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Ciccone A, Canhão P, Falcão F, Ferro JM, Sterzi R

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[Intervention Review]

Thrombolysis for cerebral vein and dural sinus thrombosis

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ABSTRACT

Background

Treatment of cerebral sinus thrombosis with thrombolytics has been reported in cases with a deteriorating clinical course despite anticoagulant therapy. The rationale of this treatment is to promote rapid recanalisation of the occluded sinus.

Objectives

To review the available evidence on the efficacy and safety of thrombolysis in confirmed cerebral sinus thrombosis.

Search methods

We searched the Cochrane Stroke Group trials register (March 2003), the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 1, 2003), MEDLINE (1966 to March 2003), EMBASE (1980 to March 2003), and reference lists of all relevant publications.

Selection criteria

We aimed to analyse separately unconfounded randomised controlled trials comparing thrombolytic agent with placebo, or thrombolytic agent with antithrombotic therapy, or thrombolytic agent and antithrombotic with antithrombotic alone, in patients with dural sinus thrombosis (confirmed by MR venography, intra-arterial venography or CT venography).

Data collection and analysis

Two groups of reviewers independently applied the inclusion criteria.

Main results

No randomised controlled trials were found.

Authors' conclusions

There is currently no available evidence from randomised controlled trials regarding the efficacy or safety of thrombolytic therapy in dural sinus thrombosis. A randomised controlled trial is justified to test this therapy especially in patients predicted to have a poor prognosis.

PLAIN LANGUAGE SUMMARY

Thrombolysis for cerebral vein and dural sinus thrombosis

There is no good evidence on the effects of thrombolysis for cerebral vein thrombosis. Blood drains from the brain into the cerebral veins and then into the cerebral venous sinuses. If a clot forms in one of these blood vessels, it can cause headaches, seizures, loss of consciousness and other neurological symptoms. Clot dissolving treatments (thrombolytic therapy) could help to clear the clot and improve the patients' condition. However, thrombolytic therapy can cause serious or even fatal bleeding in the brain. The reviewers did not find any reliable evidence from randomised trials about the balance of risk and benefit from this treatment. Randomised controlled trials of this treatment are needed.

BACKGROUND

Cerebral vein and dural sinus thrombosis (CVDST) is an uncommon condition which, over the past decade, has been diagnosed more frequently due to greater awareness and the availability of non-invasive diagnostic techniques. CVDST has a wide spectrum of clinical presentation and outcome. Headache is the presenting symptom in 70% to 100% of cases, while seizures, focal deficits, impairment of consciousness, visual disturbances and papilledema occur in 33% to 75% of cases. It has a generally good prognosis but mortality varies between 5% and 30% in case series (Bousser 1985; Allroggen 2000).

Clinical heterogeneity, rarity of the disease, and the few clinical trials available contribute to uncertainty on the best therapeutic approach. Anticoagulant therapy is widely used and many authors consider it the first line therapy (Bousser 1999; Benamer 2000; De Bruijn 2001). The Cochrane review by Stam et al showed that anticoagulants appear to be safe and are associated with an apparent reduction in the risk of death or dependency although not reaching statistical significance (Stam 2003).

The rationale of anticoagulant therapy is to avoid thrombus extension, to favour spontaneous thrombus dissolution, and to prevent pulmonary embolism. However, despite anticoagulant therapy, some patients deteriorate. In these cases systemic or local thrombolysis via selective catheterisation of the occluded sinuses is considered (Bousser 1999; Benamer 2000).

The rationale of thrombolytic therapy is to obtain a rapid recanalisation of the vessels affected and therefore stop the clinical deterioration. Some case series report an excellent outcome (Di Rocco 1981; Higashida 1989; Persson 1990; Barnwell 1991; Smith 1994; Horowitz 1995; Kermode 1995; Aoki 1997; Holder 1997; Kim 1997; Rael 1997; Renowden 1997; Smith 1997; Frey 1999; Chow 2000) but the efficacy of general use of thrombolysis in CVDST is unknown. Brain haemorrhage is the most feared complication.

A systematic review of controlled clinical trials appears necessary to evaluate the potential efficacy and safety of thrombolysis in patients with CVDST either alone or after pre-treatment with anticoagulant.

OBJECTIVES

To conduct a systematic review of randomised controlled trials (RCTs) of thrombolysis in CVDST to evaluate whether:
(1) such treatments are significantly effective in increasing complete recovery;
(2) they are safe enough for general use.

Prior to starting the review, it seemed unlikely that there would be sufficient evidence to answer these questions reliably, but there might be enough to:
(1) indicate whether it might be worthwhile doing RCTs;
(2) guide trial protocols;
(3) pre-specify the hypotheses to be tested in any future trials.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to consider all apparently unconfounded RCTs of thrombolytic agent(s) in acute CVDST, recognised within 15 days of symptoms onset. The intent was to include quasi-randomised trials as well as strictly randomised trials and whether or not outcome was assessed blind to treatment allocation.

Types of participants

Patients over 18 years of age with definite CVDST, within 15 days of symptoms onset, were to be included. Trials including patients diagnosed by brain computerised tomography (CT) scan alone were not to be included.

We defined CVDST as a symptomatic clinical condition with the demonstration of vein/sinus thrombosis by MR venography, intra-arterial venography or CT venography.

The intent was to exclude cases of involvement of the cortical veins alone, without sinus thrombosis.

Types of interventions

We aimed to analyse separately the following comparisons:
(1) thrombolysis versus placebo or open control;
(2) thrombolysis versus full dose anticoagulation (unfractionated heparin or low-molecular weight heparin followed by oral anticoagulants);
(3) thrombolysis versus less intense anticoagulant (low-dose heparin, given subcutaneously);
(4) thrombolysis versus antiplatelet treatment;
(5) thrombolysis versus 'standard therapy' (i.e. a potentially confounded therapy).

Any clot dissolving (thrombolytic) agents, regardless of duration, dosage and route of administration - either via selective catheterisation of the occluded sinus or by peripheral intravenous injection or combined - were accepted for the treatment group. The intent was to consider, in separate analyses, thrombolysis after pre-treatment or concomitant treatment with anticoagulants or alone and whether or not long-term anticoagulant treatment was used (see 'Methods of the review' section for the analyses foreseen to avoid the possible confounding effect of an interaction between thrombolytic agents and anticoagulants).

Types of outcome measures

(1) The number of patients who recovered completely (modified Rankin Scale 0 or 1) at the end of the scheduled follow up.
(2) Death from any cause at the end of the follow up.
(3) The number of patients with symptomatic fatal or non-fatal intracranial haemorrhage (any new intracranial haemorrhage or haemorrhagic transformation of a cerebral infarct that developed after randomisation, that is documented by CT or MR scanning, or at autopsy, and that caused clinically manifest deterioration of the neurological condition);
(4) The number of patients with any major extracranial haemorrhage (any bleeding that requires transfusion or significant surgical intervention, or that causes permanent disabling deficit; e.g. intra-ocular bleeding causing blindness).

We also aimed to extract any available information about safety in both the thrombolytic and control groups.

Search methods for identification of studies

See: 'Specialized register' section in Cochrane Stroke Group

Relevant trials were identified in the Cochrane Stroke Group trials register, which was last searched by the Review Group Co-ordinator in March 2003. In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1, 2003) (Appendix 1), MEDLINE (1966 to March 2003) (Appendix 1) and EMBASE (1980 to March 2003) (Appendix 2). The reference lists of all relevant studies found were screened to identify further trials.

Titles identified by the searching were inspected by AC. Abstracts of references with titles of interest were examined to determine relevance. When relevance was not clear from the abstract, or when no abstract was available, a copy of the article was obtained.

All the reviewers are involved in the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT 2003), a large multinational observational ongoing study on CVDST. Through this network they are in contact with those interested in CVDST and could potentially plan or participate in a RCT in Europe, Australia, and North, Central and South America.

Data collection and analysis

Two groups of reviewers (the Portuguese group: PC, FF and JMF; and the Italian group: AC and RS) independently selected trials for inclusion in the review from all the potential studies identified. If the trials selected by the two groups of reviewers were different, differences were resolved by discussion among all reviewers.

For each included trial the two groups of reviewers extracted information about the method of randomisation, blinding of outcome evaluators and whether all the randomised patients were accounted for in the analysis. The authors of the trials were to be contacted if the above information was not available in the published reports. This information was to be used to evaluate quality. The five reviewers were to assess the quality of the trials independently. Concealment of randomisation, blinding in outcome evaluation and intention to treat analysis were to be evaluated and graded as present (+), absent (-) or unclear (0). The interobserver agreement in the overall quality score was to be summarised using the weighted kappa statistic.

Complete recovery was selected as first outcome measure, because it is clinically relevant for patients with CVDST who have, in general, a good prognosis.

Concerning the analysis on safety, the intent was to consider only symptomatic intracranial haemorrhages, with clinical deterioration or death, and major extracranial haemorrhages requiring medical interventions or causing permanent deficiency.

To avoid the possible confounding effect of an interaction between thrombolytic agents and anticoagulants, we planned to perform analyses with and without inclusion of trials in which patients allocated to thrombolysis were also treated with anticoagulants. If the difference in the expected risks and benefits of the two modalities of treatment is more than could be attributed to chance, then the results of the two procedures should not be combined. To explore this, we aimed to test for heterogeneity using a standard chi-square test.

A weighted estimate of the treatment effects across trials (odds ratio (OR), absolute risk reduction) was to be calculated using a fixed-effect model. For interpreting the results, 95% confidence intervals (CI) will be used.

The intent was to do subgroup analyses using statistical tests for interaction for the subgroups according to site of thrombosis, age group, presence of deficits, level of consciousness and presence of haemorrhagic lesions previous to the treatment, but only if the overall results were statistically significant.

RESULTS

Description of studies

No published, ongoing or planned RCTs were identified. We found only one study of local urokinase versus systemic heparin for superior sagittal sinus thrombosis (Wasay 2001) but this was excluded from the analysis because it was non-randomised and retrospective.

Risk of bias in included studies

No studies were available for inclusion in a meta-analysis.

Effects of interventions

The results of the electronic searches were as follows.

Only additional articles found are counted (for example: the EMBASE search yielded 1091 articles not found in MEDLINE).

MEDLINE: 661 references
EMBASE: 1091 references
Cochrane Central Register of Controlled Trials: 14
Cochrane Stroke Group trials register: 0

No RCTs were found.

DISCUSSION

We searched extensively for RCTs but found none.

Three of the authors (PC, FF and JMF) recently published a systematic review of cases with CVDST treated with thrombolytics (Canhão 2003). Seventy-two publications (169 patients), found through a search from 1966 to July 2001, were analysed; thrombolytic therapy appeared to be reasonably safe but its efficacy could not be assessed as no RCTs were identified. Since then at least 15 further reports of more than 40 cases with CVDST treated with thrombolytics have been published (Del Rio 2001; Ra 2001; Wasay 2001; Chaves 2002; De Asis 2002; Funabiki 2002; Huh 2002; Kao 2002; Ming 2002; Perez-Duenas 2002; Strzyzewska 2002; Tarani 2002; Yang 2002; Soleau 2003). These articles indicate that the use of thrombolysis for CVDST is growing and, in some centres, thrombolysis is even an alternative to anticoagulant therapy in the acute phase (Wasay 2001). A RCT on thrombolytic therapy for CVDST is, therefore, ethically justifiable and urgently needed: it is more appropriate to include patients in a RCT than treating them with a therapy whose risks and benefits are still unknown.

One of the issues in designing a RCT would be how to treat the control group. A placebo-controlled study might not be approved, as in many countries anticoagulation is considered an acceptable routine treatment for CVDST, and the Cochrane review by Stam et al also suggested that anticoagulants might be beneficial (Stam 2003). Thrombolysis versus anticoagulants could be a more appropriate comparison even if it might show that thrombolysis is better than anticoagulation but not whether it is better than placebo or no treatment. On the other hand, the comparison of thrombolysis plus anticoagulant versus anticoagulant alone could be confounded by the interaction of anticoagulants and thrombolytics, which would make the interpretation of the study results difficult. Since in most cases the course is benign, some workers advocate thrombolysis only for those who deteriorate despite anticoagulants and indicate anticoagulants as a safer treatment for the others (Bousser 1999; Benamer 2000) but there are no data to argue that anticoagulation is safer than thrombolysis for CVDST or vice versa. A pragmatic RCT allowing randomisation of patients in all cases of therapeutic uncertainty, for instance those cases identified at high risk of poor prognosis in large cohorts of CVDST patients (Crassard 2003; Ferro 2003), would be probably the best solution to this issue. Another important point would be whether to test local or systemic thrombolysis. Also in this case there are no data to indicate which route of administration is better; although the systemic route is more feasible, available and less invasive, the literature is dominated by cases treated with local thrombolysis (Canhão 2003). As there is greater experience of the local route of administration, this one may be selected for being tested in a RCT.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence does not support the routine use of thrombolysis for patients with cerebral vein and dural sinus thrombosis.

Implications for research

The question of whether thrombolysis does more good than harm will be answered if this therapy is tested in the context of a RCT which is urgently needed. We discourage further publication of case series or single case reports on thrombolysis for CVDST, as they are unlikely to add more to our knowledge about the effect of this therapy.

ACKNOWLEDGEMENTS

We are very grateful to Professor Peter Sandercock for advice during the preparation of the review, to Mrs Hazel Fraser and Mrs Brenda Thomas for help in planning the literature search and finding papers, and to all the Cochrane Stroke Group for its continuous endeavour in supporting reviewers.

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Smith 1997

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Stam 2003

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Wasay 2001	Non-randomised retrospective comparison of local urokinase (20 cases) versus systemic heparin (20 cases) for superior sagittal sinus thrombosis

APPENDICES

Appendix 1. MEDLINE/CENTRAL search strategy

MEDLINE (Ovid)

1. "intracranial embolism and thrombosis"/
2. intracranial thrombosis/
3. exp sinus thrombosis, intracranial/
4. intracranial embolism/
5. cerebral veins/ or cavernous sinus/ or cranial sinuses/ or exp dura mater/
6. venous thrombosis/ or thrombosis/ or thromboembolism/
7. 5 and 6
8. ((cerebral vein or cerebral venous or sinus) adj5 thrombo$).tw.
9. (CVDST or CVT).tw.
10. 1 or 2 or 3 or 4 or 7 or 8 or 9
11. Thrombolytic therapy/
12. Fibrinolysis/
13. exp plasminogen activators/
14. Fibrinolytic agents/ or Plasmin/ or Plasminogen/
15. (thromboly$ or fibrinoly$ or clot lysis).tw.
16. (plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA).tw.
17. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or alteplase or tenecteplase or TNK).tw.
18. or/11-17
19. 10 and 18
20. limit 19 to human

Appendix 2. EMBASE search strategy

EMBASE (Ovid)

1. exp cerebral sinus thrombosis/
2. exp occlusive cerebrovascular disease/
3. brain embolism/
4. brain vein/ or cavernous sinus/ or dura mater/ or cranial sinus/
5. vein thrombosis/ or thrombosis/ or thromboembolism/
6. 4 and 5
7. ((cerebral vein or cerebral venous or sinus) adj5 thrombo$).tw.
8. (CVDST or CVT).tw.
9. 1 or 2 or 3 or 6 or 7 or 8
10. fibrinolytic therapy/
11. fibrinolysis/
12. blood clot lysis/
13. fibrinolytic agent/
14. plasmin/ or plasminogen/ or exp plasminogen activator/
15. exp thromboembolism/dt
16. recanalization/ or recanali#ation.tw.
17. (thromboly$ or fibrinoly$ or clot lysis).tw.
18. (plasminogen or plasmin or tpa or t-pa or rtpa or rt-pa).tw.
19. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or alteplase or tenecteplase or TNK).tw.
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 9 and 20
22. limit 21 to human

WHAT'S NEW

Date	Event	Description
8 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All reviewers contributed to the conception and design of this review. Dr Ciccone wrote the first draft of the review which was then checked, commented on and discussed by all other reviewers. All authors contributed to the final version of this review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cerebral Veins; *Cranial Sinuses; *Thrombolytic Therapy; Sinus Thrombosis, Intracranial [*drug therapy]; Venous Thrombosis [*drug therapy]

MeSH check words

Humans