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Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis (Review)

Coward L, Featherstone R, Brown MM

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TABLE OF CONTENTS

[Intervention Review]

Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis

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ABSTRACT

Background

Surgery for vertebral artery stenosis is technically difficult, potentially hazardous and is not considered in most centres. There is growing evidence from case series that vertebral artery stenosis may be treated endovascularly by percutaneous transluminal angioplasty and stenting. This may be a feasible alternative to surgery to relieve symptoms caused by significant stenosis.

Objectives

To assess the safety and efficacy of vertebral artery percutaneous transluminal angioplasty, with or without stenting, combined with medical care, compared to medical care alone, in patients with vertebral artery stenosis.

Search methods

We searched the Cochrane Stroke Group's trials register (last searched 28 July 2004), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 3, 2002), MEDLINE (1966 to July 2004), EMBASE (1980 to July 2004), and Science Citation Index (1981 to July 2004). We contacted researchers in the field, and balloon catheter and stent manufacturers.

Selection criteria

Randomised trials of endovascular treatment of vertebral artery stenosis combined with best medical therapy, compared with best medical therapy alone, in patients with symptomatic or asymptomatic vertebral artery stenosis.

Data collection and analysis

Two review authors independently applied the inclusion criteria, extracted data and assessed trial quality.

Main results

One completed randomised trial was found. In one subgroup of this trial, 16 patients with symptomatic severe vertebral artery stenosis were randomised to endovascular treatment (eight patients) or medical treatment alone (eight patients). There were no strokes in any arterial territory or deaths from any cause in either group within 30 days of treatment (endovascular group) or 30 days of randomisation (medical group). In the endovascular group, two patients had a posterior circulation transient ischaemic attack at the time of the procedure. In the endovascular group, the mean vessel stenosis at follow up was 47% (range 0% to 80%). Patients were followed up for a mean of 4.5 years in the endovascular group and 4.9 years in the medical group. There were no further vertebrobasilar territory strokes in either group for the duration of follow up. Morbidity and mortality was related to carotid and coronary artery disease in this study.

Authors' conclusions

There is currently insufficient evidence to assess the effects of percutaneous transluminal angioplasty with or without stenting or primary stenting for vertebral artery stenosis.

PLAIN LANGUAGE SUMMARY

Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis

Currently there is insufficient evidence to support the use of endovascular treatment for vertebral artery stenosis in routine clinical practice. The vertebral arteries supply blood to the back of the brain and if narrowing (stenosis) of the artery occurs there is a risk of causing stroke. Because of difficulty accessing the vertebral artery, standard treatment has been conservative in most centres. The narrowing can also be treated by percutaneous transluminal balloon angioplasty. This involves passing a fine tube (catheter) through the skin (percutaneously) in to the arterial system. The catheter has a small balloon at its tip. The catheter is moved through the arterial system until the balloon reaches the point of arterial narrowing in the vertebral artery. The balloon is briefly inflated which stretches the artery (angioplasty) to reduce the degree of narrowing. Sometimes a device known as a stent is then placed inside the artery to prevent it narrowing again after the angioplasty. Angioplasty and stenting are called endovascular treatment. This review found results from one arm of a trial only involving a very small number of patients. The results suggest that endovascular treatment can be carried out with a high degree of technical success at the time of treatment but there is insufficient evidence to determine whether the risk benefit ratio favours endovascular intervention over conservative management. Randomised trials need to be designed to determine whether the endovascular treatment is more successful than conservative treatment at reducing the long term risk of stroke or death.

BACKGROUND

About 25% of ischaemic strokes occur in the vertebrobasilar territory (Bamford 1991; Bogousslavsky 1988). Much less is known about the natural history of vertebrobasilar stenosis compared with carotid artery stenosis. The European Carotid Surgery Trial included over 3000 patients with any degree of symptomatic carotid stenosis of 70% or more randomised to surgery or medical treatment alone (ECST 1998). Around the same time, the North American Symptomatic Carotid Endarterectomy Trial randomised over 2800 patients with 30% or more stenosis with symptoms in the prior 3 months to surgery or medical treatment alone (NASCET 1998). Data from these two trials have recently been combined together with the results of the much smaller VA trial (VA 1991) to provide a robust data set (Rothwell 2003). Analysis of the data found that surgery was detrimental in patients with less than 30% stenosis, had no effect in those with 30% to 49% stenosis, was of marginal benefit in patients with 50% to 69% stenosis (n = 1549, relative risk (RR) of 5-year ipsilateral ischaemic stroke = 0.75, 95% confidence interval (CI) 0.56 to 0.94) and was highly beneficial in those with 70% or more without near occlusion (n = 1095, RR 0.39, 95% CI 0.28 to 0.51). More recently, the Asymptomatic Carotid Surgery Trial also reported a benefit to carotid endarterectomy. In asymptomatic patients less than 75 years of age with carotid stenosis greater than 70%, immediate surgery halved the net 5-year stroke risk from about 12% to about 6% (including a 3% perioperative stroke or death risk) (ACST 2004). In contrast, data on the prognosis of vertebrobasilar transient ischaemic attack and minor stroke from a recent systematic review, found that patients with vertebrobasilar events have a lower risk of subsequent stroke or death, after the acute phase is over, compared with patients presenting with carotid territory symptoms (Flossmann 2003). In contrast, patients presenting with vertebrobasilar events in the acute phase (up to seven days after presenting symptoms) had a higher relative risk of subsequent stroke compared to patients with symptomatic carotid disease.

Vertebral artery stenosis may occur either extra- or intracranially but is often localised to the origin of the vessel as it arises from the subclavian artery. Surgery to this region of the vertebral artery is technically difficult due to poor access to the vessel origin, hence surgery is not considered in most centres. Surgery may involve vertebral endarterectomy (technically very difficult) or more often vessel reconstruction which involves transposition of the vertebral artery, usually to the common or internal carotid artery. A retrospective review of 369 consecutive extracranial vertebral artery reconstructions found low complication rates of the procedure (procedural stroke or death rate 5.1% in the 215 patients treated prior to 1991, and 1.9% in the 154 patients treated since 1991) and good long term patency rates (92% patent at 10 years follow up) (Berger 2000). Despite this, medical treatment alone has been the standard treatment for posterior circulation stroke. To date, there have been no randomised trials of the use of different antiplatelet or anticoagulant drugs in cases of vertebral artery stenosis (Cloud 2003). Growing literature from case series suggest that endovascular intervention at this site is safe and effective. There is less information available regarding percutaneous transluminal angioplasty (PTA) and stenting for intracranial vertebral artery stenosis but reports suggest that it may also be a feasible alternative to best medical treatment as there is no surgical option for these lesions (Alazzaz 2000; Gomez 2001)

Some evidence for the efficacy of endovascular intervention for vertebrobasilar stenosis is available from non-randomised case studies. We searched the literature for papers in English which reported at least three cases of endovascular intervention for vertebrobasilar stenosis. We identified reports on 313 endovascular treatments of vertebral artery stenosis and 18 of endovascular treatment of basilar artery stenosis. Of these, 173 employed primary stenting. In these studies, there was a 30 day major stroke or death rate of 3.2% and a rate of 3.2% for TIA and non-disabling stroke (Barakate 2001; Chastain 1999; Chiras 2002; Cloud 2003b; Crawley 1998; Hauth 2004; Higashida 1993; Janssens 2004; Jenkins 2001; Kachel 1991; Levy 2002; Malek 1999; Mathias 1987; Motarjeme 1982; Mukherjee 2001; Nasher 2000; Piotin 2000; Qureshi 2000; Rasmussen 2000; Sampei 1995). Most recently, a series of stent placements in 61 vertebral or intracranial arteries was reported (SSYLVIA 2004). The series included 17 basilar and 23 vertebral arteries and a technical success rate for stenting of 95% was achieved. The 30 day post procedural stroke rate was reported to be 6.6% but it is not clear how many, if any, of these strokes occurred in the vertebrobasilar territory. In addition, the risk of stroke between 30 days and 1 year was 7.3%. However, the mean time between qualifying event and procedure was 72.8 days (median 28.5, range 1 to 959 days) with the vast majority of participants being recruited after the "acute phase". This could have led to an overestimation of the efficacy of endovascular intervention for vertebrobasilar disease, since the risk of subsequent stroke in patients more than seven days after the initial vertebrobasilar territory event is relatively low when treated medically.

We aim to systematically review all randomised controlled trials comparing vertebral artery angioplasty and stenting and medical care with medical care alone.

OBJECTIVES

(1) To determine whether endovascular treatment of vertebral artery stenosis might be an effective and safe alternative to medical care.
(2) To determine the restenosis rate after vertebral artery percutaneous transluminal angioplasty or stenting and whether restenosis leads to recurrent stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We tried to identify all unconfounded truly randomised controlled trials comparing endovascular treatment (PTA and/or stenting) with best medical care.

Types of participants

Trials including patients of any age or sex with symptomatic or asymptomatic vertebral artery stenosis were considered eligible for inclusion in the review.

Types of interventions

Trials allowing any acceptable endovascular technique for treatment of vertebral artery stenosis (for example use of simple balloon catheter or primary stenting) as well as trials which specified which technique was used were reviewed.

Types of outcome measures

We planned to analyse outcomes with an intention-to-treat approach, extracting from each trial the number of patients originally allocated to each treatment group and the outcome of all patients randomised. We then considered:

The primary outcome measure

Periprocedure stroke or death within 30 days of procedure (or within 30 days of randomisation for patients treated medically). Strokes were classified, if possible, as:
(1) disabling stroke;
(2) non-disabling stroke, i.e. not requiring help with activities of daily living at one month after onset.

The secondary outcome measures

(1) Subsequent vertebrobasilar territory stroke including primary intracerebral haemorrhage or cerebral infarction:
(a) disabling;
(b) non-disabling.

(2) Subsequent stroke in any arterial territory including primary intracerebral haemorrhage or cerebral infarction:
(a) disabling;
(b) non-disabling.

(3) Other complications of the procedure, classified as:
(a) major, requiring additional therapy or prolonged admission;
(b) minor.

(4) Restenosis rate resulting in a recurrent vertebral artery stenosis equivalent to greater than 50% by NASCET method determined by Doppler, catheter angiography or magnetic resonance angiography performed at defined intervals. Restenoses were classified as:
(a) symptomatic;
(b) asymptomatic.

Search methods for identification of studies

See: 'Specialized register' section in Cochrane Stroke Group

We searched the Cochrane Stroke Group's trials register, which was last searched by the Review Group Co-ordinator in July 2004. The Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 3, 2002), was also searched for all possibly relevant trials. In addition, all publications describing relevant trials were sought through EMBASE (1980 to July 2004) (database provider Ovid) (Appendix 1). The EMBASE search strategy was modified for use with MEDLINE (1966 to July 2004) and Science Citation Index (1981 to July 2004).

Ongoing trials were sought by personal contact with individuals active in the field. Informal enquiries were made with balloon catheter and stent manufacturers.

Data collection and analysis

Published and unpublished trials were identified and assessed, and two reviewers (LC and RF) independently selected trials for inclusion. Data were identified in published material and additional information sought from the principal investigators of included trials.

We planned to extract the following data.

(1) The method of randomisation and whether the randomising doctor was blinded to the treatment allocated.
(2) The number of patients originally allocated to each treatment group to allow intention to treat analysis.
(3) The method of measuring outcome and whether outcome assessment was independent and/or blinded.
(4) The number of exclusions and losses to follow up.
(5) Intervention characteristics.
(6) Outcome measures as defined above.

We also intended to extract the following data to allow a number of subgroup analyses.
(1) The proportion of symptomatic versus asymptomatic patients in each treatment group.
(2) The location of vertebral artery stenosis (extracranial versus intracranial and proximal versus distal).

We intended to test for heterogeneity between trial results using a standard Chi-squared test and to report results as odds ratios (i.e. the odds of an unfavourable outcome among patients treated by endovascular intervention compared to the corresponding odds amongst patients treated medically) calculated using the Peto fixed-effect method.

RESULTS

Description of studies

To date we have identified one completed randomised controlled trial comparing endovascular treatment of vertebral artery stenosis with medical care, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS 2001). The main analysis from this trial from 504 patients with carotid artery stenosis randomised to endovascular or surgical treatment was published in 2001. A separate subgroup of the trial randomised 16 patients with symptomatic vertebral artery stenosis to receive endovascular treatment and best medical care or best medical care alone. The data from this subgroup of the trial have not yet been published but were presented at the 2003 European Stroke Conference (Coward 2003).

To our knowledge, there are no ongoing randomised trials involving patients with vertebral artery stenosis.

Risk of bias in included studies

Due to study design and the nature of the intervention, health workers, patients and assessors were not blinded to treatment or outcome.

Centre and patient requirements

CAVATAS is an international, multicentre trial in which long term follow up (more than five years) is ongoing. Each centre had to have a neurologist or physician interested in vascular disease to follow up patients and either a vascular radiologist with angioplasty experience or an interventional neuroradiologist to perform vertebral angioplasty and stenting. Six centres contributed patients with symptomatic vertebral artery stenosis suitable for endovascular treatment who were randomised between endovascular treatment and medical care and medical care alone. All endovascular techniques were allowed (e.g. balloon angioplasty with or without cerebral protection devices or stenting).

Randomisation method

Patients were randomly assigned treatment by telephone call or fax to the randomisation centre at the Clinical Trial Service Unit in Oxford, UK, allocation concealment was judged to be adequate. Patients were randomly assigned by computer with a minimisation algorithm, taking account of centre and timing of symptoms. Sixteen patients were enrolled in this subgroup of CAVATAS, eight patients were allocated to each treatment group.

Follow up

Patients were followed up 1 month after treatment and then again at 6 months, 12 months, and yearly following randomisation by the independent participating neurologist or clinician who was not directly involved in treatment. The mean duration of follow up was 4.5 years in the endovascular group and 4.9 years in the medical group.

Assessment of functional outcome

Stroke outcome events were classified as fatal if death occurred as a direct result of stroke at any time after the event, or as disabling if survivors required help from another person as a result of stroke to undertake everyday activities for more than 30 days after the onset of symptoms (equivalent to modified Rankin grade three or worse). The remainder of stroke outcome events were classified as non-disabling if symptoms lasted more than seven days or minor if symptoms lasted less than seven days. Transient ischaemic attack (TIA) was also reported.

Analysis of data

Analysis was by intention to treat. All patients received their allocated treatment.

Effects of interventions

Sixteen patients were randomised in the vertebral artery stenosis subgroup of CAVATAS. Eight patients were randomised to endovascular treatment and medical care and eight to medical care alone. The two groups were matched in terms of age, gender and baseline vascular risk factors (Coward 2003).

All 16 patients had symptoms attributable to their vertebral artery stenosis, with 15 of 16 patients (94%) having symptoms within the six months prior to randomisation. Four patients from the endovascular group and five from the medical group presented with at least one vertebrobasilar transient ischaemic attack, and four patients from the endovascular and three from the medical group had a vertebrobasilar territory stroke prior to study entry. The mean time between symptom onset and randomisation was 92 days (range 5 to 376). The mean time to treatment following randomisation was 45 days (range 7 to 148 days) (Coward 2004).

All patients had severe vertebral artery stenosis (greater than 50%) with a mean baseline stenosis of 75.0% (standard deviation (SD) 12.1) in the endovascular and 76.1% (SD 14.3) in the medical groups as determined by catheter angiography. In one patient in the medical group, the randomised stenosis affected the distal intracranial portion of the vertebral artery; in the remaining 15 patients the stenosis was at the origin of the vessel.

CAVATAS began randomising in 1992 before stents were available and consequently six patients allocated endovascular treatment received simple balloon angioplasty as their initial treatment, with the last two randomised receiving PTA and stenting.

With regards the primary outcome measure, there were no strokes in any arterial territory or deaths from any cause in either group within 30 days of treatment (endovascular group) or 30 days of randomisation (medical group). In the endovascular group, two patients had a posterior circulation TIA at the time of the procedure. These were classified as minor complications of the procedure as they did not require additional treatment or prolong admission. Endovascular treatment was technically successful in all eight treated patients at the first attempt. The mean vessel stenosis was significantly reduced from 75% (+/-12.1) at baseline to a mean of 26% (+/- 24.6) immediately following angioplasty or stenting (P = 0.003; paired t test).

Follow up imaging was performed in seven out of eight patients in the endovascular group. The mean vessel stenosis at follow up was 47% (range 0 to 80%). Of the six patients treated with simple balloon angioplasty, three had restenosis (greater than 50% by NASCET criteria) on follow up imaging.

Patients were followed up for a mean of 4.5 years in the endovascular group and 4.9 years in the medical group. The length of follow up in the 15 patients who survived more than 6 months after randomisation ranged from 2.8 to 8.2 years. There were no further vertebrobasilar territory strokes in either group for the duration of follow up. Two patients from each treatment group had at least one further vertebrobasilar TIA. One patient in each group died following a carotid territory stroke and two from each group died as a consequence of ischaemic heart disease.

The combined annual rate of carotid territory stroke or death was 11% in the endovascular group and 8% in the medically treated group (P = 0.85 based on hazard ratios from Cox regression).

DISCUSSION

To date there are too little data to draw any reliable conclusions on the preferred therapy for vertebral artery stenosis. Hence there is a need for further randomised trials.

Published case series suggest that endovascular treatment of vertebral artery stenosis is safe and effective, although selection bias with regard to patients (symptomatic or not), location of lesion (origin or distal vertebral artery), severity of stenosis, and time from initial event to treatment may reduce apparent complication rates. Only one completed randomised study comparing endovascular treatment of vertebral artery stenosis with medical treatment has been identified. The data benefit from being from a randomised trial although the number of patients enrolled was very small.

The results from this subgroup of CAVATAS suggest that endovascular treatment of vertebral artery stenosis achieves a good technical result at the time of the procedure and may be safe, although two out of eight patients had a vertebrobasilar TIA at the time of treatment. The potential benefits of endovascular intervention could not be assessed from these data. The prognosis of vertebral artery stenosis treated medically in terms of recurrent same territory stroke may be benign compared with recently symptomatic carotid artery stenosis which carries a risk of recurrent ipsilateral stroke of 20.6% over three years (ECST 1998). However, all patients in this subgroup of CAVATAS were treated after

the acute phase avoiding the early period after symptoms when the risk of recurrence may have been much higher. It is possible that a benefit to endovascular treatment in reducing recurrent stroke might have been demonstrated if patients had been recruited and treated within seven days of their initial event.

There was a high rate of restenosis in the group that received endovascular intervention but this did not seem to be associated with an increased risk of recurrent stroke. However, it is not possible to determine from this study whether restenosis following treatment is clinically important due to the very small number of patients with restenosis (N = 3).

Carotid and coronary vascular disease were the main causes of morbidity and mortality in this study. Patients with vertebral artery stenosis should therefore be investigated thoroughly for the presence of carotid and coronary disease.

Technically, endovascular treatment of vertebral artery stenosis looks promising, however whether it is of any benefit to patients remains unknown.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence to support the routine use of PTA and stenting for vertebral artery stenosis. Endovascular treatment of vertebral artery stenosis should only be performed within the context of randomised controlled trials.

Implications for research

Little is known about the natural history of vertebral artery stenosis and what constitutes best medical treatment. Future trials should concentrate on comparing different medical treatments such as antiplatelet and anticoagulant drugs as well as comparing endovascular intervention with medical treatment.

ACKNOWLEDGEMENTS

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If anyone is aware of completed or ongoing trials of vertebral angioplasty and stenting, please contact Professor Brown at the above address.

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CHARACTERISTICS OF STUDIES

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

CAVATAS 2001

Methods	Multicentre, central telephone randomisation, follow up at 1, 6, 12 months then annually by independent neurologist, intention-to-treat analysis.
Participants	Patients of any age with symptomatic or asymptomatic vertebral artery stenosis formed a small subset of the CAVATAS trial which also included over 550 patients with carotid artery stenosis. Patients who

CAVATAS 2001 *(Continued)*

	were unable to give informed consent or were unwilling to undergo the procedure or who had a disabling stroke with no useful recovery of function within the region supplied by the treatable artery were excluded.
Interventions	Patients were assigned to endovascular treatment or medical care. Patients in the endovascular group given minimum 150 mg aspirin daily for at least 24 hours prior to the procedure. Heparin was given at the time of procedure and for 24 hours after.
Outcomes	The primary outcome was specified as disabling stroke or death within 30 days of treatment or for the duration of follow up. The secondary outcome measures were same territory stroke lasting more than 7 days and death or ipsilateral disabling stroke within 30 days of treatment and for the duration of follow up.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

APPENDICES

Appendix 1. EMBASE search strategy

001 vertebral artery
002 vertebrobasilar
003 1 or 2
004 endovascular
005 stent
006 angioplasty
007 4 or 5 or 6
008 stroke
009 cerebrovascular disease
010 8 or 9
011 3 and 7 and 10

WHAT'S NEW

Date	Event	Description
22 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 1997
Review first published: Issue 4, 1997

Date	Event	Description
1 December 2004	New search has been performed	For the 2004 update of this review; one trial cited in the previous version as ongoing has been included (CAVATAS 2001). There are

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		currently no other completed or ongoing randomised trials of vertebral artery stenting. Sixteen patients with vertebral artery stenosis were included in this arm of CAVATAS. The methodological quality, results and discussion sections have been substantially revised to incorporate the data from the included trial. Minor changes have been made to the objectives of the review to reflect improving knowledge since the last version. The conclusion of the review is that there is currently insufficient evidence to support the routine use of endovascular treatment of vertebral artery stenosis and it should only be performed within the context of randomised controlled trials.

CONTRIBUTIONS OF AUTHORS

All reviewers contributed to the collection and interpretation of data.
LC and RF drafted the review.
MMB contributed to the critical revision of the review and gave final approval of the version to be published.

DECLARATIONS OF INTEREST

The authors were involved with one trial (CAVATAS 2001) cited in this review. Sanofi-Synthelabo have no commercial interest in the findings of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- European Commission, Belgium.
- Sanofi-Synthelabo, UK.
- Reta Lila Weston Trust for Medical Research, UK.
- The Stroke Association, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Stents; Angioplasty, Balloon [*methods]; Randomized Controlled Trials as Topic; Vertebrobasilar Insufficiency [*therapy]

MeSH check words

Humans