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Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD000985.

DOI: [10.1002/14651858.CD000985.pub3](https://doi.org/10.1002/14651858.CD000985.pub3).

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[Intervention Review]

Infusion techniques for peripheral arterial thrombolysis

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ABSTRACT

Background

Acute limb ischaemia usually is caused by a blood clot blocking an artery or a bypass graft. Severe acute ischaemia will lead to irreversible damage to muscles and nerves if blood flow is not restored in a few hours. Once irreversible damage occurs, amputation will be necessary and the condition can be life-threatening. Infusion of clot-busting drugs (thrombolysis) is a useful tool in the management of acute limb ischaemia. Fibrinolytic drugs are used to disperse blood clots (thrombi) to clear arterial occlusion and restore blood flow. Thrombolysis is less invasive than surgery. A variety of techniques are used to deliver fibrinolytic agents. This is an update of a review first published in 2004.

Objectives

To compare the effects of infusion techniques during peripheral arterial thrombolysis for treatment of patients with acute limb ischaemia.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registries to 20 October 2020. We undertook reference checking to identify additional studies.

Selection criteria

We included all randomised controlled trials (RCTs) comparing infusion techniques for fibrinolytic agents in the treatment of acute limb ischaemia.

Data collection and analysis

We used standard methodological procedures as recommended by Cochrane. We assessed the risk of bias in included trials using the Cochrane 'Risk of bias' tool. We evaluated certainty of evidence using GRADE. For dichotomous outcomes, we calculated the odds ratio (OR) with the corresponding 95% confidence interval (CI). We were not able to carry out meta-analyses due to clinical heterogeneity, so we have reported the results and performed the comparisons narratively. The main outcomes of interest were amputation-free survival or limb salvage, amputation, mortality, vessel patency, duration of thrombolysis, and complications such as cerebrovascular accident and major and minor bleeding.

Main results

Nine studies with a total of 671 participants are included in this update. Trials covered a variety of infusion techniques, dosage regimens, and adjunctive agents. We grouped trials according to types of techniques assessed (e.g. intravenous and intra-arterial delivery of the agent, 'high-' and 'low-dose' regimens of the agent, continuous infusion and 'forced infusion' of the agent, use of adjunctive antiplatelet agents). We assessed the certainty of evidence as very low to low due to the limited power of individual studies to deliver clinically relevant results, small and heterogeneous study populations, use of different inclusion criteria by each study in terms of severity and duration of

ischaemia, considerably different outcome measures between trials, and use of different fibrinolytic agents. This heterogeneity prevented pooling of data in meta-analyses.

No regimen has been shown to confer benefit in terms of amputation-free survival (at 30 days), amputation, or death. For vessel patency, complete success was more likely with intra-arterial (IA) than with intravenous (IV) infusion (odds ratio (OR) 13.22, 95% confidence interval (CI) 2.79 to 62.67; 1 study, 40 participants; low-certainty evidence); radiological failure may be more likely with IV infusion (OR 0.02, 95% CI 0.00 to 0.38; 1 study, 40 participants; low-certainty evidence). Due to the small numbers involved in each arm and design differences between arms, it is not possible to conclude whether any technique offered any advantage over another. None of the treatment strategies clearly affected complications such as cerebrovascular accident or major bleeding requiring surgery or blood transfusion. Minor bleeding complications were more frequent in systemic (intravenous) therapy compared to intra-arterial infusion (OR 0.03, 95% CI 0.00 to 0.56; 1 study, 40 participants), and in high-dose compared to low-dose therapy (OR 0.11, 95% CI 0.01 to 0.96; 1 study, 63 participants).

Limited evidence from individual trials appears to indicate that high-dose and forced-infusion regimens reduce the duration of thrombolysis. In one trial, the median duration of infusion was 4 hours (range 0.25 to 46) for the high-dose group and 20 hours (range 2 to 46) for the low-dose group. In a second trial, treatment using pulse spray was continued for a median of 120 minutes (range 40 to 310) compared with low-dose infusion for a median of 25 hours (range 2 to 60). In a third trial, the median duration of therapy was reduced with pulse spray at 195 minutes (range 90 to 1260 minutes) compared to continuous infusion at 1390 minutes (range 300 to 2400 minutes). However, none of the studies individually showed improvement in limb salvage at 30 days nor benefit for the amputation rate related to the technique of drug delivery. Similarly, no studies reported a clear difference in occurrence of cerebrovascular accident or major bleeding. Although 'high-dose' and 'forced-infusion' techniques achieved vessel patency in less time than 'low-dose' infusion, more minor bleeding complications may be associated (OR 0.11, 95% CI 0.01 to 0.96; 1 study, 72 participants; and OR 0.48, 95% CI 0.17 to 1.32; 1 study, 121 participants, respectively). Use of adjunctive platelet glycoprotein IIb/IIIa antagonists did not improve outcomes, and results were limited by inclusion of participants with non-limb-threatening ischaemia.

Authors' conclusions

There is insufficient evidence to show that any thrombolytic regimen provides a benefit over any other in terms of amputation-free survival, amputation, or 30-day mortality. The rate of CVA or major bleeding requiring surgery or blood transfusion did not clearly differ between regimens but may occur more frequently in high dose and IV regimens. This evidence was limited and of very low certainty. Minor bleeding may be more common with high-dose and IV regimens.

In this context, thrombolysis may be an acceptable therapy for patients with marginally threatened limbs (Rutherford grade IIa) compared with surgery. Caution is advised for patients who do not have limb-threatening ischaemia (Rutherford grade I) because of risks of major haemorrhage, cerebrovascular accident, and death from thrombolysis.

PLAIN LANGUAGE SUMMARY

Infusion techniques for peripheral arterial thrombolysis

Background

Abrupt reduction in blood flow to a limb (acute limb ischaemia) usually is caused by a blood clot (thrombus) blocking an artery or a bypass graft. Severe acute ischaemia will lead to irreversible damage to muscles and nerves if blood flow is not restored in a few hours. Once irreversible damage occurs, amputation will be necessary and the condition can be life-threatening. Infusion of clot-busting drugs (thrombolysis) can restore blood flow by dispersing the clot; this approach is less invasive than open surgery.

Is any infusion technique for delivering thrombolysis better than another?

We wanted to know if any method of delivering clot-busting drugs offered greater benefit compared to another for important outcomes such as preventing amputation and death, restoring blood flow, and reducing length of time needed to deliver drugs; and if any technique caused greater harm than another (such as stroke or bleeding)?

How did we identify and evaluate the evidence?

First, we searched the medical literature for randomised controlled trials (RCTs) - clinical studies where people are randomly put into one of two or more treatment groups. This type of study provides the most robust evidence about effects of treatment. We then compared trial results and summarised the evidence from all studies. Finally, we assessed how certain the evidence was. To do this, we considered factors such as the way studies were conducted, study size, and consistency of findings across studies. Based on our assessments, we categorised the evidence as very low, low, moderate, or high certainty.

What did we find?

We found nine RCTs with a total of 671 participants with varying severity of ischaemia who were randomised to receive thrombolysis by different infusion techniques. These studies used very different trial designs, which prevented pooling of data. Two studies compared intra-arterial and intravenous drug delivery using different thrombolytic agents. Six studies compared high- and low-dose regimens, or

continuous infusion and forced-infusion (pulse spray) regimens. Studies provided no definition of what high or low dose was, used different agents with or without initial lacing of the clot with a high dose of the agent (bolus), and delivered agents into the artery or the thrombus. One study compared use of additional antiplatelet agents with thrombolysis.

Limited evidence of very low and low certainty from individual studies may indicate that greater benefit is seen when the thrombolytic agent is delivered into the thrombus: systemic intravenous thrombolysis is less effective than intra-arterial thrombolysis. 'High-dose' and 'forced-infusion' techniques, or use of adjunctive agents such as platelet glycoprotein IIb/IIIa inhibitors, may speed up thrombolysis, but these techniques are generally more labour-intensive and seem to be associated with increased bleeding complications compared to low-dose regimens, and there is no evidence that they lead to improved outcomes (e.g. lower amputation rates). 'Low-dose continuous infusion', following initial lacing of the thrombus with a high dose of the thrombolytic agent, is the least labour-intensive technique. Thrombolysis appears to be an acceptable therapy for patients with marginally threatened limbs (Rutherford grade IIa), but, because of risks of bleeding, stroke, and death, thrombolysis should be used with caution in patients who do not have limb-threatening ischaemia (Rutherford grade I). Regimens that decrease the time needed to restore blood flow may permit treatment of patients with immediately threatened limbs (Rutherford grade IIb).

More research is needed to confirm these findings.

How up-to date is this review?

Evidence in this Cochrane Review is current to 20 October 2020.