomography (CT) is increasingly used to direct blocks, rather than using anatomical landmarks or image intensifier techniques. The facilities required and the number of procedures required to maintain clinical skills would suggest that fewer people are regularly performing these blocks. Although ultrasound is becoming more widely used for chronic pain blocks, its use for sympathectomy appears to be uncommon.

Why it is important to do this review

Because neuropathic pain is a common disease and sympathectomy is an invasive intervention with potentially serious complications (Furlan 2000), there is a need for a systematic review of the efficacy and associated harms of sympathectomy for neuropathic pain, using strict inclusion criteria regarding study quality and validity that minimise biases.

The first review in 2003 included one randomised trial that was not blinded, two retrospective chart reviews and one prospective observational study. In the first update we chose to exclude studies that were not both randomised and double blind because such studies are known to be prone to biases and have significant potential to mislead (Moore 2006). Important non-randomised or non-double blind studies are no longer included among the results section of this systematic review but are dealt with in the discussion section. For this second update we have searched for additional studies, expanded the Risk of bias assessment, and included a Summary of findings table in keeping with improved standards in recent Cochrane reviews.

OBJECTIVES

To review the evidence from randomised, double blind, controlled trials on the efficacy and safety of chemical and surgical sympathectomy for neuropathic pain, including complex regional pain syndrome. Sympathectomy may be compared with placebo (sham) or other active treatment, provided both participants and outcome assessors are blind to treatment group allocation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double blind, controlled trials comparing sympathectomy with placebo (sham) or other active treatment for neuropathic pain or CRPS, with at least ten participants per treatment arm. Studies could be conducted in any setting (inpatients or outpatients). Studies published only as abstracts, and uncontrolled studies (case series, case reports, uncontrolled before and after studies) and studies in which participants and outcome assessors were not blinded to treatment group allocation were not included in this review.

Types of participants

Participants of any age, with any duration of neuropathic pain (acute, sub-acute, or chronic), were included.

Participants with neuropathic pains affecting the face and upper or lower extremities were included. Participants with pain affecting thoracic or abdominal viscera were excluded.

Pain origin: Participants with central or peripheral neuropathic pain syndromes were included in this review. However, participants with cancer pain were excluded: studies of cancer pain will include participants with both nociceptive and neuropathic pain, as the discrimination between the two pain mechanisms is rarely attempted or reported.

Types of interventions

Only studies of destructive surgical or chemical sympathectomy were included. Studies of temporary sympathetic blockade were not considered in this review because it is a non-destructive technique and its effect is of shorter duration.

Surgical sympathectomy in this review is defined as the surgical ablation or coagulation of the cervico-thoracic or lumbar sympathetic chain by means of open, endoscopic, laser, or radiofrequency procedures. Trials of surgical ablation of the celiac plexus were excluded.

Chemical sympathectomy is defined as the percutaneous ablation of the cervico-thoracic or lumbar sympathetic chain by the injection of phenol or alcohol solution. This procedure promotes a prolonged but not permanent sympathetic denervation. Studies of celiac and trigeminal blocks were excluded.

Types of outcome measures

Information was sought on participant characteristics: age, sex, condition treated, and duration of condition.

Primary outcomes

The primary outcome sought was participant-reported pain relief lasting for a minimum of 4 weeks. We chose dichotomous outcomes corresponding with definitions of moderate or substantial benefit as defined by the IMMPACT group (Dworkin 2008) and a recent proposal for a universal pain outcome (Moore 2013).

- Participants with ≥ 30% pain relief over baseline, or at least "much improved" on the Patient Global Impression of Change (PGIC) scale.
- Participants with ≥ 50% pain relief over baseline, or "very much improved" on the PGIC scale.
- Participants with no worse than mild pain.

Secondary outcomes

Secondary outcomes sought included:

- participants with < 30% pain relief over baseline or "mild" pain relief, or with undefined pain improvement;
- pain relief lasting < 4 weeks;
- adverse events and complications; and
- occurrence of persistent serious new or expanded pain (e.g. long-lasting post-sympathectomy neuralgia or other neuralgias).

Search methods for identification of studies

Electronic searches

The following databases were searched.

- MEDLINE (via Ovid) to May 2010 for the first update and to 24 June 2013 for this update.
- EMBASE (via Ovid) to May 2010 for the first update and to 24 June 2013 for this update.
- Cochrane Central Register of Controlled Trials (CENTRAL, 2010, Issue 5 in *The Cochrane Library* for the first update, and 2013, Issue 6 for this update).
- Oxford Pain Relief Database (Jadad 1996) for the first update.

See Appendix 1 for the search strategy for MEDLINE (via Ovid), Appendix 2 for the search strategy for EMBASE (via Ovid), and Appendix 3 for the search strategy for CENTRAL.

There were no language restrictions.

Searching other resources

Reference lists of review articles and both included and excluded studies were searched.

For this update we searched two clinical trials databases: clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We had personal communications with experts in the field of neuropathic pain, including the editorial board of the Cochrane Pain, Palliative and Supportive Care review group.

Data collection and analysis

Review authors were not blinded to the authors' names and institutions, journal of publication, or study results at any stage of the review. Two review authors independently selected the studies for inclusion, assessed methodological quality, and extracted data. Disagreements were resolved through discussion.

Selection of studies

Titles and abstracts of studies identified by the searches were reviewed on screen to eliminate those that clearly did not satisfy inclusion criteria. Full reports of the remaining studies were obtained to determine inclusion in the review.

Data extraction and management

Two review authors independently extracted data from included studies using a standard data extraction form. Disagreements were settled by discussion with a third review author. Data would be entered into RevMan 5 by one review author if appropriate. The following data were sought from all studies:

- Demographics: age and sex of participants.
- Pain type.
- Duration of symptoms.
- Previous and present treatments.
- Number of sympathetic blocks before sympathectomy.
- Whether the sympathetic blocks were considered successful enough to warrant sympathectomy.
- Type and approach of sympathetic block.
- Levels of denervation.
- Primary and secondary outcomes.
- Duration of follow up.
- Incidence of immediate and late complications.
- Type of complication.

For continuous variables, means and standard deviations of changes would be extracted if appropriate.

Assessment of risk of bias in included studies

Studies were assessed for methodological quality using the five-point Oxford Quality Scale (Jadad 1996) that considers randomisation, blinding, and study withdrawals and dropouts,

and for trial validity using the 16-point Oxford Pain Validity Scale (Smith 2000). Risk of bias tables were completed for randomisation, allocation concealment, blinding, incomplete outcome assessment, and study size.

Measures of treatment effect

Relative risk (or Risk ratio, RR) would be used to establish statistical differences. NNTs, numbers needed to treat to harm (NNHs) and pooled percentages would be used as absolute measures of benefit or harm.

Unit of analysis issues

We accepted randomisation to individual participant only.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, received the assigned study intervention, and provided at least one post-baseline assessment. Missing participants would be assigned zero improvement.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining only studies that examined similar conditions. We would assess statistical heterogeneity visually (L'Abbé 1987) and with the use of the I^2 statistic. If I^2 was greater than 50%, we would consider possible reasons.

Data synthesis

It was planned that data would be combined for analysis where there were at least two studies and 200 participants (Moore 1998). RR of benefit or harm would be calculated with 95% CIs using a fixed-effect model (Morris 1995). NNTs and NNHs with 95% CIs would be calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control would be assumed when the 95% CI of the relative risk of benefit or harm did not include the number one.

Subgroup analysis and investigation of heterogeneity

We planned for all analyses to be performed according to individual painful conditions because placebo response rates with the same outcome can vary between conditions (Moore 2009).

Issues for potential subgroup analysis were method of ablation (surgical or chemical), and anatomical location of the lesions, although it was anticipated that there would be too few data for meaningful analysis.

Sensitivity analysis

No sensitivity analyses were planned, since it was thought unlikely that there would be sufficient data.

RESULTS

Description of studies

Included studies

We did not identify any additional studies that satisfied the inclusion criteria in the updated searches. Only one randomised double blind study qualified for inclusion in this review, and this study did not compare sympathectomy versus sham or placebo. Manjunath 2008 randomised 20 participants with lower limb CRPS type I to receive either percutaneous radiofrequency thermal lumbar sympathectomy or lumbar sympathetic neurolysis with phenol. Ten participants were randomised to each group. Participants were required to satisfy the diagnostic criteria for CRPS (Bruehl 1999), have symptoms lasting for more than six months despite management in a multidisciplinary setting, have been unresponsive to medications for longer than six months (visual analogue scale (VAS) score of > 6/10), and have responded to a diagnostic block with 1% lidocaine on three occasions.

Radiofrequency treatment was performed with a radiofrequency cannula introduced 5 cm lateral to the spinous processes of L2, L3, and L4. The cannula position was assessed radiographically in anteroposterior and lateral views. A volume of 0.5 mL to 1 mL of ionic radio contrast medium (urografin 75%) was injected. Radiofrequency lesioning was performed for 90 seconds at a temperature of 80°C; a second lesion was made 5 mm anterior to the first. In the phenol group, 3 mL of 7% phenol was injected at each level.

Pain was assessed with a number of pain scores (VAS score, intensity of pain, sharp pain, hot pain, dull pain, sensitive sensation, deep pain, and surface pain), each measured on a 0 to 10 scale at baseline and at 1 day, 7 days, 2 months, and 4 months after the procedure.

Details are in the 'Characteristics of included studies' table.

Excluded studies

The four studies included in the first review did not meet our inclusion criteria for randomised, double blind studies (AbuRahma 1994; Greipp 1990; Haynsworth 1991; Mailis 1994). Details are in the 'Characteristics of excluded studies' table. Other articles identified in the searches could be eliminated on the basis of their titles and abstracts, without reading the full report.

Risk of bias in included studies

The one included study achieved the maximum score of five on the Oxford Quality Scale and 13/16 on the Oxford Pain Validity Scale, where points were lost because of the small group sizes.

The Risk of bias assessment showed that the study did not report on the method of allocation concealment, but was not at high risk of bias.

Details are in the 'Characteristics of included studies' table.

Effects of interventions

See: **Summary of findings for the main comparison**

Efficacy

In both treatment groups there were statistically significant reductions from baseline in all the utilised pain scores. One participant in the phenol group had post sympathectomy neuralgia and was excluded from the efficacy analysis. In both groups initial average pain scores of 8 to 9/10 fell to about 4/10 initially (after 1 day) and remained at 3 to 5 over four months. There were no significant between-group differences in mean pain scores, except for the "unpleasant sensation" score, which was higher in the

radiofrequency group. No dichotomous efficacy outcomes were reported.

Adverse events

All participants complained of soreness lasting 5 to 7 days at the site of injections. One participant in the phenol group experienced post sympathectomy neuralgia. Two participants in the radiofrequency group and one in the phenol group complained of paraesthesia during needle positioning. The number of participants with serious adverse events was not reported.

DISCUSSION

Summary of main results

We found only one double blind randomised controlled trial (RCT) assessing the efficacy of this intervention that qualified for inclusion in this review. Based on very limited evidence from a pilot study, radiofrequency lumbar sympathectomy and lumbar sympathectomy with phenol seem about equally efficacious.

Overall completeness and applicability of evidence

Evidence from randomised trials for sympathectomy (both surgical and chemical) for neuropathic pain and CRPS is virtually absent. Evidence that we have found is of extremely limited applicability.

Quality of the evidence

The evidence from the single trial is of poor quality because of the small size.

Potential biases in the review process

We know of no potential biases in the review process.

Agreements and disagreements with other studies or reviews

Lower quality evidence on the effectiveness of sympathectomy is largely positive. A meta-analysis on causalgia (Hassantash 2003) included 110 articles (case series and case reports) and 1528 participants. Seven hundred and ninety-one participants were treated with sympathectomy of the diseased extremity. In 721 participants (91%) the condition responded. In 21 cases where the first sympathectomy was unsuccessful, a second sympathectomy was performed and was always successful. According to Hassantash 2003, therefore, a total of 94% of participants were "cured" by sympathectomy. A systematic review on the effectiveness and complications of chemical sympathectomy for neuropathic pain of the extremities, including controlled and non-controlled studies, described meaningful pain relief (there defined based on degree and duration (> 2 weeks) of pain relief) in 28/63 (44%) participants and non-meaningful pain relief in 12/63 participants (19%); in 23/63 participants (37%) the pain relief could not be classified (Furlan 2001).

In comparison with other treatments, lower quality evidence suggests that sympathectomy is at least not inferior. A retrospective review of patient charts of 27 CRPS patients (Greipp 1990) found that the four treatment methods physiotherapy, physiotherapy plus transcutaneous electrical nerve stimulation (TENS), nerve blocks, and sympathectomy provided participants with at best temporary pain relief. Outcomes were similar with the different treatment methods.

Similarly, current evidence does not support large differences in efficacy between different types of sympathectomy. A randomised but not double blind trial with 17 participants with reflex sympathetic dystrophy of the lower extremities (CRPS type I) (Haynsworth 1991) found that radiofrequency sympathectomy produced sympatholysis similar to that produced by phenol, although with a lower incidence of post-sympathectomy neuralgia. A non-randomised and non-blinded prospective observational study with 14 participants with upper or lower extremity CRPS (Mailis 1994) found that surgical and phenol sympathectomy produced similar rates of pain relief in the short term. In the long term there was a non-significant trend for better outcomes in the phenol group. More recently, 12 of 16 patients with a CRPS type II of the upper or lower limb showed significant improvement in limb function, the visual analogue scale, and the Nottingham Health Profile following regional subcutaneous venous sympathectomy (Happak 2012).

Regarding adverse events, the study included in this review found that all participants complained of soreness at the site of injections lasting 5 to 7 days and that one participant in the phenol group experienced post sympathectomy neuralgia. A systematic review investigating the late complications of surgical sympathectomies for a range of indications (Furlan 2000) found that neuropathic complications (after cervico-dorsal and lumbar surgical sympathectomy) occurred in 11.9% of all participants. However, they were more common if the indication was neuropathic pain rather than palmar hyperhidrosis (25.2% versus 9.8%). The same review found that, with cervico-dorsal sympathectomy, compensatory hyperhidrosis occurred in 52.3%, gustatory sweating in 32.3%, phantom sweating in 38.6%, and Horner's syndrome in 2.4% of participants.

There were no studies or reviews comparing sympathectomy with SCS. This is important in the UK, where the National Institute for Health and Clinical Excellence (NICE) has issued a technology appraisal guidance for SCS as a treatment option for adults with chronic pain of neuropathic origin who continue to experience chronic pain (at least 50 mm on a 0 to 100 mm visual analogue scale) for at least six months despite appropriate conventional medical management, and who have had a successful trial of stimulation, but not for pain of ischaemic origin, except as part of a clinical trial (NICE 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The first update (Straube 2010) of a previous Cochrane review (Mailis-Gagnon 2003) used refined inclusion criteria. It demonstrated that the practice of sympathectomy for neuropathic pain is based on little high quality evidence. This current update did not identify any additional information. Only one pilot study, with 20 participants and in CRPS type I (which cannot serve as a model for other neuropathic pain conditions), satisfied our inclusion criteria. There was no comparison of sympathectomy versus sham or placebo. Lower quality evidence seems to suggest that sympathectomy for neuropathic pain can work, at least in some cases. The risk-benefit assessment is complicated by the fact that serious complications of sympathectomy are common. Because

there is no good evidence for the effectiveness of sympathectomy —particularly with regard to long term effectiveness outcomes —it should be used with caution, in carefully selected patients, after thorough assessment, and probably only after failure of other treatment options or in palliative cases, or both. This stands in contrast to the use of pharmacotherapy in neuropathic pain, where there is high quality evidence (see, for example, Moore 2009 and Moore 2011).

Implications for research

High quality evidence from double blind RCTs with placebo (sham) comparators would be needed to determine whether sympathectomy is effective in the relief of neuropathic pain. Studies would need to be conducted in different neuropathic pain syndromes to determine when—if at all—sympathectomy is effective. Studies would also need to assess different types of sympathectomy to determine which is best. Furthermore, comparison would be needed with less invasive techniques (neuropathic pain medications, local anaesthetic blocks, and botulinum toxin). Double-blinding is needed to ensure high study quality and guard against biases but would be a considerable challenge in direct comparisons between sympathectomy and less invasive techniques and would probably involve sham procedures in some participants.

Given the adverse event profile associated with sympathectomy and given the known, albeit limited, efficacy for pharmacotherapy in neuropathic pain, the question arises of whether large double blind RCTs are likely to be conducted. Furthermore, there may be ethical arguments against conducting such trials other than in selected individuals (after failure of pharmacotherapy). It would, however, be helpful to compile a registry of sympathectomy cases.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Manjunath 2008

Methods	Randomised, double blind, active control Radiofrequency lesioning carried out at 80°C for 90 s at each site; phenol ablation carried out with 7% phenol. For both procedures, radiofrequency cannula was positioned, with stimulation at 50 and 2 Hz to identify proximity to sensory and motor nerves, and maintain blinding. Participants remained in prone position for 30 minutes Participants monitored on ward for 24 hours. Follow up at 1 and 7 days, and 2 and 4 months
Participants	Complex regional pain syndrome. History of failure to respond (pain intensity > 6/10) to treatment with oral pregabalin, amitriptyline, carbamazepine over >6 months, and response (pain intensity < 4/10) after diagnostic sympathetic block with lidocaine on three occasions N = 20 Males/females not reported Mean age 52 years in radiofrequency group, 39 years in phenol group
Interventions	Radiofrequency lumbar sympathectomy, n = 10 Phenol lumbar sympathectomy, n = 10
Outcomes	Nine pain outcomes, each assessed on a 0 to 10 scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1; Total = 5/5 Oxford Pain Validity Score: 13/16

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated" random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants blinded by creating similar scene for both procedures. Investigator collecting data not involved in procedures and unaware of the groups to which participants were assigned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant in the phenol group was not included in the efficacy analysis
Size	High risk	< 50 participants per treatment group

DB = double blinding; N = number of participants in study; n = number of participants in treatment group; R = randomisation; W = withdrawals

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AbuRahma 1994	Not RCT (included in 2002 review)
Greipp 1990	Not RCT (included in 2002 review)
Haynsworth 1991	Not double blind (included in 2002 review)
Mailis 1994	Not RCT (included in 2002 review)

APPENDICES

Appendix 1. Search strategy for MEDLINE (via Ovid)

1. Exp Sympathectomy/
2. (sympathectomy OR sympatholysis OR sympathicotomy).mp.
3. 1 OR 2
4. Exp Neuralgia/
5. (complex regional pain syndrome OR reflex sympathetic dystrophy OR causalgia OR phantom limb pain OR allodynia OR diabetic neuropath* OR trigeminal neuralgia OR post-herpetic neuralgia OR neuropathic adj2 pain).mp.
6. 4 OR 5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.
11. randomly.ab.
12. trial.ab.
13. groups.ab.
14. OR/7-13
15. 3 AND 6 AND 14

Appendix 2. Search strategy for EMBASE (via Ovid)

1. Exp Sympathectomy/
2. (sympathectomy OR sympatholysis OR sympathicotomy).mp.
3. 1 OR 2
4. Exp Neuralgia/
5. (complex regional pain syndrome OR reflex sympathetic dystrophy OR causalgia OR phantom limb pain OR allodynia OR diabetic neuropath* OR trigeminal neuralgia OR post-herpetic neuralgia OR neuropathic adj2 pain).mp.
6. 4 OR 5
7. clinical trials.sh.
8. controlled clinical trials.sh.
9. randomized controlled trial.sh.
10. double-blind procedure.sh.
11. (clin* adj25 trial*).ab.
12. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.
13. placebo*.ab.
14. random*.ab.
15. OR/7-14

16.3 AND 6 AND 15

Appendix 3. Search strategy for CENTRAL

1. Exp MESH descriptor Sympathectomy
2. (sympathectomy OR sympatholysis OR sympathicotomy):ti,ab,kw
3. 1 OR 2
4. Exp MESH descriptor Neuralgia
5. ("complex regional pain syndrome" OR "reflex sympathetic dystrophy" OR causalgia OR "phantom limb pain" OR allodynia OR "diabetic neuropath*" OR "trigeminal neuralgia" OR "post-herpetic neuralgia" OR "neuropathic adj2 pain"):ti,ab,kw
6. 4 OR 5
7. Randomized controlled trial:pt
8. MESH descriptor Double-blind Method
9. random*:ti,ab,kw
10. OR/7-9
11. 3 AND 6 AND 10
12. Limit 11 to Clinical Trials (CENTRAL)

WHAT'S NEW

Date	Event	Description
1 April 2020	Review declared as stable	See our updated Published notes.

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 2, 2003

Date	Event	Description
26 February 2018	Review declared as stable	See Published notes
26 February 2014	Review declared as stable	This review has been assessed as stable and will be reassessed in 2018.
3 September 2013	Amended	Wording amended for one author's declaration of interest.
2 July 2013	New citation required but conclusions have not changed	Conclusions unchanged, but Risk of bias assessment expanded and Summary of findings table added.
2 July 2013	New search has been performed	New searches carried out, but no new studies identified for inclusion.
27 June 2012	Amended	Contact details updated.
15 January 2010	New search has been performed	This review was updated with a new search in December 2009. The review title was changed to reflect the scope of the review more accurately. Study inclusion criteria and primary outcomes were revised: review now includes only studies of the highest methodological quality (randomised and double blind), and uses more rigorous outcomes as defined by the IMMPACT group. Further searching to May 2010 found no additional studies.

Date	Event	Description
15 January 2010	New citation required and conclusions have changed	One study (Manjunath 2008), with 20 participants, satisfied the inclusion criteria. It did not show a difference between radiofrequency lumbar sympathectomy and lumbar sympathectomy with phenol over 4 months following the intervention. The practice of sympathectomy for neuropathic pain is based on little high quality evidence and carries a risk of serious complications. The four studies included in the earlier review were excluded because they were not randomised, double blind, controlled trials.
13 May 2009	Amended	Contact details updated.
14 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

For the previous update SS and SD carried out searches, identified studies for inclusion, and extracted data. All review authors were involved in discussions about updating the Methods section (Inclusion criteria and Outcomes) and in writing the final review. All authors read and approved the final manuscript.

For this update SD and RAM carried out searches. All review authors were involved in updating the Methods and Risk of bias sections and preparing a Summary of findings table. All review authors read and approved the final manuscript.

DECLARATIONS OF INTEREST

SS, RAM, and SD have received grants and research support from charities, government, academic, and industry sources at various times. RAM has consulted for various pharmaceutical companies. RAM and PC have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. SS has received a lecture fee from and consulted for Oxford Medical Knowledge, both related to analgesics. No pharmaceutical company had any involvement in funding or carrying out this review.

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Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The first update differed from the earlier review primarily in the methodological quality of the included studies and the choice of efficacy outcomes. It included only studies of the highest methodological quality (randomised and double blind) because these are known to be less prone to bias (Moore 2006), which is of utmost importance in pain studies where outcomes are subjective, and used more rigorous outcomes as defined by the IMMPACT group (Dworkin 2008).

This update did not identify any new studies, but the Risk of bias assessment has been expanded and a Summary of findings table included, in keeping with methodological advances in recent Cochrane reviews.

NOTES

2018

A restricted search in February 2018 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

2020

We assessed a second updated search in March 2020 and again did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years.

INDEX TERMS

Medical Subject Headings (MeSH)

Catheter Ablation [*methods]; Complex Regional Pain Syndromes [*therapy]; Leg [innervation]; Neck; Neuralgia [*therapy]; Phenol; Randomized Controlled Trials as Topic; Sympathectomy [*methods]; Sympathectomy, Chemical [methods]; Sympatholytics; Thorax

MeSH check words

Humans