Cochrane
Library

Cochrane Database of Systematic Reviews

Interventions for acute non-arteritic central retinal artery occlusion (Review)

Fraser SG, Adams W

Fraser SG, Adams W.
Interventions for acute non-arteritic central retinal artery occlusion.
Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001989.
DOI: [10.1002/14651858.CD001989.pub2](https://doi.org/10.1002/14651858.CD001989.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	1
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	5
DISCUSSION	6
AUTHORS' CONCLUSIONS	7
ACKNOWLEDGEMENTS	7
REFERENCES	8
CHARACTERISTICS OF STUDIES	10
APPENDICES	12
WHAT'S NEW	14
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	14
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	14
INDEX TERMS	14

[Intervention Review]

Interventions for acute non-arteritic central retinal artery occlusion

Scott G Fraser¹, Wendy Adams¹¹Sunderland Eye Infirmary, Sunderland, UK**Contact address:** Scott G Fraser, Sunderland Eye Infirmary, Queen Alexandra Road, Sunderland, SR2 9HB, UK. s.g.fraser@ncl.ac.uk.**Editorial group:** Cochrane Eyes and Vision Group.**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 1, 2010.**Citation:** Fraser SG, Adams W. Interventions for acute non-arteritic central retinal artery occlusion. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD001989. DOI: [10.1002/14651858.CD001989.pub2](https://doi.org/10.1002/14651858.CD001989.pub2).

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Acute central retinal artery occlusion (CRAO) occurs as a sudden interruption of the blood supply to the retina and results in an almost complete loss of vision in the affected eye. There is no generally agreed treatment regimen although a number of therapeutic interventions have been proposed.

Objectives

The objective of this review was to examine the effects of treatments used for acute non-arteritic CRAO.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library*, Issue 3, 2008), MEDLINE (January 1966 to September 2008), EMBASE (January 1980 to September 2008) and the reference lists of relevant papers.

Selection criteria

We included randomised controlled trials (RCTs) only in which one treatment aimed to re-establish blood supply to the retina in people with acute CRAO was compared to another treatment.

Data collection and analysis

Two authors independently assessed the search results for relevant trials. Discrepancies were resolved by discussion.

Main results

We found two RCTs that met our inclusion criteria.

Authors' conclusions

The included studies in this review were small and from single centres. Neither study was completely clear about its method of treatment allocation. One study described the use of pentoxifylline tablets (three 600 mg tablets daily) and the other the use of enhanced external counterpulsation (EECP) combined with haemodilution. Both studies indicated improved retinal perfusion in the non-control group but neither showed an improvement in vision. Large, well-designed RCTs are still required to establish the most effective treatment for acute CRAO. These studies should be looking at factors important to the patient i.e. improved vision with acceptable risk/side-effects.

PLAIN LANGUAGE SUMMARY

Treatments for acute central retinal artery occlusion (blockage of the blood supply to the retina of the eye)

Central retinal artery occlusion occurs when the blood supply to the inner part of the retina (the light sensitive layer inside the eye) is suddenly stopped. If the blockage is removed in time, and the blood supply returns to the retina, full recovery is possible. However, if the blockage is prolonged the retina dies. Various methods have been tried in an attempt to remove the blockage including massaging the eye, lowering the pressure inside the eye and dissolving clots with drugs. Which of these methods is best for re-establishing the blood supply is not known and some of the treatments can be associated with serious adverse effects. This review did find two studies that suggested that the blood supply to the retina could be improved with the treatments they tested - although vision was not shown to be improved with either method in the study population. These were, however, small studies and did have potential flaws so more research is still needed.

BACKGROUND

Introduction

Central retinal artery occlusion (CRAO) occurs as a sudden event when the blood supply to the inner part of the retina is blocked. The resulting ischaemia causes an almost immediate and profound loss of vision. The blood supply may be interrupted in several ways. The artery may be blocked by an embolus (a small piece of blood clot, cholesterol or calcium that has entered the bloodstream, usually from the wall of the carotid artery or sometimes the heart). Alternatively there may be a sudden narrowing of one of the vessels that supplies the central retinal artery or of the central artery itself (i.e. haemorrhage into an atheromatous plaque in the vessel wall). This review does not deal with CRAO associated with inflammation of the central retinal artery (arteritic CRAO) such as that seen secondary to temporal arteritis (a chronic condition involving inflammation of many arteries supplying blood to the head and neck and sometimes inflammation of the optic nerve).

Epidemiology

The true incidence of CRAO in the population is unknown. [Rumelt 1999](#) estimated an incidence of acute (less than 48 hours) CRAO of 0.85/100,000 population/year at their institution. Over 75% of patients with CRAO have evidence of atherosclerosis and there is an association with diabetes and systemic hypertension ([Ffytche 1974](#)).

Treatment options

There is debate about how long after the artery is blocked permanent visual loss occurs. If the blockage is removed in time, either spontaneously or with treatment, then full visual recovery is possible. Hayreh et al. have shown that the primate retina can tolerate up to 105 minutes of ischaemia but beyond this time irreparable damage occurs ([Hayreh 1980](#)). Extrapolation of this information to the human has led to the theory that treatment is only beneficial if commenced within eight hours of the occlusion. More recently, authors have reported beneficial effects from treatments given up to 24 hours after the onset of symptoms ([Richard 1999](#)) and Augsburger reported significant visual improvement after 48 hours of ischaemia ([Augsburger 1980](#)). However, studies suggest that shorter occlusion time results in better eventual visual recovery, usually as measured by Snellen visual acuity ([Rumelt 1999](#)). The devastating nature of the condition on the vision has led to a number of therapies being tried.

Waiting

Spontaneous resolution of the block (e.g. embolus moving on from the ophthalmic circulation) is reported by some authors to occur in less than 1% to 8% of cases ([Rumelt 1999](#); [Schmidt 1992](#)). Others have suggested up to 15% ([Atebara 1995](#)).

Dilation of artery

Various methods have been used to try to dilate the artery thereby allowing an increased blood flow and/or removal of the blockage. They have the potential disadvantage that they can also produce systemic vasodilatation and therefore reduce the systemic blood pressure. Vasodilators described in the literature include:

- sublingual isosorbide dinitrate ([Rumelt 1999](#));
- rebreathing of expired carbon dioxide ([Harino 1995](#));

- breathing in a fixed mixture of 95% oxygen and 5% carbon dioxide (called carbogen) ([Atebara 1995](#); [Deutsch 1983](#); [Schmetterer 1996](#)).

Physical removal of obstruction

This is only likely to work when the cause of the obstruction is an embolus to the central retinal artery. The aim of treatment is to physically dislodge this embolus so that it passes through the ophthalmic circulation. Methods described include the patient massaging their own eye (this usually involves gently pressing on one side of the eye and then the other through closed lids) ([Ffytche 1974](#)) or the practitioner massaging the patient's eye with fingers or a contact lens (the latter allows the retinal circulation to be viewed at the same time) ([Rumelt 1999](#)).

Increasing perfusion pressure by reduction of intraocular pressure

Ocular perfusion (blood flow through the eye) increases if intraocular pressure decreases. It has therefore been suggested that a sudden decrease in intraocular pressure may prompt an increase in perfusion pressure and a consequent reduction in retinal ischaemia. Methods of reducing intraocular pressure include:

- anterior chamber paracentesis: this involves putting a small needle into the anterior chamber of the eye and withdrawing a small amount of aqueous (fluid in the front chamber of the eye) ([Atebara 1995](#); [Ffytche 1974](#));
- intravenous acetazolamide (a carbonic anhydrase inhibitor) ([Ffytche 1974](#); [Rassam 1993](#));
- intravenous mannitol (an osmotic diuretic) ([Rumelt 1999](#));
- trabeculectomy: a surgical procedure that involves the creation of an aqueous fistula (channel) between the anterior chamber and the subconjunctival space ([Harvey 2000](#)).

Thrombolysis (dissolving the clot)

Thrombolysis or fibrinolysis is a recognised treatment for acute myocardial infarctions and some types of stroke. The principle of lysis of the clot with subsequent restoration of the circulation has been extended to CRAO. The thrombolytic agent is administered intravenously and may be given locally or systemically. Local intra-arterial fibrinolysis (LIF) involves super-selective administration of the thrombolytic agent directly into the ophthalmic artery. A review and meta-analysis of the published data on this treatment has been prepared by [Beatty 2000](#). Fibrinolytics used include urokinase ([Arnold 2005](#)) and recombinant tissue plasminogen activator (rt-PA) ([Pettersen 2005](#)). Recombinant tissue plasminogen activator has been used for some time in acute myocardial infarction and stroke - of all the thrombolytics studied this has the most data and is thought to be associated with less hazard and more benefit than other thrombolytics ([Wardlaw 2007](#)).

Antiplatelet therapy

It is known that in patients with acute ischaemic stroke (which has some analogy to CRAO), platelets become activated and this can worsen the ischaemia. Administration of antiplatelet drugs may reduce the progression of cerebral thrombosis and therefore the ischaemia ([Sandercock 2003](#)). [Holschermann 2005](#) used intravenous tirofiban - this is nonpeptide inhibitor of the platelet glycoprotein IIb/IIIa receptor which has been used for acute ischaemic events in other organs. Although there are no formal studies identified, evidence from the stroke literature would

suggest that all patients who have sustained a CRAO in one eye should be on long-term aspirin to reduce the risk in the fellow eye (Neubauer 2000). Clopidogrel is an alternative for patients in whom aspirin is contraindicated (Kattah 2002).

Reducing red blood cell rigidity

The less deformable red blood cells are the harder it is for them to pass through the capillaries and the greater the tissue ischaemia (Iwafune 1980). Pentoxifylline has been shown to increase red blood cell deformability and has been used orally on patients with CRAO (Iwafune 1980; Kieswetter 1983). It has been used for other vascular conditions associated with reduced tissue perfusion including 'multi-infarct' dementia (Frampton 1995). A Cochrane review of its use in acute ischaemic stroke did not find enough evidence to support its use (Bath 2004).

Systemic steroids

Vascular endothelial oedema (swelling from excess fluid) has been suggested as a contributory factor to tissue damage following CRAO. Because of this, intravenous steroids have been suggested as a treatment option (Hausmann 1991).

Enhanced external counterpulsation (EECP)

This non-invasive technique has been used in patients with ischaemic heart disease and reported to help relieve angina, improve exercise tolerance and improve cardiac perfusion (Arora 1999). The technique involves wrapping three sets of pneumatic cuffs around the lower extremities and monitoring the cardiac rhythm. The cuffs are inflated sequentially at the onset of diastole causing aortic counter pulsation and increased venous return (Pettersson 2006). At the onset of systole the cuffs are released producing a decrease in systolic pressure (Pettersson 2006). The results of these haemodynamic changes are increased coronary blood flow and a reduction in myocardial ischaemia.

Enhanced external counterpulsation has been suggested for use in other diseases with ischaemic problems e.g. hepatorenal syndrome, erectile dysfunction and restless leg syndrome (Manchanda 2007). It has also been suggested that it may have a role in the treatment of CRAO (Werner 2004).

Combinations of treatment

Some researchers (and probably most clinicians) have used combinations of the above. Kattah et al. used a combination of anterior chamber paracentesis (if the intraocular pressure in the affected eye was greater than 12 mmHg) and all patients were given intra-arterial rtPA (Kattah 2002). This was followed by heparin and then warfarin for one month. The latter was replaced with aspirin or clopidogrel after one month. Arnold et al. used a combination of intraocular pressure lowering, intravenous urokinase and aspirin in their patients (Arnold 2005).

Rationale for a systematic review

There is no generally agreed standard treatment regimen for CRAO and this is exemplified by the number of different treatments that have been tried. Many of the treatment options have potential side effects, including serious haemorrhagic complications. This needs to be considered when assessing the value of interventions for a condition that sometimes resolves spontaneously. It is not known how many hours after the event any potential treatment would be effective. Nor has there been any analysis comparing the cost of the treatment with the costs of visual loss.

Finally, it is important to be aware that experimental studies have shown that retinal damage may arise not only from the period of non-perfusion, but also from the cascade of oxidative damage which occurs with reperfusion (Brown 1994) i.e. there is the potential for a 'successful' treatment to make the ocular damage worse.

OBJECTIVES

The objective of this review was to assess the effects of treatments for non-arteritic CRAO.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) only.

Types of participants

We considered trials that included participants with acute non-arteritic CRAO in one or both eyes.

Types of interventions

We considered any intervention that has been used as a treatment for acute non-arteritic CRAO. These include:

1. waiting (i.e. no intervention);
2. dilation of artery;
3. physical removal of obstruction;
4. increasing perfusion pressure by reduction of intraocular pressure;
5. thrombolysis (dissolving the clot);
6. antiplatelet therapy;
7. reducing red blood cell rigidity;
8. systemic steroids;
9. EECP;
10. any combinations of the above.

Types of outcome measures

Primary outcomes

The primary outcome for this review was visual acuity.

Secondary outcomes

Secondary outcomes included adverse ocular effects, adverse systemic effects and quality of life measures.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library*, Issue 3, 2008), MEDLINE (January 1966 to September 2008) and EMBASE (January 1980 to September 2008). There were no language or date restrictions in the search for trials. All databases were last searched on 16 September 2008.

See: Appendices for details of search strategies for CENTRAL ([Appendix 1](#)), MEDLINE ([Appendix 2](#)) and EMBASE ([Appendix 3](#)).

Searching other resources

We searched the reference lists of relevant papers for further trials.

Data collection and analysis

Selection of studies

Two authors independently assessed the titles and abstracts resulting from the electronic searches. The full reports of all relevant and possibly relevant studies were obtained for assessment according to the definitions in the 'Criteria for considering studies for this review'.

Data extraction and management

Two authors independently extracted the data using a form developed for use by the Cochrane Eyes and Vision Group. Relevant data were entered into RevMan.

Assessment of risk of bias in included studies

Two authors independently assessed trial quality and disagreements were resolved by discussion. Review authors were not masked to any trial details during the assessment. Trial quality was assessed according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)). Five parameters were considered: allocation concealment, method of allocation to treatment, documentation of exclusions, masking of outcome assessment and completeness of follow-up. Each parameter of trial quality was graded Yes: low risk of bias, No; high risk of bias or Unclear. Trials graded Unclear on allocation concealment were excluded.

Data synthesis

For future updates and where available, data from studies collecting the same outcome measure with similar types of interventions will be summarised using the Peto method, after testing for heterogeneity between trial results using a standard chi-square test.

Sensitivity analysis

For future updates, sensitivity analyses will be conducted to determine the impact of study quality on effect size.

Updates to this review

This review will be updated every two years to include new trials that may have been published.

RESULTS

Description of studies

Results of the search

The initial electronic searches resulted in 164 titles and abstracts. Nine papers were retrieved in full for further assessment but no RCTs were identified. Some studies ([Rumelt 1999](#); [Schmidt 1992](#); [Weber 1998](#)) did use control groups but assignment to groups was not random.

Updated searches

Updates to the searches conducted in September 2005 retrieved a further 305 titles and abstracts. Six papers were retrieved in full for further assessment. Four papers were rejected after reading the full paper ([Arnold 2005](#); [Drago 1982](#); [Gu 1999](#); [Kattah 2002](#)). Two studies, [Incandela 2002](#) and [Werner 2004](#) were included in the review.

An updated search was done in June 2007 which yielded a further 203 reports of studies. The Trials Search Co-ordinator scanned the search results and removed any references which were not relevant to the scope of the review. Two papers were assessed for potential inclusion but were excluded ([Holschermann 2005](#); [Pettersen 2005](#)).

An update search was run in September 2008 which yielded a further 110 reports of studies. The abstracts were scanned but no references were relevant to the scope of the review.

Included studies

Two studies were included in the review. See Table: [Characteristics of included studies](#) for further details.

[Incandela 2002](#) reported a study that used oral pentoxifylline in patients with 'sudden loss of vision'. Inclusion criteria was sudden loss of vision associated with thrombosis of the central retinal artery (i.e. CRAO) and patients were randomised to either pentoxifylline tablets (three 600 mg tablets daily) or placebo for four weeks. The endpoint measurement was both objective (change in central retinal artery flow velocity) and subjective - the patients were asked, using an analogue scale, how much they felt their vision had improved after treatment? There is no mention in the paper of how the analogue score was administered or what questions the patients were asked. The suggestion in the paper is that the lower the score the 'better' the patients felt they were after treatment.

The paper mentions that during treatment patients 'had to avoid smoking' though there is no mention of how many patients did this, or whether there was a difference between cases and controls in regard to smoking. From the description in the paper, patients seemed to be demographically similar. There is no mention of the number of patients who declined to be randomised for the study.

There is no mention in the paper of how the patients were allocated to the two treatment groups. An attempt was therefore made to contact the authors but, to date, there has been no response.

[Werner 2004](#) reported a study where patients with acute (defined as within five days) CRAO or BRAO were given a short treatment of EECF. The diagnosis of arterial occlusion was made clinically. The study was prospective and randomised but non-masked and had 20 participants. There is no description in the paper of how the treatment was allocated. Ten patients were given haemodilution therapy plus two hours of EECF whilst the other 10 were given 'regular' haemodilution only (the word 'regular' is taken from the authors description). Haemodilution involved 500 ml of intravenous hydroxyethyl starch or if the patient had compromised cardiac function, 500 ml of electrolyte solution was used (this alternative was used in four of the EECF group and five of the 'control' group). Fifteen patients were excluded from the study and their characteristics are described in the paper.

The outcome used was change in retinal perfusion measured by scanning laser Doppler flowmetry. This was initially measured during haemodilution, 30 minutes after EECF (or 30 minutes after

when EECF would have been given - for the control group) and finally 48 hours later. Visual acuity was also measured after initial admission with the event and just before the final perfusion measurement (i.e. 48 hours after the end of treatment). The patients were also monitored for any adverse events during the treatments.

Excluded studies

See Table: [Characteristics of excluded studies](#) for further details.

Risk of bias in included studies

Both studies had a risk of bias.

Incandela 2002: The study was small (10 participants) and in a single centre. The method of treatment allocation is not clear from the paper and the authors have not been contactable. A placebo was used but it is not possible to gauge from the paper if the practitioners were masked - either those who dispensed the treatment or those who measured the central retinal artery flow velocity.

Werner 2004: Again the study was small with 20 participants and again was in a single centre. It is difficult to be sure of the method of treatment allocation - the main author was contacted and stated that 'lots' were drawn by a colleague to decide treatment allocation but could not give further detail. The therapy was non-masked but it is not known if the Doppler flow readings were taken by a masked observer. Further contamination comes from the fact that both EECF and non-EECF groups had haemodilution.

Effects of interventions

Incandela 2002: There are a number of unanswered questions in relation to this study. Never the less this is the first study in patients with CRAO, that we identified, that attempted to randomly allocate treatment. There is no mention of the duration of visual loss of the patients enrolled in the study. The results presented showed an increase in retinal blood flow velocity and a decrease in analogue score in both case and controls. The authors report a greater increase in blood flow parameters in cases compared to controls and a 'significant' difference in analogue score decrease with a greater decrease in the treated group. As both groups contained very small numbers it would be difficult to see how statistical significance could be reached. Surprisingly the paper does not give any details of changes in visual acuity in cases or controls. The paper does not discuss any adverse events associated with the treatment. There is no discussion of the economic aspects of the trial.

Werner 2004: No adverse effects were reported in either group. The EECF group were found to have significantly greater retinal perfusion than the non-EECF group at the three hour post-treatment measurement. At the 48 hour measurement, both EECF and non-EECF groups showed increased perfusion from baseline but there was no longer a significant difference between the measurements of the two groups. There was no significant difference between the final visual acuity of the EECF group and non-EECF group. Again there was no discussion of the economic aspects of the trial.

DISCUSSION

Summary of main results

Our previous version of this review concluded that no RCTs of treatment options for non-arteritic CRAO could be found. We suggested that there remained a number of treatments that are of unproven efficacy but may have a role in the treatment of the condition but that we could not make a recommendation of which may be the best. However, we now report two RCTs of treatments for CRAO which, although potentially flawed, suggest that oral pentoxifylline and/or EECF may have a role in treatment.

Incandela 2002 indicated that the treated group had better retinal artery flow rates than the untreated group but how this translated into clinical benefit is harder to say (there seems little point in having better retinal artery blood flow if this does not lead to improved visual acuity). It is to the author's credit that they attempted to look at the results from the patients perspective but odd that they did not publish the final visual acuities of cases and controls.

Werner 2004 also indicated a potentially improved retinal perfusion after EECF - but again this did not translate into better vision for the study patients. The study is complicated by the fact that both groups also underwent haemodilution and it is not, therefore, possible to know if this had a positive or negative effect on the EECF.

Quality of the evidence

The limitations of the trials are discussed above. Amongst other problems both have small numbers and short follow-ups making it difficult to generalise their findings; even more so when both studies come from single centres. Neither trial gave precise information about allocation of treatment and this brings a further element of doubt to their findings. There are also issues about the standardisation criteria for entry to the trials i.e. how long after CRAO should treatment be started? The Werner trial was further complicated by the use of haemodilution in both groups.

We discussed in our previous version of this review the need for an RCT in CRAO treatment - to reduce the effect of other variables (e.g. smoking, diabetes, spontaneous resolution) and suggested some ideal characteristics of a trial. Amongst the suggestions we made was that the trial should be a multicentre study - to allow adequate recruitment and to improve generalisability. Robust (objective) entry criteria would be required as would measurable endpoints - including patient orientated outcomes. It would appear that such a trial is currently being undertaken in Europe. The European Assessment Group for Lysis in the Eye (EAGLE) is a prospective, randomised, multicentre study (**Feltgen 2006**). Inclusion criteria are patients with CRAO of less than 20 hours and a visual acuity of less than 0.32. After randomisation, patients are allocated to either conservative treatment or local intra-arterial thrombolysis using rtPA. Endpoint is visual acuity one month after treatment (compared with that at presentation). The study was started in 2002 and the latest paper (**Feltgen 2006**) reports that by April 2005 47 patients were recruited. The calculated sample size was 100 participants in each arm.

AUTHORS' CONCLUSIONS

Implications for practice

This review found two small RCTs; one that suggested a positive effect for oral pentoxifylline in the treatment of non-arteritic CRAO and the other for EECF (combined with haemodilution). The small size of the studies, potential for bias and the lack of data on final vision means that we do not have convincing evidence at present to support the routine use of pentoxifylline or of EECF in patients with CRAO. However in the absence of other proven therapies, the relative apparent safety of both these treatment modalities would lead us to suggest that if treatment is deemed necessary then either or both would be justified. No treatment is without its potential hazards and it is important that the practitioner allows the patient to balance the risks of these interventions with the possibility of a positive clinical effect. Results from the EAGLE study will, we hope, allow us to determine if there is a role for more invasive, thrombolysis therapies.

Implications for research

This review identified one trial that suggested a positive effect for oral pentoxifylline and one that suggested a role for EECF

(combined with haemodilution). Both studies did, however, appear to have limitations that make generalisation difficult. There is a large RCT of intra-arterial thrombolysis currently underway and the results are potentially interesting. We would also suggest that a large RCT was devised using oral pentoxifylline in one arm and EECF in another versus either placebo or intra-arterial thrombolysis (depending upon the results of the EAGLE trial). If possible this study should be designed using the same entry criteria and outcomes measures as the EAGLE trial to allow future meta-analysis.

ACKNOWLEDGEMENTS

The Cochrane Eyes and Vision Group (CEVG) editorial team developed the search strategies and undertook the electronic searches. We thank Dilani Siriwardena for her contributions to the original published version of this review. We are grateful to Philip Griffiths, Graeme Hankey, Timothy ffytche and Graeme Hankey for their peer review comments. Thanks to Dr Dierk Werner for his helpful replies to our queries and for the constant support and assistance of Anupa Shah, RGC for CEVG throughout the process.

REFERENCES

References to studies included in this review

Incandela 2002 {published data only}

Incandela L, Cesarone MR, Belcaro G, Steigerwalt R, De Sanctis MT, Nicolaides AN, et al. Treatment of vascular retinal disease with pentoxifylline: a controlled, randomized trial. *Angiology* 2002;**53**(Suppl 1):S31-4.

Werner 2004 {published data only}

Werner D, Michalk F, Harazny J, Hugo C, Daniel WG, Michelson G. Accelerated reperfusion of poorly perfused retinal areas in central retinal artery occlusion and branch retinal artery occlusion after a short treatment with enhanced external counterpulsation. *Retina* 2004;**24**(4):541-7.

References to studies excluded from this review

Arnold 2005 {published data only}

Arnold M, Koerner U, Remonda L, Nedeltchev K, Mattle HP, Schroth G, et al. Comparison of intra-arterial thrombolysis with conventional treatment in patients with acute central retinal artery occlusion. *Journal of Neurology, Neurosurgery & Psychiatry* 2005;**76**(2):196-9.

Atebara 1995 {published data only}

Atebara NH, Brown GC, Cater J. Efficacy of anterior chamber paracentesis and Carbogen in treating acute nonarteritic central retinal artery occlusion. *Ophthalmology* 1995;**102**(12):2029-34.

Augsburger 1980 {published data only}

Augsburger JJ, Magargal LE. Visual prognosis following treatment of acute central retinal artery obstruction. *British Journal of Ophthalmology* 1980;**64**(12):913-7.

Drago 1982 {published data only}

Drago F, Amico-Roxas M, Matera M. Effects of L-acetyl-carnitine on the electroretinographic responses in patients with central retinal artery occlusion. *Acta Therapeutica* 1982;**8**(3):201-8.

Gu 1999 {published data only}

Gu WZ, Pu RX, Wang YG, Zhou LX, Dong L, Liu H. Analysis on the curative effects of GEQI oral in treatment of retinal artery occlusion. *Aerospace Medicine* 1999;**10**(2):64-6.

Holschermann 2005 {published data only}

Holschermann H, Krombach C, Jung A, Jacobi F, Tillmanns H, Weinand F. Treatment of acute central retinal artery occlusion with the platelet glycoprotein IIb/IIIa receptor inhibitor tirofiban. *Thrombosis & Haemostasis* 2005;**94**(3):684-6.

Iwafune 1980 {published data only}

Iwafune Y, Yoshimoto H. Clinical use of pentoxifylline in haemorrhagic disorders of the retina. *Pharmatherapeutica* 1980;**2**(7):429-38.

Kattah 2002 {published data only}

Kattah JC, Wang DZ, Reddy C. Intravenous Recombinant Tissue-Type Plasminogen Activator Thrombolysis in Treatment of

Central Retinal Artery Occlusion. *Archives of Ophthalmology* 2002;**120**(9):1234-6.

Neubauer 2000 {published data only}

Neubauer AS, Mueller AJ, Schriever S, Gruterich M, Ulbig M, Kampik A. Minimally invasive therapy for clinically complete central retinal artery occlusion - results and meta-analysis of literature [Minimal invasive Therapie bei klinisch komplettem Zentralarterienverschluss - eigene Ergebnisse und Literaturvergleich]. *Klinische Monatsblätter für Augenheilkunde* 2000;**217**(1):30-6.

Pettersen 2005 {published data only}

Pettersen JA, Hill MD, Demchuk AM, Morrish W, Hudon ME, Hu W, et al. Intra-arterial thrombolysis for retinal artery occlusion: the Calgary experience. *Canadian Journal of Neurological Sciences* 2005;**32**(4):507-11.

Richard 1999 {published data only}

Richard G, Lerche RC, Knospe V, Zeumer H. Treatment of retinal arterial occlusion with local fibrinolysis using recombinant tissue plasminogen activator. *Ophthalmology* 1999;**106**(4):768-73.

Rumelt 1999 {published data only}

Rumelt S, Dorenboim Y, Rehany U. Aggressive systematic treatment for central retinal artery occlusion. *American Journal of Ophthalmology* 1999;**128**(6):733-8.

Schmidt 1992 {published data only}

Schmidt D, Schumacher M, Wakhloo AK. Microcatheter urokinase infusion in central retinal artery occlusion. *American Journal of Ophthalmology* 1992;**113**(4):429-34.

Schumacher 1993 {published data only}

Schumacher M, Schmidt D, Wakhloo AK. Intra-arterial fibrinolytic therapy in central retinal artery occlusion. *Neuroradiology* 1993;**35**(8):600-5.

Weber 1998 {published data only}

Weber J, Remonda L, Mattle HP, Koerner U, Baumgartner RW, Sturzenegger M, et al. Selective intra-arterial fibrinolysis of acute central retinal artery occlusion. *Stroke* 1998;**29**(10):2076-9.

Additional references

Arora 1999

Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, McKiernan T, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *Journal of the American College of Cardiology* 1999;**33**(7):1833-40.

Bath 2004

Bath PMW, Bath-Hextall FJ. Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke. *Cochrane Database*

of *Systematic Reviews* 2004, Issue 3. [Art. No.: CD000162. DOI: 10.1002/14651858.CD000162.pub2]

Beatty 2000

Beatty S, Au Eong KG. Local intra-arterial fibrinolysis for acute occlusion of the central retinal artery: a meta-analysis of the published data. *British Journal of Ophthalmology* 2000;**84**(8):914-6.

Brown 1994

Brown GC. Retinal arterial obstructive disease. In: Ryan SJ editor(s). *Retina*. 2nd Edition. Philadelphia: CV Mosby Co, 1994:1361-77.

Deutsch 1983

Deutsch TA, Read JS, Ernest JT, Goldstick TK. Effects of oxygen and carbon dioxide on the retinal vasculature in humans. *Archives of Ophthalmology* 1983;**101**(8):1278-80.

Feltgen 2006

Feltgen N, Neubauer A, Jurklics B, Schmoor C, Schmidt D, Wanke J, et al. Multicenter study of the European Assessment Group for Lysis in the Eye (EAGLE) for the treatment of central retinal artery occlusion: design issues and implications. EAGLE Study report no. 1 : EAGLE Study report no. 1. *Graefes Archive for Clinical and Experimental Ophthalmology* 2006;**244**(8):950-6.

Ffytche 1974

Ffytche TJ. A rationalization of treatment of central retinal artery occlusion. *Transactions of the Ophthalmological Societies of the United Kingdom* 1974;**94**(2):468-79.

Frampton 1995

Frampton JE, Brogden RN. Pentoxifylline (oxpentifylline). A review of its therapeutic efficacy in the management of peripheral vascular and cerebrovascular disorders. *Drugs Aging* 1995;**7**(6):480-503.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

Harino 1995

Harino S, Grunwald JE, Petrig BJ, Riva CE. Rebreathing into a bag increases human retinal macular blood velocity. *British Journal of Ophthalmology* 1995;**79**(4):380-3.

Harvey 2000

Harvey PA, Winder S, Talbot JF. Trabeculectomy for central retinal artery occlusion. *Eye* 2000;**14**(Pt 2):256-7.

Hausmann 1991

Hausmann N, Richard G. Effect of high dose steroid bolus on occlusion of ocular central artery: angiographic study. *BMJ* 1991;**303**(6815):1445-6.

Hayreh 1980

Hayreh SS, Kolder HE, Weingeist TA. Central retinal artery occlusion and retinal tolerance time. *Ophthalmology* 1980;**87**(1):75-8.

Higgins 2008

Higgins JPT, Altman DG (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 (updated February 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Kieswetter 1983

Kieswetter H, Korber N, Jung F, Reim M. Rheologic findings in patients with acute central retinal artery occlusion. *Graefes Archive for Clinical and Experimental Ophthalmology* 1983;**220**(2):92-5.

Manchanda 2007

Manchanda A, Soran O. Enhanced external counterpulsation and future directions: step beyond medical management for patients with angina and heart failure. *Journal of the American College of Cardiology* 2007;**50**(16):1523-31.

Pettersson 2006

Pettersson T, Bondesson S, Cojocaru D, Ohlsson O, Wackenfors A, Edvinsson L. One year follow-up of patients with refractory angina pectoris treated with enhanced external counterpulsation. *BMC Cardiovascular Disorders* 2006;**6**:28.

Rassam 1993

Rassam SM, Patel V, Kohner EM. The effect of acetazolamide on the retinal circulation. *Eye* 1993;**7**(Pt 5):697-702.

Sandercock 2003

Sandercock P, Gubitz G, Foley P, Counsell C. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: [10.1002/14651858.CD000029](https://doi.org/10.1002/14651858.CD000029)]

Schmetterer 1996

Schmetterer L, Lexer F, Findl O, Graselli U, Eichler HG, Wolzt M. The effect of inhalation of different mixtures of O₂ and CO₂ on ocular fundus pulsations. *Experimental Eye Research* 1996;**63**(4):351-5.

Wardlaw 2007

Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [Art. No.: CD000213. DOI: [10.1002/14651858.CD000213](https://doi.org/10.1002/14651858.CD000213)]

References to other published versions of this review

Fraser 2002

Fraser S, Siriwardena D. Interventions for acute non-arteritic central retinal artery occlusion. *Cochrane Database of Systematic Reviews* 2002, Issue 1. [DOI: [10.1002/14651858.CD001989](https://doi.org/10.1002/14651858.CD001989)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Incandela 2002

Methods	Method of allocation: unclear Masking: participant - yes, provider - yes, outcome - unclear Exclusions after randomisation: unclear Losses to follow-up: unclear Unusual study design: no
Participants	Country: Italy Number randomised: 10 Age: comparable Sex: comparable Inclusion criteria: sudden loss of vision associated with thrombosis of the retinal artery Exclusion criteria: previous coronary or vascular surgery, heart or renal failure, diabetes mellitus
Interventions	Treatment: pentoxifylline tablets 600 mg three times a day Control: placebo Duration: both for 4 weeks
Outcomes	Change in central retinal artery flow velocity. Self-reported clinical improvement measured on an analogue scale line (0 to 10)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	The method of sequence generation not clear from the paper and the authors have not been contactable
Allocation concealment?	Unclear risk	The method of treatment allocation is not clear from the paper and the authors have not been contactable
Blinding? Participants	Low risk	Placebo received by participants
Blinding? Outcome assessors	Unclear risk	Not clear if either those administering treatment or those measuring the effects were masked to patient status
Incomplete outcome data addressed? Visual acuity (primary outcome)	Unclear risk	Not discussed in paper
Free of selective reporting?	Unclear risk	Not clear from paper
Free of other bias?	Unclear risk	Not clear from paper

Werner 2004

Methods	Method of allocation: 'lots' drawn. No further detail of method for drawing the lots available
---------	--

Werner 2004 (Continued)

Masking: participant - no, provider - no
Exclusions after randomisation: unclear
Losses to follow-up: unclear
Unusual study design: no

Participants	Country: Germany Number randomised: 20 Age: comparable Sex: comparable Inclusion criteria: sudden loss of vision associated with thrombosis of a retinal artery (within 5 days) Exclusion criteria: contraindications to EECP, unable to measure retinal blood flow e.g. cataract
Interventions	Treatment: All patients given haemodilution. 10 patients also given EECP Control: no EECP - haemodilution only Duration: Haemodilution was for 4 days. EECP was for 2 hours
Outcomes	Retinal perfusion as measured by Doppler flowmetry Visual acuity

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'Lots' were drawn. Author contacted but no further details of method given
Allocation concealment?	Unclear risk	Not clear from paper. Author contacted but no further details of method given
Blinding? Participants	High risk	No, participants would be aware if they had received treatment
Blinding? Outcome assessors	High risk	Not clear from paper if those taking Doppler measurements were masked to patients status
Incomplete outcome data addressed? Visual acuity (primary outcome)	Low risk	Not clear from paper or author contact
Free of selective reporting?	Unclear risk	Not addressed in paper

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Arnold 2005	Retrospective case-control study. 37 patients were treated with intra-arterial urokinase within 6 hours of onset of symptoms, they were also given aspirin. 19 patients who also sustained a CRAO within 6 hours but did not have thrombolysis (for a variety of patient and non-patient reasons) were used as controls and were given aspirin or heparin. Some cases and some controls had lowering of their IOP by either paracentesis or intravenous Diamox® - the decision to give this was 'according to the preference of the treating ophthalmologist'

Study	Reason for exclusion
Atebara 1995	Comparison of paracentesis with carbogen (95% oxygen and 5% carbon dioxide). Retrospective, case-notes review
Augsburger 1980	32 patients with CRAO. Standard treatment of paracentesis, massage, carbogen, acetazolamide and aspirin. No control group
Drago 1982	Not a trial
Gu 1999	Not a trial
Holschermann 2005	Pilot non-controlled study. Used tirofiban (intravenous platelet inhibitor) in 18 consecutive patients
Iwafune 1980	Compared pentoxifylline with various 'conventional fibrinolytic agents'. Only 2 CRAO cases and 3 controls. Non-randomised, non-standardised treatment of controls
Kattah 2002	Case series of 12 patients with CRAO. Patients who presented with IOP of more than 12 mmHg had anterior chamber paracentesis initially. All were given intra-arterial rtPA. This was followed by heparin and then warfarin for 1 month. The latter was replaced with aspirin or clopidogrel after one month
Neubauer 2000	Retrospective uncontrolled review of a number of non-invasive treatments for CRAO
Pettersen 2005	Retrospective notes review of 8 cases. All given rtPA intra-arterially
Richard 1999	46 patients with CRAO underwent local intra-arterial fibrinolysis with rtPA. Retrospective study with no control group
Rumelt 1999	11 patients with CRAO were treated with an 'aggressive' systematic regimen until retinal circulation improved or treatment modalities were exhausted. The results were compared with 5 patients who were treated in an 'arbitrary non-systematic manner'. Thus there was no true control group and multiple interventions were compared
Schmidt 1992	14 consecutive patients with CRAO treated with urokinase via the ophthalmic artery. Confounded as patients were then heparinized for three days. Control group consisted of 41 consecutive patients but there is no mention of how these patients were chosen
Schumacher 1993	23 patients with CRAO underwent local intra-arterial fibrinolysis. No control group
Weber 1998	Retrospective and non-randomised. Ophthalmic artery urokinase given to 17 patients compared with 15 patients who did not receive fibrinolysis. In both groups some of the patients received other treatments such as paracentesis

CRAO: central retinal artery occlusion

IOP: intraocular pressure

rtPA: recombinant tissue plasminogen activator

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Retinal Artery

#2 MeSH descriptor Retinal Artery Occlusion

#3 retina* near arter*

#4 occlus* or obstruct* or clos* or stricture* or steno* or block* or embolism*

Interventions for acute non-arteritic central retinal artery occlusion (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

#5 (#3 AND #4)
#6 CRAO
#7 (#1 OR #2 OR #5 OR #6)

Appendix 2. MEDLINE search strategy

1 exp clinical trial/ [publication type]
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/
10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp retinal artery/
14 exp retinal artery occlusion/
15 (retina\$ adj3 arter\$).tw.
16 (occlus\$ or obstruct\$ or clos\$ or stricture\$ or steno\$ or block\$ or embolism\$).tw.
17 15 and 16
18 13 or 14 or 17
19 12 and 18

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville ([Glanville 2006](#)).

Appendix 3. EMBASE search strategy

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random\$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin\$ adj3 trial\$).tw.
14 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15 exp placebo/
16 placebo\$.tw.
17 random\$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control\$ or prospectiv\$ or volunteer\$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp retina artery/

34 exp retina artery occlusion/
35 (retina\$ adj3 arter\$).tw.
36 (occlus\$ or obstruct\$ or clos\$ or stricture\$ or steno\$ or block\$ or embolism\$).tw.
37 35 and 36
38 33 or 34 or 37
39 32 and 38

WHAT'S NEW

Date	Event	Description
5 November 2008	New citation required but conclusions have not changed	Issue 1 2009: Enhanced external counterpulsation (EECP) has been added as an intervention and 2 trials have been included.
23 October 2008	New search has been performed	Searches updated.
10 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Screening search results: SF, DS
Assessing trials according to inclusion criteria: SF, DS
Assessing quality of trials: SF, DS
Extracting data: SF, DS
Writing the text of the review: SF, DSF
Updating the review: SF, WA

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2008 update: The intervention enhanced external counterpulsation (EECP) was added to the inclusion criteria of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Counterpulsation [methods]; Hemodilution [methods]; Pentoxifylline [therapeutic use]; Randomized Controlled Trials as Topic; Retinal Artery Occlusion [*therapy]; Vasodilator Agents [therapeutic use]

MeSH check words

Humans