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Lumbar sympathectomy techniques for critical lower limb ischaemia due to non-reconstructable peripheral arterial disease (Review)

Karanth VKL, Karanth TK, Karanth L

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TABLE OF CONTENTS

[Intervention Review]

Lumbar sympathectomy techniques for critical lower limb ischaemia due to non-reconstructable peripheral arterial disease

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ABSTRACT

Background

Critical lower limb ischaemia (CLI) is a manifestation of peripheral arterial disease (PAD) that is seen in patients with typical chronic ischaemic rest pain or patients with ischaemic skin lesions - ulcers or gangrene - for longer than 2 weeks. Critical lower limb ischaemia is the most severe form of PAD, and interventions to improve arterial perfusion become necessary. Although surgical bypass has been the gold standard for revascularisation, the extent or the site of disease may be such that the artery cannot be reconstructed or bypassed. These patients require other modalities of treatment, for example, vasodilatation by drugs or lumbar sympathectomy to relieve pain at rest and to avoid amputations. A systematic review of randomised controlled trials is required to evaluate the effects of lumbar sympathectomy in treating patients with CLI due to non-reconstructable PAD.

Objectives

The objective of this review is to assess the effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with CLI due to non-reconstructable PAD.

Search methods

The Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (January 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 12). In addition, the CIS searched clinical trials databases for details of ongoing and unpublished studies.

Selection criteria

Randomised controlled trials (RCTs) comparing any of the treatment modalities of lumbar sympathectomy, such as open, laparoscopic and chemical percutaneous methods, with no treatment or with any other method of lumbar sympathectomy for CLI due to non-reconstructable PAD were eligible. To decrease the bias of including participants that may be incorrectly diagnosed with CLI, review authors defined CLI as persistently recurring ischaemic rest pain requiring regular analgesia for more than two weeks, or ulceration or gangrene of the foot or toes, attributable to objectively proven arterial occlusive disease by measurement of ankle pressure of < 50 mmHg or toe pressure < 30 mmHg. We defined non-reconstructable PAD as a resting ankle brachial index (ABI) < 0.9 when no reasonable open surgical or endovascular revascularisation treatment option is available, as determined by individual trial vascular specialists.

Data collection and analysis

Two review authors independently assessed studies identified for potential inclusion in the review. We planned to conduct data collection and analysis in accordance with the *Cochrane Handbook for Systematic Review of Interventions*.

Main results

We identified no studies that met the predefined inclusion criteria. To decrease the bias of including participants who may be incorrectly diagnosed with CLI, we based our inclusion criteria on objective tests, as described above. The randomised trials identified by the literature search were performed before such objective criteria for selection were applied and therefore were not eligible for inclusion in the review.

Authors' conclusions

We identified no RCTs assessing effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with CLI due to non-reconstructable PAD. High-quality studies are needed.

PLAIN LANGUAGE SUMMARY

Lumbar sympathectomy techniques for critical lower limb ischaemia due to non-reconstructable peripheral arterial disease

Background

Peripheral arterial disease (PAD) refers to a common condition of narrowing of the arteries of the lower limbs that restricts blood flow; in the most severe cases, PAD can cause pain at rest, ulcers and gangrene. Amputation may be required if resistant pain or sepsis ensues, unless an intervention is undertaken to improve arterial perfusion (delivery of blood to cells and tissues). One such intervention is lumbar sympathectomy, whereby nerves that stimulate constriction of arteries are destroyed. This is done mainly when other treatments such as reconstruction are not possible and when no treatment would result in amputation.

Key results

No randomised controlled trials (current until January 2016) have assessed effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with critical lower limb ischaemia (CLI) due to non-reconstructable peripheral arterial disease (PAD). Our inclusion criteria were based on objective tests proposed by the Second European Consensus document on chronic critical leg ischaemia and the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Randomised trials identified by the literature search were performed before such objective criteria for selection were applied and therefore were not eligible for inclusion in the review. High-quality studies are needed.

Quality of evidence

It was not possible to evaluate the quality of evidence in the absence of studies eligible for inclusion in the review.

BACKGROUND

Description of the condition

Peripheral arterial disease (PAD) of the lower limb, or narrowing of the arteries of the lower limb restricting blood flow, is common; it affects 20% of people over 70 years of age and 4% to 12% of those 55 to 70 years of age and is more common among men (Dormandy 1999; Fowkes 2008). Peripheral arterial disease encompasses a spectrum of disease severity and in its early stages may be asymptomatic. The most common symptom, intermittent claudication, occurs in approximately 0.5% to 40% of the population, depending on age, sex and geographical location (Balkau 1994; Dormandy 1999; Fowkes 1998). In America, approximately 500 to 1000 new cases of critical lower limb ischaemia, the most severe form of PAD, are diagnosed per million per year (Norgren 2007).

Peripheral arterial disease is categorised according to the Fontaine classification (Fontaine 1954; NICE 2012). Patients with stages I to IV PAD are symptomatic with intermittent claudication (IC) and have rest pain and trophic ulcers. In IC, pain is felt in the muscle bulk of the buttocks, thighs and calf. This pain is not continuous, as aching stops during rest. When PAD becomes more severe, pain becomes continuous and is experienced even on resting. Patients with ulceration or gangrene have critical lower limb ischaemia (CLI). Most patients have mild symptoms of IC, but up to one-fifth require reconstructive surgery, and amputation is necessary in 1% to 2% of patients with PAD (Kannel 1985; Leng 1993). Quality of life is low in patients with IC, as their ambulatory life is restricted (Belch 2003).

The gold standard non-invasive method of diagnosing PAD involves measuring the ankle brachial index (ABI). Angiogram-positive disease can be detected by an ABI < 0.9, which is 95% sensitive in symptomatic individuals and almost 100% specific in healthy individuals (Norgren 2007). In CLI, the diagnosis of PAD centres around the diagnosis and quantification of arterial flow, described by Norgren 2007 as ankle pressure of 50 to 70 mmHg in patients with ischaemic ulcers and 30 to 50 mmHg in those with ischaemic rest pain, as well as toe pressure (including diabetic patients) < 50 mmHg, transcutaneous oxygen measurement ($tcPO_2$) < 30 mmHg or investigation of microcirculation such as capillaroscopy, fluorescence videomicroscopy or laser doppler fluxometry (Norgren 2007).

Critical lower limb ischaemia may progress to amputation unless an intervention is provided that improves arterial perfusion. In patients with limb-threatening ischaemia, the rate of limb loss is increased when factors reduce microvascular flow (e.g. diabetes, renal failure) and conditions require increased microvascular flow (e.g. infection in skin, subcutaneous tissue and bones). Treatment of patients with CLI involves tackling risk factors and administering specific interventions to relieve symptoms. Reducing smoking, blood pressure and cholesterol levels may help to slow progression of the disease in the lower limb (Norgren 2007). Conservative measures such as use of antiplatelet agents, exercise regimens and therapy with vasodilators are largely ineffective; severe symptoms such as short-distance claudication, rest pain, ulcers and gangrene may be addressed with interventions such as angioplasty and bypass surgery (Leng 2000; Wong 2011). If treatment does work well in the first few months, it is doubtful whether initial success will be sustained after 12 months (Fowkes 1998).

Description of the intervention

Intermittent claudication may progress to rest pain and CLI, and interventions to improve arterial perfusion may become necessary. Failing this, the disease may progress further and amputation may become necessary to treat the ensuing gangrene and severe rest pain. Surgical bypass has been the gold standard for revascularisation in patients with CLI (Ferket 2012). In some patients, however, the extent or the site of disease is such that the artery cannot be reconstructed or bypassed. These patients can be treated with medication such as vasodilators (agents given to widen the capillaries) or with a procedure such as lumbar sympathectomy (an operation on the sympathetic nerves performed to help the arteries widen and to reduce pain) in an attempt to relieve rest pain and avoid amputation (Allemang 2013). Lumbar sympathectomy can be performed chemically (when drugs such as marcaine, bupivacaine, phenol or absolute alcohol can be instilled at the site of the lumbar sympathetic ganglion under computerised tomographic guidance), by laparoscopy (when the lumbar sympathetic ganglion can be ablated by radiofrequency or thermal percutaneous ablation under imaging guidance) or by open surgical techniques. During lumbar sympathectomy, the nerves of the sympathetic ganglion are destroyed; this may relieve rest pain by stopping the flow of efferent pain.

How the intervention might work

Atherosclerosis in the peripheral arteries of the legs leads to an insufficient blood supply during exercise, which in turn causes anaerobic metabolism in the muscles and production of lactic acid and other metabolites, resulting in pain (Pipinos 2008). When a patient exercises with relative ischaemia, maximal vasodilation occurs as a response to locally produced metabolic substances. The sympathetic nerves cause blood vessels to narrow when activated, and this narrowing or vasoconstriction is prevented when the nerves are cut. Lumbar sympathectomy cuts off sympathetic nerve connections at the lumbar vertebral (lower backbone) level. Sympathectomy decreases peripheral resistance and opens up arteriovenous anastomotic collaterals to increase the flow of blood through the blood vessels (Cronenwett 1977; Moore 1973; Scarpino 1971). Sympathetic denervation therefore increases blood flow to a normal limb. Increased blood flow, effects on collateral circulation, and alterations in the transmission of pain impulses are noted in the extremity affected by arterial occlusive disease. Lumbar sympathectomy techniques can be used to treat patients with PAD, as destruction of the sympathetic chain improves skin blood flow and modifies pain perception. After lumbar sympathectomy, rest pain is relieved in 60% to 75% of patients at short-term follow-up, and effectiveness of treatment is seen in 50% of patients over the long term (Cotton 1985).

The benefits of lumbar sympathectomy for conservation of the limb are unsatisfactory. Vasomotor tone is normalised within two weeks to six months after lumbar sympathectomy. Benefits are increased in younger patients and in patients who have had the condition for a short time, are without co-morbidities and have ceased smoking. The success of lumbar sympathectomy is greater if the vessels involved are more distal, systolic pressure at the ankles has not dropped to below 60 mmHg, the ABI is maintained at greater than 0.3 and a patent femoral artery is present (Janoff 1985; Lantsberg 1996; Shigematsu 1999; Walker 1978). Deep-seated infection can lead to a poor prognosis and can make it difficult to verify whether

sympathetic denervation was successfully completed (Altomare 1994; Bohler 1996).

Why it is important to do this review

Peripheral arterial disease of the lower limbs progresses from IC to rest pain, ischaemic ulcers and finally gangrene. If definitive vascular reconstruction is not possible, amputation may be required. Medical therapy, chemical sympathectomy and lumbar sympathectomy have been used to treat patients with severe, non-reconstructable disease, with varied results. A Cochrane review comparing lumbar sympathectomy with prostanoids for CLI due to non-reconstructable PAD is currently in progress (Sen 2011). Cotton 1985 reported that sympathectomy may be beneficial when compared with no intervention in relieving rest pain in 60% to 75% of patients at short-term follow-up, and long-term effectiveness has been noted in up to 50% of patients (Cotton 1985). Therefore, a systematic review of randomised controlled trials is required to compare the effects of lumbar sympathectomy with no treatment or with any other method of lumbar sympathectomy for treating patients with CLI due to non-reconstructable PAD.

OBJECTIVES

The objective of this review is to assess the effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with CLI due to non-reconstructable PAD.

METHODS

Criteria for considering studies for this review

Types of studies

We searched open access databases and trial registries for randomised controlled trials comparing lumbar sympathectomy performed by open, laparoscopic and chemical percutaneous methods for CLI due to non-reconstructable PAD.

Types of participants

We planned to include patients with CLI due to non-reconstructable PAD.

There is no universally agreed definition of CLI. We have used the definition according to the Second European Consensus document on chronic critical leg ischaemia (Consensus 1992) and the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) (Norgren 2007):

Persistently recurring ischaemic rest pain requiring regular analgesia for more than two weeks, or ulceration or gangrene of the foot or toes, attributable to objectively proven arterial occlusive disease by measurement of ankle pressure of < 50 mmHg or toe pressure < 30 mmHg.

Other definitions of CLI are available including those using higher pressures to include subacute CLI or using other additional measures such as transcutaneous oxygen measurement (tcPO2).

Non-reconstructable PAD is defined as a resting ABI < 0.9 when no reasonable open surgical or endovascular revascularisation treatment option is available, as determined by individual trial vascular specialists.

We excluded patients with PAD due to diabetes, as this condition follows a different pathophysiological course.

Types of interventions

Intervention

Lumbar sympathectomy by any method such as open, laparoscopic and percutaneous techniques via chemical, radiofrequency or thermal methods.

Comparison

Comparison with no treatment administered or any other method of lumbar sympathectomy (including open, laparoscopic and percutaneous techniques via chemical, radiofrequency or thermal methods) as a control.

We excluded studies comparing lumbar sympathectomy with prostanoids, as this topic is covered in a Cochrane protocol by Sen 2011.

Types of outcome measures

Primary outcomes

- Ulcer healing
- Amputation-free survival
- Quality of life (QoL), measured by postoperative pain scores

Secondary outcomes

- Length of hospital stay
- Progression of disease: whether improving, remaining static or worsening in the immediate postoperative period and at follow-up examinations at short-term intervals (one to six months) and at long-term follow-up (six months to five years)
- Rest pain severity (using standard pain score charts)
- Absolute claudication distance
- ABI
- Lower limb skin temperatures measured with skin temperature probes
- Complications due to intervention (injury to ureter, blood vessels, nerves and intraperitoneal organs or retroperitoneal structures, sexual problems)

Search methods for identification of studies

We applied no language restrictions when searching for publications.

Electronic searches

The Cochrane Vascular Information specialist (CIS) searched the Specialised Register (January 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 12), part of the Cochrane Library (www.cochranelibrary.com). (See Appendix 1 for details of the search strategy used to search CENTRAL.) The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Allied and Complementary Medicine Database (AMED), and after handsearching of relevant journals. We have presented the

full list of the databases, journals and conference proceedings that have been searched, as well as the search strategies used, in the Specialised Register section of the Cochrane Vascular Module in the Cochrane Library (www.cochranelibrary.com).

The CIS searched the following trial databases for details of ongoing and unpublished studies, using the term "lumbar sympathectomy".

- World Health Organization International Clinical Trials Registry Platform (//apps.who.int/trialsearch/).
- ClinicalTrials.gov (//clinicaltrials.gov/).
- International Standard Randomised Controlled Trial Number (ISRCTN) registry (//www.controlled-trials.com/).

Searching other resources

We searched the reference lists of relevant articles retrieved by electronic searches for additional citations. We planned to contact the authors of ongoing trials to request data.

Data collection and analysis

Selection of studies

VK and TK independently reviewed all identified abstracts and reports retrieved from searches of databases and other sources. We obtained a full-text copy of references that appeared relevant to the review topic, so we could independently review them for inclusion or exclusion in the review. We assessed retrieved studies according to the inclusion and exclusion criteria and resolved disagreements by discussion with a third review author (LK).

To date, we have found no trials identified by the searches that met the criteria prescribed by the review protocol. For future updates, should any trials be included, the review authors will adhere to the protocol outlined below.

Data extraction and management

We planned that two review authors (VK and TK) would independently extract data from the reports of included studies. We planned for both review authors to extract data using specially designed data collection forms. We planned to resolve disagreements by discussion with a third review author (LK) and to seek unpublished information that is missing from included studies by requesting data from individuals or organisations involved. We planned to collect and utilise the most detailed numerical data that might facilitate similar analyses of included studies.

Assessment of risk of bias in included studies

We planned that two review authors (VK and TK) would independently assess the risk of bias of each included trial on the basis of the following components: sequence generation, allocation concealment, blinding or masking, incomplete outcome data, selective outcome reporting and other biases. For each of these components, we planned to assign a judgement regarding risk of bias as high, low or unclear (Higgins 2011). We planned to make these judgements separately for objectively and subjectively ascertained measures for the domains of blinding and incomplete outcome data. We planned to record these assessments for each included study in standard risk of bias tables. We planned to use these assessments in making judgements on overall study quality while preparing summary of findings tables. We planned to attempt to contact trial authors for clarification when methodological details were unclear and to resolve differences by discussion.

Measures of treatment effect

We planned to present the results for dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous data, we planned to use mean differences (MDs). When the same outcome was measured using different methods, we planned to use standardised mean differences (SMDs). For both, the CIs would be 95%.

Unit of analysis issues

We included no randomised trials, so we encountered no issues regarding unit of analysis. For future updates, the unit for randomisation will be individuals participating in the randomised trials.

Dealing with missing data

We planned to attempt to obtain missing data from trial authors. When possible, we planned to extract data for an intention-to-treat analysis, in which all randomised participants would be analysed in the groups to which they were originally assigned. If we noted any discrepancy in the numbers randomised and the numbers analysed in each treatment group, we planned to calculate the percentage lost to follow-up in each group and report this information. If dropouts exceeded 10% for any trial, for dichotomous outcomes we planned to assign the worst outcome to those lost to follow-up and to assess the impact of this in sensitivity analyses by using the results of completers.

For continuous data that are missing standard deviations (SDs), we planned to calculate the SDs from other available data such as standard errors (SEs) or to impute them using methods suggested in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2008). We planned to refrain from making any assumptions about losses to follow-up for continuous data and to analyse the results for those who completed the trial.

Assessment of heterogeneity

We planned to assess heterogeneity among studies by inspecting the forest plots and using the Chi^2 test and the I^2 statistic for heterogeneity with a statistical significance level of $P < 0.10$.

We planned to interpret the I^2 statistic as follows.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity.

Final interpretation of the I^2 value would depend on the number of trials and sample sizes.

Assessment of reporting biases

We planned to investigate potential reporting biases by using a funnel plot, if we identified a sufficient number of studies. We planned to use a linear regression approach to measure funnel plot asymmetry on the logarithm scale of the RR, and if we found an asymmetrical funnel plot, we planned to explore alternative causes along with publication bias.

Data synthesis

We planned to carry out statistical analysis by using Review Manager software (Revman 2012). We planned to use a fixed-effect model meta-analysis in combining data when it was reasonable to assume that studies were estimating the same underlying treatment effect, that is, when trials examined the same intervention and trial populations and methods had low heterogeneity. If clinical heterogeneity was sufficient to suggest that underlying treatment effects differed between trials, or if we detected substantial statistical heterogeneity (I^2 = 60% to 90%), we planned to use random-effects model meta-analysis to produce an overall summary of an average treatment effect across trials to determine whether the treatment effect would be considered clinically meaningful. We planned to treat the random-effects model summary as the average range of possible treatment effects.

When we planned to use random-effects model analyses, we expected to present results as the average treatment effect with 95% CI, together with estimates of I^2.

Subgroup analysis and investigation of heterogeneity

As we included no randomised trials, we analysed no subgroups. For future updates, if data permit, we will carry out subgroup analyses based on age, gender, disease aetiology (thromboangiitis obliterans (TAO), vasculitis, atherosclerosis), disease severity, presence of co-morbidities, duration of and response to analgesic drugs and prostacyclins and duration of follow-up (short, medium or long term).

Sensitivity analysis

We planned to perform sensitivity analyses that excluded studies with high risk of bias.

Summary of findings tables

We planned to create a summary of findings table and to use the GRADE approach to interpret findings. We planned to develop a summary of findings table for the primary outcomes of this review, as described in detail in Primary outcomes, by using GRADE Profiler software (GRADEpro). We planned to assess the quality of the body of evidence by considering the overall risk of bias of included studies, directness of the evidence, inconsistency of the results, precision of the estimates and risk of publication bias (Grade Working Group 2004).

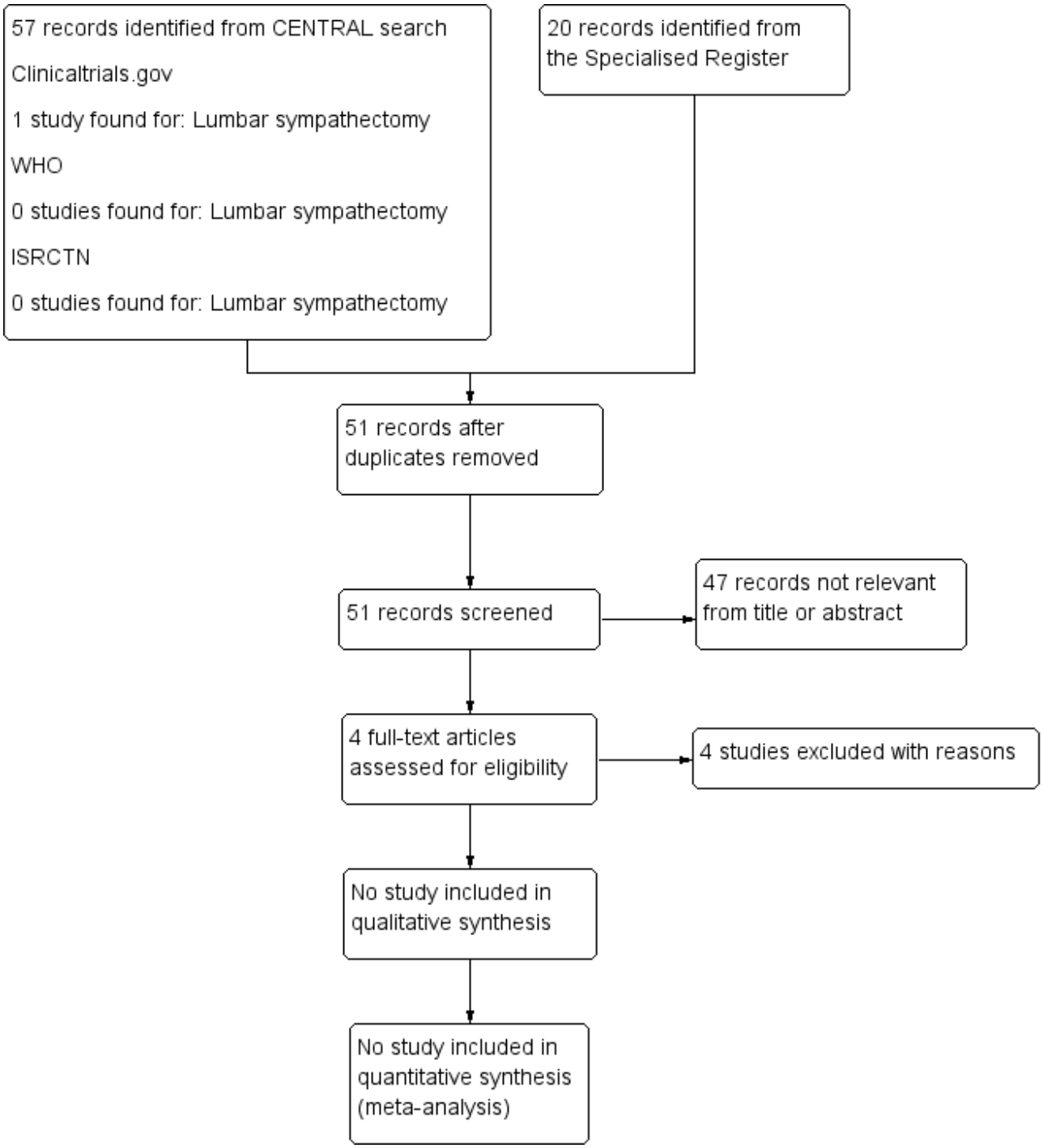
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



We studied four randomised controlled trials (RCTs) for the possibility of inclusion. We identified no relevant ongoing trials.

Included studies

No RCTs met the inclusion criteria for this review.

Excluded studies

See Characteristics of excluded studies.

We excluded four studies, as the criteria for selection of participants did not adhere to the objective criteria of the protocol (Cousins 1979; Cross 1985; Fyfe 1975; Waibel 1977).

Risk of bias in included studies

We included no RCTs and therefore could not assess methodological quality.

Effects of interventions

We identified no RCTs assessing effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with critical lower limb ischaemia (CLI) due to non-reconstructable peripheral arterial disease (PAD).

DISCUSSION

Summary of main results

We identified no randomised controlled trials (RCTs) assessing the effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with critical lower limb ischaemia (CLI) due to non-reconstructable peripheral arterial disease (PAD).

Overall completeness and applicability of evidence

We identified no RCTs assessing the effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with CLI due to non-reconstructable PAD using objective selection criteria specified for this review. We used objective selection criteria to decrease the bias of including participants who may be incorrectly diagnosed with CLI. The randomised trials identified by the literature search were conducted between 1975 and 1985 - before such objective criteria for selection were used - and therefore were not eligible for inclusion in the review. Further research is needed.

Quality of the evidence

We identified no RCTs assessing the effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with CLI due to non-reconstructable PAD.

Potential biases in the review process

We applied no language restrictions on publications including ongoing trials.

The Cochrane Vascular Information Specialist (CIS) searched the Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL), as outlined above. The CIS searched ongoing trials in the World Health Organization (WHO) International Clinical Trials Registry Platform, ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number (ISRCTN) registry. To further expand the search, we studied the reference lists of relevant articles retrieved by the above searches.

To decrease bias in this review, we used objective selection criteria for CLI, as described by Consensus 1992 and Norgren 2007. Unfortunately, we had to exclude most of the studies selected for review, as they were conducted between 1975 and 1985, when most of the currently available objective methods were not in use.

Agreements and disagreements with other studies or reviews

A systematic review performed by Ruiz-Aragón and colleagues, including four clinical trials and four observational studies, suggested no statistical differences in mortality and amputation rates in treatment with lumbar sympathectomy compared with conventional treatment among patients with occlusive peripheral arterial occlusive disease (Ruiz-Aragón 2010).

Further investigation of the excluded studies of our Cochrane review (Characteristics of excluded studies) showed that neurolytic and surgical sympathectomies were able to ablate local sympathetic innervation for approximately six months (Cousins 1979). Cousins 1979 also showed that the percutaneous approach offered advantages such as amelioration of symptoms without perioperative risks, availability as an outpatient procedure, reduced postoperative complications including those resulting from anaesthesia, ease of performance on the other side and decreased expense for the patient (Cousins 1979). Cross 1985 reported that 83.5% of patients were relieved of rest pain and 66% remained free of rest pain after six months. Fyfe 1975 and Waibel 1977 showed that this procedure was of little value for patients with intermittent claudication (Fyfe 1975; Waibel 1977).

AUTHORS' CONCLUSIONS

Implications for practice

We identified no RCTs conducted to assess the effects of lumbar sympathectomy by open, laparoscopic and percutaneous methods compared with no treatment or compared with any other method of lumbar sympathectomy in patients with CLI due to non-reconstructable PAD.

Implications for research

Lower limb ischaemia due to peripheral arterial disease can be treated with vascular reconstruction surgery. Patients who have non-reconstructable peripheral arterial disease describe severe rest pain and may require amputation when overwhelming infection threatens the patient's life, when rest pain cannot be controlled or when extensive necrosis has destroyed the foot. Lumbar sympathectomy has resulted in documented relief of pain and avoidance of required amputation. Newer percutaneous sympathectomy techniques have also been attempted. This review has identified a lack of randomised controlled trials with stringent objective patient selection criteria to assess the benefits and risks of lumbar sympathectomy as a means of preventing pain and amputation in patients with non-reconstructable peripheral arterial disease. With advancement of investigative techniques, it is now possible to objectively define CLI, and hence it is possible to select and randomise study participants effectively. A randomised controlled trial with stringent inclusion criteria conducted to assess the benefits of this intervention will be beneficial, as prior studies (Cousins 1979; Cross 1985) reported encouraging results. Such research will inform best practice to alleviate rest pain, heal ulcers and avoid amputation in patients with critical lower limb ischaemia due to non-reconstructable peripheral arterial disease.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Cousins 1979	Criteria for selection of participants are not consistent with our protocol: investigators included patients with rest pain and gangrenous changes that are not advocated for surgical reconstruc-

Study	Reason for exclusion
	tion. This is a subjective assessment of CLI, and it has not been defined in any objective method described in our protocol. Hence we excluded this study.
Cross 1985	Criteria for selection of participants are not consistent with our protocol: investigators included patients on the basis of rest pain, defined as severe pain in the foot for at least 3 weeks that was worse at night and required strong analgesia for relief. Cross 1985 mentioned that a particular cut-off was not defined according to an objective assessment method such as ankle brachial pressure, as described in our protocol. Patients were included in a subjective manner, hence we excluded this study.
Fyfe 1975	Criteria for selection of participants are not consistent with our protocol: investigators included patients with history of intermittent claudication, predominantly affecting one limb, that has been stable for at least 3 months. Patients had palpable femoral pulses with diminished or absent pulses distally, and all showed a drop in calf blood pressure in the affected leg after exercise. Inclusion criteria do not define the exact location or degree of the block, whether it was surgically non-reconstructable and the extent of drop in calf blood pressure on exercise. Hence, we excluded this study.
Waibel 1977	Criteria for selection of participants are not consistent with our protocol: investigators included patients with non-reconstructable peripheral vascular disease with stage II CLI, which is intermittent claudication. This is not consistent with our protocol, wherein an objective description of CLI includes stage III and IV CLI. Hence, we excluded this study.

CLI: chronic lower limb ischaemia

APPENDICES

Appendix 1. CENTRAL search strategy

ID	Search	Hits
#1	MeSH descriptor: [Arteriosclerosis] this term only	896
#2	MeSH descriptor: [Arteriolosclerosis] this term only	0
#3	MeSH descriptor: [Arteriosclerosis Obliterans] this term only	73
#4	MeSH descriptor: [Atherosclerosis] this term only	540
#5	MeSH descriptor: [Arterial Occlusive Diseases] this term only	820
#6	MeSH descriptor: [Intermittent Claudication] this term only	782
#7	MeSH descriptor: [Ischemia] this term only	837
#8	MeSH descriptor: [Peripheral Vascular Diseases] explode all trees	2352
#9	MeSH descriptor: [Vascular Diseases] this term only	431
#10	MeSH descriptor: [Leg] explode all trees and with qualifier(s): [Blood supply - BS]	1149
#11	MeSH descriptor: [Femoral Artery] explode all trees	819

(Continued)

#12	MeSH descriptor: [Popliteal Artery] explode all trees	301
#13	MeSH descriptor: [Iliac Artery] explode all trees	161
#14	MeSH descriptor: [Tibial Arteries] explode all trees	34
#15	(atherosclero* or arteriosclero* or PVD or PAOD or PAD)	21155
#16	(arter*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	7481
#17	(vascular) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1901
#18	(vein*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1249
#19	(veno*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1325
#20	(peripher*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	2102
#21	peripheral near/3 dis*	4320
#22	arteriopathic	33
#23	(claudic* or hinken*)	1777
#24	(isch* or CLI)	24362
#25	dysvascular*	44
#26	leg near/4 (obstruct* or occlus* or steno* or block* or obliter*)	202
#27	limb near/4 (obstruct* or occlus* or steno* or block* or obliter*)	265
#28	(lower near/3 extrem*) near/4 (obstruct* or occlus* or steno* or block* or obliter*)	184
#29	(aort* or iliac or femoral or popliteal or femoro* or fempop* or crural) near/3 (obstruct* or occlus* or reconstruct*)	634
#30	MeSH descriptor: [Ulcer] explode all trees	158
#31	ulcer	12753
#32	MeSH descriptor: [Gangrene] explode all trees	70
#33	gangren*	445
#34	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33	65710
#35	MeSH descriptor: [Sympathectomy] explode all trees	130
#36	sympathectomy or sympatholysis or sympathicotomy:ti,ab,kw (Word variations have been searched)	246
#37	#35 or #36 in Trials	218

(Continued)

#38	#34 and #37 in Trials	57

CONTRIBUTIONS OF AUTHORS

Dr Veena Karanth and Tulasi Kota Karanth searched data relevant to the topic and wrote the protocol and the review, together with Dr Laxminarayan Karanth.

DECLARATIONS OF INTEREST

VK: none known.
TK: none known.
LK: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added clarification that we planned to exclude patients with peripheral arterial disease due to diabetes, as this condition follows a different pathophysiological course.

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Ischemia [etiology] [*surgery]; Lower Extremity [*blood supply]; Lumbosacral Plexus [*surgery]; Peripheral Arterial Disease [*complications]; Sympathectomy [*methods]; Sympathectomy, Chemical

MeSH check words

Humans