

Surgical sympathectomy for Buerger's disease

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Summary

Buerger's disease is characterized by recurring progressive inflammation and occlusions in small and medium arteries and veins of the limbs. Its cause is unknown, but it is most common in young men with a history of tobacco use. It is responsible for ischemic ulcers and extreme pain in the hands and feet. In many cases, notably in patients with the most severe presentations, there is no possibility of improving the condition with surgery (limb revascularisation), and therefore, alternative therapies (e.g. sympathectomy) is used. This review assessed the effectiveness of surgical sympathectomy compared with any other therapy in patients with Buerger's disease. As a result, only one randomised controlled study (162 participants) compared sympathectomy with prostacyclin analogue (iloprost) was incorporated to the review. Such comparison shown that iloprost is more effective than sympathectomy to complete healing ulcers at four weeks (risk ratio 0.65; 95% confidence interval 0.45 to 0.95; $P=0.02$; very low quality evidence) and at twenty four weeks (risk ratio 0.62; 95% confidence interval 0.48 to 0.82; $P < 0.01$; very low quality evidence) after the start of treatment and to relief rest pain at four weeks (risk ratio 1.90; 95% confidence interval 1.17 to 3.10; $P=0.01$; very low quality evidence) but not more effective at twenty four weeks (risk ratio 1.68; 95% confidence interval 1.00 to 2.84; $P=0.10$; very low quality evidence) after the start of treatment.

We concluded, with very low quality of evidence, that intravenous iloprost is more effective than lumbar sympathectomy in the healing of ischemic ulcers and pain at rest in patients with Buerger's disease. Therefore, until now, the preference of the usage of intravenous iloprost over the lumbar sympathectomy (and vice versa) does not find robust evidence for its routine use.

Keywords

Thromboangiitis obliterans, sympathectomy, iloprost, review

and nerves in the upper and lower extremities.¹ Von Winiwarter² first described a patient with the disease in 1879, but it was Leo Buerger,³ in 1908, who published a detailed description of the pathological findings on 11 amputated limbs and named the disease.

The aetiology is unknown, but involves tobacco exposure, hereditary susceptibility, infectious, immune and coagulation responses.⁴ Features distinguishing Buerger's disease from atherosclerosis include the distribution of pathology (with involvement of both the upper and lower extremities), associated superficial venous thrombosis, a paucity of atherosclerotic risk factors and normal proximal large arteries.⁵

Why it is important to do this review?

Buerger's disease is a debilitating condition which can affect productive, young people. In patients with critical limb ischaemia and poor chances of surgical revascularisation, as seen in many patients diagnosed with Buerger's disease, alternative treatments, as surgical sympathectomy, are often performed. Thus, a systematic review about effectiveness of surgical sympathectomy in patients with Buerger's disease is opportune and extremely relevant.

Objective

To assess the effectiveness of surgical sympathectomy compared with any other therapy in patients with Buerger's disease.

Materials and methods

Study design. Systematic review of randomised controlled studies. Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42016037911.

Introduction

Buerger's disease (thromboangiitis obliterans) is a non-atherosclerotic, occlusive, thrombotic, segmental inflammatory pathology that most commonly affects the small- and medium-sized arteries, veins

Searches. We searched in the Specialised Register and the Cochrane Register of Studies (CRS –<http://www.metaxis.com/CRSWeb/Index.asp>), LILACS (Latin American and Caribbean Health Sciences Literature (<http://lilacs.bvsalud.org>) and the grey literature produced in Europe by consulting the OpenGrey Database (www.opengrey.eu). The Specialised Register is performed from weekly electronic searches of Medical Literature Analysis and Retrieval System Online, Excerpta Medica dataBASE, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine *Databases* and through handsearching relevant journals. There were no language restrictions. We used the terms ‘Buerger’s disease’, ‘thromboangiitis obliterans’, ‘von Winiwarter disease’ and word variations to perform the search. The entire search was done on 8 April 2016. Search strategy is available in Appendix 1.

Selection criteria. We included studies designed as randomised controlled trials involving patients clinically diagnosed with Buerger’s disease (e.g. Shionoya’s criteria⁶) and submitted to surgical sympathectomy (without previous revascularisation of the affected member). Two review authors independently assessed all studies that were identified by the search strategy for inclusion. Disagreements were solved by discussion.

Data extraction. For all eligible studies, two review authors (DGC and DHM) extracted data using the Cochrane Vascular’s data extraction table. We entered the data into Review Manager 5.3. Primary outcomes collected were ulcer healing, pain, rate of amputation and death. Secondary outcomes collected were surgical sympathectomy complications (e.g. bleeding, infection, etc.) and side effects.

Risk of bias (quality) assessment. Two review authors independently assessed the included studies for risk of bias using Cochrane’s ‘Risk of bias’ tool as described in the Cochrane Handbook for Systematic Reviews of Interventions (available in <http://handbook.cochrane.org/>). The information about the risk of bias of the included studies was presented in the form of a table.

Statistical analysis. As measures of treatment effect were used as follows: (a) for dichotomous (categorical) data: presented as summary risk ratios with 95% confidence intervals; (b) for continuous data: presented as mean difference with 95% where there was consistency in the outcome measure, or the standardised mean difference to combine trials that measured the same outcome but used different confidence

intervals methods; and (c) time-to-event data: presented as hazard ratios with 95% confidence intervals to measure the treatment effect for any time-to-event outcomes. We used RevManager 5.3 to perform statistical analysis (method Mantel–Haenszel).

Heterogeneity. Heterogeneity among the eligible studies was quantified using the Chi square test and I^2 statistic, specifically using the formula $I^2 = (Q - df/Q) \times 100\%$ where Q was the Chi square statistic and df represented the degree of freedom. The I^2 statistic values were interpreted as follows: 0–25% = low heterogeneity, 25–75% = moderate heterogeneity, more than 75% = substantial heterogeneity.⁶ Where substantial heterogeneity was detected, according to the criteria above, we had planned to perform a further investigation based on the prespecified subgroup analysis.

Analysis of subgroups. We planned to perform subgroup analyses according to the following features: (a) tobacco exposure (cigarette, cannabis or any other form of smoking either measured in a laboratory or declared) after the intervention; (b) severity of the ischaemia, according to the Fontaine or Rutherford classification and (c) ischaemic territory (upper or lower limb).

Missing data. We contacted contact authors of included trials about methodological queries but none of them answered the solicitation. Where possible, we had planned to analyse all outcome measures on an ‘intention-to-treat’ basis by including data from all participants assessed.

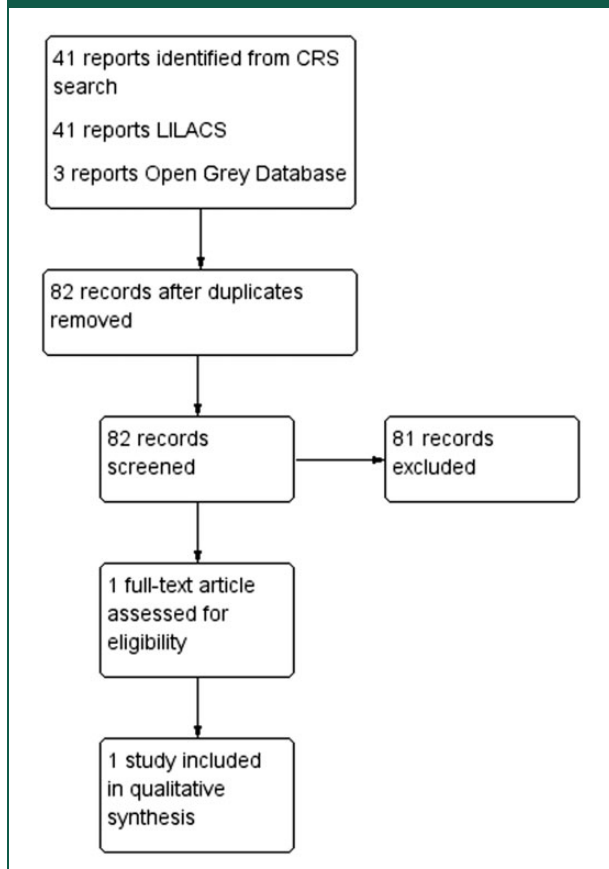
Summary of findings. We presented the main findings of the review results for the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the primary outcomes in ‘Summary of findings’ tables, according to Higgins and Green⁷ and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working group.⁸ Since we assessed different intervention comparisons, a ‘Summary of findings’ table was developed for each comparison included in the ‘Results’ section. The GRADEprofiler software was used to assist in the preparation of the ‘Summary of findings’ tables.

Results

Results of the search

A flow diagram of the search results is shown in Figure 1.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



Included studies

Only one randomised controlled study was included in this review. Bozkurt *et al.*⁹ reported on a study of 162 participants with Buerger's disease (Fontaine III and IV of ischaemia), who were submitted to lumbar sympathectomy and a prostacyclin analogue (iloprost) for four weeks. They compared complete healing rate, analgesic requirement, size of the ulcer, 50% reduction of the ulcer size and the SVS/ISCS (Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery) grading scale, with follow up of 24 weeks. More details about characteristics of included studies are given in Table 1.

Risk of bias. Risk of bias of the included trial is shown in Table 2.

Effects of interventions

Surgical sympathectomy versus oral prostacyclin analogue (iloprost). One study assessed this comparison.⁹

Primary outcomes

(1) Ulcer healing: assessed at the end of treatment (four weeks) and 24 weeks after the start of treatment. After four weeks (end of treatment), complete healing of all ulcers was 41% in the surgical sympathectomy group (23/57 participants) versus 61.9% in the iloprost group (36/58 participants). These findings were statistically significant (risk ratio 0.65; 95% confidence interval 0.45–0.95; $P = 0.02$). After 24 weeks, complete healing of all ulcers was 52.3% in the surgical sympathectomy group (30/57 participants) versus 85.3% in the iloprost group (49/58 participants). These findings were statistically significant (risk ratio 0.62; 95% confidence interval 0.48–0.82; $P < 0.01$).

Bozkurt *et al.*⁹ also reported 50% reduction of the ulcer size. Such reduction was found in 41.5% in the surgical sympathectomy group (23/57 participants) versus 75% in the iloprost group (43/58 participants). These findings were statistically significant (risk ratio 0.54; 95% confidence interval 0.38–0.7; $P < 0.01$). After 24 weeks, 50% reduction of the ulcer size was 68.4% in the surgical sympathectomy group (30/57 participants) versus 89.8% in the iloprost group (52/58 participants). These findings were statistically significant (risk ratio 0.76; 95% confidence interval 0.63–0.93; $P < 0.01$).

(2) Pain: assessed at the end of treatment (four weeks) and 24 weeks after the start of treatment. After four weeks (end of treatment), total relief of rest pain (without analgesic requirement) was 43.1% in the surgical sympathectomy group (30/70 participants) versus 22.2% in the iloprost group (18/80 participants). These findings were statistically significant (risk ratio 1.90; 95% confidence interval 1.17–3.10; $P = 0.01$). After 24 weeks, total relief of rest pain (without analgesic requirement) was 36.7% in the surgical sympathectomy group (25/70 participants) versus 21.1% in the iloprost group (17/80 participants). These findings were not statistically significant (risk ratio 1.68; 95% confidence interval 1.00–2.84; $P = 0.10$).

Secondary outcomes

Side effects: Bozkurt *et al.*⁹ described the fact that more participants reported side effects in the iloprost group, including headache (45.3%), flushing (43.06%), nausea (28.38%) and abdominal discomfort (12.12%). According to the authors, in one participant these symptoms were severe enough to stop the treatment. Minor wound infection occurred in five patients following surgical procedure.

Table 1. Characteristic of the included study.⁹

Methods	Study design: Multicentre randomised controlled trial
Participants	Country: Turkey (12 centres) Setting: hospital and community No of patients: 162 (84 in iloprost group and 78 in lumbar sympathectomy group) Mean age: iloprost group – 40.8 years; sympathectomy group: 39.7 years Gender – Group (% male vs. %female): iloprost group (97.6% vs. 2.4%); sympathectomy group (91% vs. 9%) Continued smoking: iloprost group: 19.7%; sympathectomy group: 21% Inclusion criteria: Shionoya criteria in patients with critical limb ischaemia Exclusion criteria: not specified
Interventions	Treatment: Iloprost group: iloprost 1 ng/kg/min – 6 h/day iloprost intravenously (started at 0.5 ng/kg/min and, if the patient tolerated the initial dose, the normal dose was administered for 28 days) Sympathectomy group: quote ‘Lumbar sympathectomy was carried out using the conventional technique. Lumbar 2nd, 3rd and 4th chains were excised unilaterally and the specimens were sent for pathological confirmation’. Duration of treatment: four weeks Follow-up: 24 weeks
Outcomes	Primary: complete healing rate Secondary: analgesic requirement, size of the ulcer, 50% reduction of the ulcer size and the SVS/ISCS (Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery) grading scale.
Notes	Research supported by ‘Research Fund of Istanbul University’

Table 2. Risk of bias table.

<i>Bias</i>	<i>Author’s judgement</i>	<i>Support for judgement</i>
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias)	High risk	Unable to blind
Blinding of outcome assessment (detection bias)	Unclear risk	Does not describe whether the outcome assessments were done by the same person responsible for recruitment
Incomplete outcome data (attrition bias)	High risk	Losses were not justified. Adoption of ‘as-treated’ (per protocol) analyses
Selective reporting (reporting bias)	High risk	Does not describe a relevant outcome: amputation rate
Other bias	Unclear risk	Conflict of interest was not described

Other outcomes

Rate of amputation, amputation-free survival, walking distance or pain-free walking, and ankle brachial index were not assessed by Bozkurt *et al.*⁹

Discussion

The purpose of this systematic review was to collect the largest number of studies on the usage of the sympathectomy for the treatment of patients with Buerger’s disease, in order to establish the best available

Table 3. Summary of findings (sympathectomy vs. iloprost for Buerger's disease).

Sympathectomy vs. iloprost for Buerger's disease					
Patient or population: patients with Buerger's disease					
Settings: hospital and community					
Intervention: Sympathectomy vs. iloprost					
Illustrative comparative risks* (95% CI)					
Assumed risk		Corresponding risk			
Control	Sympathectomy vs. iloprost	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Complete healing four weeks					
Study population			115 (1)	⊕⊕⊕⊕ ^{1,2,3,4,5}	Very low
621 per 1000	403 per 1000 (279–590)	RR 0.65 (0.45–0.95)			
Moderate					
621 per 1000	404 per 1000 (279–590)				
Complete healing 24 weeks					
Study population			115 (1)	⊕⊕⊕⊕ ^{1,2,3,4,5}	Very low
845 per 1000	524 per 1000 (406–693)	RR 0.62 (0.48–0.82)			
Moderate					
845 per 1000	524 per 1000 (406–693)				
Analgesic requirement four weeks					
Study population			150 (1)	⊕⊕⊕⊕ ^{1,2,3,4,5}	Very low
225 per 1000	428 per 1000 (263–697)	RR 1.9 (1.17–3.1)			
Moderate					
225 per 1000	428 per 1000 (263–697)				
Analgesic requirement 24 weeks					
Study population			150 (1)	⊕⊕⊕⊕ ^{1,2,3,4,5}	Very low
212 per 1000	357 per 1000 (210–603)	RR 1.68 (0.99–2.84)			
Moderate					
213 per 1000	358 per 1000 (211–605)				

(continued)

Table 3. Continued.

Sympathectomy vs. iloprost for Buerger's disease							
Patient or population: patients with Buerger's disease							
Settings: hospital and community							
Intervention: Sympathectomy vs. iloprost							
Illustrative comparative risks* (95% CI)							
Assumed risk		Corresponding risk		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Control	Sympathectomy vs. iloprost	Control	Sympathectomy vs. iloprost				
Reduction 50% ulcer size four weeks	Study population	Study population		RR 0.54 (0.38–0.77)	115 (1)	⊕⊖⊖⊖ ^{1,2,3,4,5} Very low	
	741 per 1000	400 per 1000 (282–571)					
	Moderate						
	741 per 1000	400 per 1000 (282–571)					
Reduction 50% ulcer size 24 weeks	Study population	Study population		RR 0.76 (0.63–0.93)	115 (1)	⊕⊖⊖⊖ ^{1,2,3,4,5} Very low	
	897 per 1000	681 per 1000 (565–834)					
	Moderate						
	897 per 1000	682 per 1000 (565–834)					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio 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

¹Not blinded, downgraded by one level.

²Losses were not justified, downgraded by one level.

³Adoption of 'as-treated' (per protocol) analyses, downgraded by one level.

⁴Selective reporting (does not describe amputation rate), downgraded by one level.

⁵One single study (doubt about reproducibility of data), downgraded by one level.

evidence to date. Although it is one of the oldest treatments for patients with Buerger's disease in critical limb ischaemia, the lumbar sympathectomy was investigated by only one study capable of generating good quality evidence, that is a randomised and controlled clinical trial, by comparing the lumbar surgical sympathectomy to the intravenous iloprost (prostacyclin analogue). Accordingly, the generated evidence has been limited to one study and one comparison.

The researched outcomes were intended to treat patients with critical limb ischaemia, which is the improvement in pain at rest and ulcers healing. However, what draws attention is the lack of information related to amputation rate and amputation-free survival, relevant data for patients with critical ischaemia.

Regarding the risk of bias, we have observed that the only study about the review was considered to be high risk in most of the categories. Except for the absence of blinding of the involved patients (prevented by the very nature of surgical versus medicated treatment comparison), the other studied categories such as allocation concealment, outcome evaluators blinding, the protocol analysis and not by intention-to-treat analysis (which reduces the randomised effect) and the description of reasons for the remarkable number of losses (about 20% of the sympathectomy group) could have been evaded by the study authors. These methodological failures unquestionably jeopardise not only the rate but also the course of the observed effect.

The main evidence found on this study refers to the greater effectiveness of iloprost in relation to the lumbar sympathectomy on the healing of ischaemic ulcers and pain at rest on patients with the Buerger's disease. The greater effectiveness of iloprost in patients with Buerger's disease and critical limb ischaemia was verified by recent Cochrane systematic review with moderate quality evidence when compared to treatment with aspirin. However, because of the high risk of bias presented by the only study selected in this review and following the GRADE parameters,⁸ the observed evidence was ranked very low. We summarised the quality of the evidence in Table 3.

As for implications for future studies, we emphasise the need for further and good quality studies, incorporating the same comparison (sympathectomy versus intravenous iloprost), other types of drugs (e.g. cilostazol, pentoxifylline, clopidogrel, etc.), other therapeutic (use of stem cells, omental transplantation, foot venous arch arterialisation, acupuncture, etc.) against surgical sympathectomy.

As for implications for practice, we can say that in view of the fragile evidence found here regarding the treatment for Buerger's disease in patients with critical limb ischaemia, the preference for the use of

intravenous iloprost in relation to lumbar sympathectomy for this profile of patients is not fully based.

Conclusions

Very low evidence suggests that intravenous iloprost is more effective than the lumbar sympathectomy in the healing of ischaemic ulcers and pain at rest in patients with Buerger's disease. Therefore, until now, the preference of the usage of intravenous iloprost over the lumbar sympathectomy (and *vice versa*) is not supported by robust evidence for its routine use.

Declarations

Competing Interests: None declared.

Funding: None declared.

Ethical approval: Not applicable.

Guarantor: DGC

Contributorship: DGC is the contact person with the editorial base.

DGC drafted the clinical section of the background.

DGC, DHM, LCUN, JCCBS contributed to writing the protocol.

DGC, DHM wrote the final draft of the protocol and review.

DGC, DHM selected studies, extracted data, performed data analysis and wrote the review.

DGC is the guarantor of the final review.

LCUN, JCCBS: methodological supervision.

Acknowledgements: None

Provenance: Not commissioned; peer-reviewed by Richard Downing.

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Appendix 1

Cochrane Register of Studies search strategy

#1	Buerger:TI,AB,KY	25
#2	Buerger*:TI,AB,KY	25
#3	MESH DESCRIPTOR Thromboangiitis Obliterans	13
#4	(thromboang* near/2 oblit*)	0
#5	(thromboang* near oblit*)	31
#6	(endangitis obliterans)	0
#7	Winiwarter	1
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	41

Latin American and Caribbean Health Sciences Literature search strategy

(MH:“Thromboangiitis Obliterans” OR “Tromboangeítis Obliterante” OR “Tromboangeíte Obliterante” OR “Doença de Buerger” OR “C14.907.137.870” OR “C14.907.940.905”) AND (DB: (“IBECS” OR “LILACS”)) 41 records

OpenGrey Database search strategy

buerger's disease	3
thromboangiitis obliterans	2
von Winiwarter disease	0
buerger's disease OR thromboangiitis obliterans OR von Winiwarter disease	3