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[Intervention Review]

Prostacyclin and analogues for acute ischaemic stroke

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ABSTRACT

Background

Prostacyclin is an agent with a number of effects on platelets, blood vessels and nerve cells which might improve outcome after acute ischaemic stroke.

Objectives

To assess the effect of prostacyclin or analogues on survival in people with acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched November 2003). For the first version, we also searched EMBASE (1980 to 1999), MEDLINE (1966 to 1999), Science Citation Index (1981 to 1999) and the Ottawa Stroke Trials Registry. We also contacted the manufacturers of prostacyclin and the principal investigators of the identified trials.

Selection criteria

Randomised trials comparing prostacyclin or analogues with placebo or control. Trials where people were entered within one week of stroke onset were included.

Data collection and analysis

Information on the methods of randomisation, blinding, analysis, the number of patients randomised, dose and timing of prostacyclin or analogue, patient withdrawals, the number of deaths occurring in each trial, and trial quality, were collected and assessed.

Main results

Five trials involving 191 people were included. Six early deaths (within four weeks) occurred with prostacyclin, and nine with placebo (odds ratio (OR) 0.63, 95% confidence interval (CI) 0.22 to 1.85). One trial of 32 patients reported late deaths (by 10 to 18 months) in 50% of patients in each group.

Authors' conclusions

Too few patients have been studied in randomised trials to allow conclusions to be drawn about the effect of prostacyclin treatment on survival of people with acute stroke.

PLAIN LANGUAGE SUMMARY

Prostacyclin and analogues for acute ischaemic stroke

Prostacyclin and related drugs, which can dilate brain blood vessels, are of no apparent benefit in the early treatment of strokes caused by blood clots. Most strokes are caused by a blood clot which then reduces blood flow in the affected part of the brain. Without an adequate blood supply, the brain quickly suffers damage which is often permanent. Drugs which can thin blood and improve brain blood flow might reduce damage and improve outcome after stroke. Prostacyclin and related drugs have the ability to thin blood and increase brain blood flow. This systematic review assesses whether this type of drug improves outcome after stroke. The review identified five small trials which, when taken together, did not find any benefit. The limited amount of data mean that there is no evidence at present to suggest that prostacyclin and related drugs should be used in acute stroke.

BACKGROUND

Stroke is the third most common cause of death in the Western world and the most common cause of long-term adult disability. However, no acute therapeutic intervention has yet been shown to be effective in reducing mortality or morbidity. Prostacyclin is an endothelium-derived prostenoid which has vasodilating, antiplatelet ([Moncada 1983](#)), antileucocyte ([Bath 1991](#)), fibrinolytic and cytoprotective effects. Prostacyclin synthesis appears to be reduced in stroke ([Gryglewski 1982](#)) whilst cerebral infarction is characterised by thrombosis, platelet and leucocyte aggregation, and leucocyte infiltration. Hence, prostacyclin is a candidate treatment for acute ischaemic stroke.

Pre-clinical studies suggest that prostacyclin may be effective in animal models of cerebral infarction (e.g. [Akopov 1992](#)). Several non-randomised trials of prostacyclin in acute ischaemic stroke have been reported which suggest that prostacyclin reduces morbidity following stroke and is safe to administer ([Gryglewski 1982](#); [Gryglewski 1983](#); [Hakim 1984](#); [Miller 1984](#); [Miller 1985](#); [Pokrupa 1986](#)). As a result, a number of randomised controlled trials in acute ischaemic stroke have been undertaken. This Cochrane review presents an overview analysis of these randomised controlled trials.

OBJECTIVES

To determine whether prostacyclin is a safe treatment for patients with ischaemic stroke when administered acutely and whether it reduces the risk of early and late death.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled parallel group trials examining the effects of prostacyclin administered within one week of acute presumed ischaemic stroke.

Types of participants

Patients with acute stroke, where attempts were made to exclude primary intracerebral haemorrhage, were included in the analysis.

Types of interventions

Intravenous prostacyclin or analogue versus placebo. The analogues considered were: TRK-100, ONO-41483, HOE 892, OP-2507 and ZK 36374.

Types of outcome measures

The primary outcome measure was the frequency of early (within one month) death. The only secondary outcome was late (within eighteen months) death from all causes. Morbidity was not analysed since the trial publications do not give sufficient information.

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 November 2003.

For the first version of this review, we also searched EMBASE (1980 to 1999), MEDLINE (1966 to 1999), Science Citation Index (1981 to 1999), and the Ottawa Stroke Trials Registry. Electronic search terms included: (stroke or cerebr*) and (prostacyclin or epoprostenol or ciprostone or clioprost or iloprost or isocarbacyclin or beraprost or TRK-100 or ONO-41483 or HOE 892 or OP-2507 or ZK 36374); the latter compounds are analogues of prostacyclin.

In an effort to identify unpublished trials, we contacted the manufacturers of prostacyclin: Wellcome Foundation, UK, and Upjohn Company, UK. Additional information was sought from the principal investigators of the identified trials. Reviews of prostacyclin in cerebrovascular disease were also searched ([Chen 1986](#); [Martindale 1993](#); [Moncada 1983](#)). Note: prostacyclin was first identified in 1976 and studied in man in 1978.

Data collection and analysis

We (PB, FB) selected trials for inclusion in the review and sought additional information from the principal investigators of all trials that appeared to meet the inclusion criteria.

We noted information on the methods of randomisation, blinding, analysis, the number of patients randomised, dose and timing of prostacyclin or analogue, patient withdrawals, and the number of deaths occurring in each trial. The primary outcome was early (within one month) death.

We tested for heterogeneity and calculated a weighted estimate of the typical treatment effect across trials (odds ratio) using the Cochrane Review Manager software, RevMan 4.2.

RESULTS

Description of studies

Five trials, each of which used sodium prostacyclin, met our inclusion criteria and have been included in the analysis, as summarised in [Characteristics of included studies](#). One further trial of 427 patients, published within a paper which also describes several non-stroke studies, involved the administration of a prostacyclin analogue ([Mizushima 1994](#)); this trial has been excluded as no information has been received from the authors. Altogether, five trials were excluded (see [Characteristics of excluded studies](#)).

The average age of the patients in the trials was approximately 65 years, and slightly more men than women were included.

Risk of bias in included studies

Prostacyclin caused frequent but essentially mild adverse effects (e.g. headaches, nausea, 'warmth', dizziness, and facial flushing); as a result, it is unlikely that any of the trials of prostacyclin were ever truly blinded since both patients and staff may have been aware whether drug or placebo was administered. Two trials used independent neurological assessors who were not present during infusions to minimise bias in outcome assessment ([Martin 1985](#); [Pokrupa 1986](#)); at present, this is of no relevance to this review because death is the only available outcome.

Three of the included trials delayed administration of prostacyclin until after 24 hours following stroke onset to exclude patients with transient ischaemic attack. Hsu studied all patients within 24 hours (Hsu 1986) whilst Pokrupa included patients up to 48 hours post-ictus (Pokrupa 1986). Only one trial reported deaths at one year (Martin 1985). Three trials used CT scans to exclude cerebral haemorrhage (Hsu 1986; Martin 1985; Pokrupa 1986); the other two used a combination of EEG and CSF analysis (Huczynski 1985; Huczynski 1988) which means that some patients with primary intracerebral haemorrhage may have inadvertently been studied.

One trial randomised patients by sealed numbered opaque envelope (Pokrupa 1986); the other trial reports do not give explicit information on how randomisation was undertaken although all declare they were randomised. Furthermore, none of the studies explicitly state that they were analysed by intention to treat; however, it is clear in three trials that no patients were lost to follow up (Huczynski 1985; Martin 1985; Pokrupa 1986). However, we have performed an intention-to-treat analysis since outcome data relating to deaths are available for all patients whether withdrawn from treatment or not.

Effects of interventions

The total number of participants included in the five analysed trials amounted to 191. There was no evidence of statistical heterogeneity in the analysis ($\chi^2 = 0.78$, $2P > 0.1$). The five trials showed a non-significant 37% reduction in the odds of early death (within one month) (95% confidence interval (CI), 78% reduction to 85% excess); however, this difference is due to three less deaths in the prostacyclin group across two trials (Hsu 1986; Pokrupa 1986). Only one trial assessed late deaths (total deaths at 10 to 18 months) and found no difference although the confidence intervals were wide (Martin 1985).

Prostacyclin is a vasodilator which induces dose-dependent falls in blood pressure. Hypotension during the acute phase of stroke may be associated with poor outcome (Bath 1995). Four of the trials reported the effect of prostacyclin on blood pressure; Martin and Pokrupa found no statistical difference between active and placebo groups with respect to blood pressure and heart rate (Martin 1985; Pokrupa 1986). Two patients receiving prostacyclin in the former study had to have the dose halved because of hypotension (Martin 1985). In contrast, Hsu reported that prostacyclin reduced blood pressure and increased heart rate (Hsu 1986). Although Huczynski did not compare active and placebo groups, one patient receiving prostacyclin was withdrawn from the trial because of hypotension (Huczynski 1988). One trial found that facial flushing, a recognised adverse effect of prostacyclin, occurred in six patients receiving active medication but none taking placebo (Hsu 1986). Eleven patients in one study had the prostacyclin infusion rate reduced due to the development of adverse effects (Pokrupa 1986).

DISCUSSION

This review analyses apparently randomised controlled trials of intravenous prostacyclin in acute ischaemic stroke. The results do not support the hypothesis that prostacyclin reduces early all cause case fatality. However, the confidence intervals are wide reflecting the low numbers of patients studied, and prostacyclin could equally reduce short-term case fatality by 78% or increase it by 85%. One trial examined the effect of prostacyclin on late deaths and found no difference. The protocols used can

be criticised in the light of current practice. Firstly, prostacyclin was only administered to all patients within 24 hours of stroke onset in one trial; three other trials delayed treatment beyond 24 hours when ischaemic damage is likely to be fixed and not amenable to pharmacological intervention. Secondly, prostacyclin was administered discontinuously in four trials leading to the potential for rebound vasoconstriction and platelet/leucocyte activation between infusions. Thirdly, two trials used EEG and CSF criteria to exclude primary intracerebral haemorrhage which raises the possibility that patients with haemorrhage were included. Lastly, it is currently unclear how patients were randomised in four of the five studies.

In spite of the biological rationale for administering prostacyclin in acute ischaemic stroke, it is also possible that it may worsen outcome since infusions in normal people paradoxically reduce cerebral blood flow (Brown 1982; Cook 1983).

In summary, analysis of five trials of prostacyclin do not show evidence that it reduces case fatality following acute presumed ischaemic stroke. However, the numbers of trials and participants studied were too small and trial designs were suboptimal so that further research is required.

AUTHORS' CONCLUSIONS

Implications for practice

Prostacyclin should not currently be used in the routine management of acute ischaemic stroke.

Implications for research

The existing trials show no evidence that prostacyclin is harmful or beneficial in patients with acute ischaemic stroke. However, the trials included few patients and mostly administered prostacyclin late (after 24 hours) and in a discontinuous fashion. Hence, one or more larger trials of prostacyclin, or a longer acting analogue, are warranted in acute ischaemic stroke. It is suggested that a new trial might enrol upwards of 2000 patients within 12 hours of the onset of ischaemic stroke. Prostacyclin or analogue should be infused over five days continuously, as in (Hsu 1986), to prevent potential rebound platelet hyperfunction (Sinzinger 1981) and perhaps reduce adverse effects. Aspirin would be given to all patients, as is standard now, with the benefit of inhibiting the endogenous synthesis of vasoconstricting proaggregatory prostenoids (e.g. thromboxane A₂) (Huczynski 1988).

ACKNOWLEDGEMENTS

We are grateful to Dr Wojtek Rakowicz for translating the Polish language paper, Dr David Moher of the Ottawa Stroke Trials Registry for helping to identify relevant trials, the individual prostacyclin trialists for providing further information, and to the Cochrane Stroke Group Editorial Board and external peer reviewers for making constructive comments on this review. Dr Philip Bath was Wolfson Senior Lecturer in Stroke Medicine, and is Stroke Association Professor of Stroke Medicine. Dr Fiona Bath contributed (co-ordination, searching, data collation, management, entry, and analysis) to the first version of the review.

Ongoing trials

We are not aware of any ongoing trials of prostacyclin or analogues and would be grateful to be informed of any, or of any other relevant trials not covered here.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hsu 1986

Methods	Randomisation technique not stated Double-blind, placebo-controlled trial Analysis by intention to treat Stratified by thrombotic and embolic CI Five centre trial
Participants	USA 49 males, 31 females Mean age 64 years Stroke type: atherothrombotic 66, embolic 14 Enrolment within 24 hours 100% CT pre-entry
Interventions	Rx: PGI ₂ (epoprostenol sodium, Upjohn Co, USA, and Wellcome, Foundation, UK) Pl: buffer/diluent
Outcomes	Death at 4 weeks Neurological impairment assessed using Turnhill score at entry, day 3, weeks 1, 2 + 4
Notes	Ex: stupor, coma, psychiatric disorder, clinical intracranial hypertension, organ or systemic disease, bleeding risk, heparin FU: 4 weeks Further information unavailable because original data discarded

Risk of bias

Bias	Authors' judgement	Support for judgement
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Hsu 1986 (Continued)

Allocation concealment?	Unclear risk	B - Unclear
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Huczynski 1985

Methods	Randomisation technique not stated Double-blind, placebo controlled No loss to FU
Participants	Poland 15 male, 11 female Mean age 67 years Enrolment between 48 hours and 5 days 100% EEG and CSF pre-entry diagnosis of CI
Interventions	Rx: PGI ₂ (epoprostenol, Wellcome, UK, and Upjohn Co, USA), 5 x 6 hour consecutive 2.5 to 5 ng/kg/min iv infusions (depending on patients tolerance), separated by 6 hour intervals Pl: solvent Duration: 54 hours
Outcomes	Death at 2 weeks Neurological impairment assessed using modified Matthew score at baseline, after 6 and 54 hours, 2 weeks
Notes	Ex: heart failure, hyperglycaemia, uraemia, hyperpyrexia, previous stroke FU: 2 weeks Further information unavailable since original data discarded

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Huczynski 1988

Methods	Randomisation technique not stated Double-blind, placebo controlled Not intention-to-treat Withdrawals: PGI ₂ 4, Pl 1 from treatment
Participants	Poland 16 male, 14 female Mean age 61 years Enrolment 24 to 72 hours after CI 100% EEG and CSF pre-entry diagnosis of CI
Interventions	Rx: PGI ₂ (Wellcome, UK, or Chinoin, WRL), daily 6 hour iv infusions at 2.5 to 5 ng/kg/ min Pl: glycine solvent Duration: 2 weeks All patients given low molecular weight dextran
Outcomes	Death at 4 weeks

Huczynski 1988 (Continued)

Neurological impairment assessed using modified Matthew score assessed at baseline, after each infusion, 3 and 4 weeks

Notes Ex: heart failure, hyperglycaemia, uraemia, arrhythmia, hyperpyrexia, previous stroke, mild stroke
FU: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Martin 1985

Methods Randomisation technique not stated (randomisation in blocks of 4)
Double-blind, placebo-controlled
Not intention-to-treat
Withdrawal: PGI2 1 from treatment

Participants UK. 32 patients (gender numbers not given)
Mean age 68 years
Enrolment between 24 and 36 hours of stroke
100% CT exclusion of PICH

Interventions Rx: PGI2 (epoprostenol, Wellcome, UK), 5 x 6 hour alternating prostacyclin 5 ng/kg/min and saline iv infusions
Pl: solvent
Duration: 54 hours

Outcomes Death at 2 weeks and 10 to 18 months
Neurological impairment assessed using modified Matthew Score, Token speech test, and WHO disability status at 2 and 4 weeks
CT infarct volume at 2 weeks
Cerebral blood transit time pre and post-infusion

Notes Ex: ICH
FU: 2 weeks and 10 to 18 months
Further information unavailable since original data discarded

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pokrupa 1986

Methods Randomisation by sealed numbered opaque envelope
Double-blind, placebo-controlled, single-centre trial
Intention-to-treat
No loss to FU

Participants Canada
11 male, 12 female

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Pokrupa 1986 (Continued)

Mean age 63 years
100% CT pre-entry
Enrolment within 48 hours of ictus

Interventions	Rx: PGI2 ("Cycloprostin", Upjohn Co., USA) 5 daily 8 hour consecutive infusions weaned up from 2 to 10 ng/kg/min and tapered over last hour Pl: sterile diluent buffer (NaCl 0.147 w/v, glycine 0.188 w/v, NaOH, pH 10.5 +/- 0.3) Duration: 5 days
Outcomes	Death at 5 days, and 1, 2 and 4 weeks Neurological impairment rating at 5 days, and 1, 2 and 4 weeks CT and PET at 5 to 9 days
Notes	Ex: coma, complicating neurological conditions, heparin, malignant hypertension, uncontrolled diabetes mellitus, heart attack within 2 months, recent surgery FU: 5 days, and 1, 2, and 4 weeks Original data available

Risk of bias

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

CI: cerebral infarction

Ex: exclusion

FU: follow up

PICH: primary intracerebral haemorrhage

iv: intravenous

PGI2: prostacyclin

Pl: placebo

Rx: treatment

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Hakim 1984	5 patients with acute ischaemic stroke (< 48 hours of onset) given prostacyclin (2 to 10 ng/kg/min iv over 8 hours daily for 5 days) Excluded: non-controlled study
Hoshi 1990	Patients post cerebral infarction Excluded: (i) cross-over trial; (ii) one month post stroke, i.e. trial not acute
Isaka 1990	5 patients with carotid atheroma post ischaemic stroke Assessment of carotid platelet deposition (indium 111 scintigraphy) on TRK-100 or placebo Excluded: (i) crossover trial; (ii) no relevant outcomes
Mizushima 1994	Patients with mixed group of diagnoses Excluded: (i) data relating to stroke patients unavailable
Zhao 1991	18 patients with acute cerebral infarction (< 72 hours of onset) given prostacyclin (2-5 ng/kg/min iv; n = 11) versus dextran (n = 7) Excluded: (i) confounded; (ii) not randomised

DATA AND ANALYSES

Comparison 1. Prostacyclin vs control in ischaemic stroke: all trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause case fatality, early (within 4 weeks)	5	191	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.22, 1.85]
2 All cause case fatality, late (up to 18 months)	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.26, 3.91]

Analysis 1.1. Comparison 1 Prostacyclin vs control in ischaemic stroke: all trials, Outcome 1 All cause case fatality, early (within 4 weeks).

Analysis 1.2. Comparison 1 Prostacyclin vs control in ischaemic stroke: all trials, Outcome 2 All cause case fatality, late (up to 18 months).

WHAT'S NEW

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

HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 1, 1995

Date	Event	Description
16 March 2004	New search has been performed	<p>November 2003</p> <ul style="list-style-type: none"> • Further search. • Addition of two excluded trials (Hakim 1984; Isaka 1990). • Minor changes to text <p>January 1998</p> <ul style="list-style-type: none"> • Further search • Addition of an excluded trial (Zhao 1991) • Exclusion of the trial of Mizushima (Mizushima 1994) since no data have been made available by the authors <p>January 1996</p> <ul style="list-style-type: none"> • Further information on the trial of Hsu et al (Hsu 1986) obtained from an internal Upjohn Company report • Data from the trial of Pokrupa and colleagues (Pokrupa 1986) made available as individual patient data and from an unpublished manuscript <p>NOTE: This review covers an area where no active research is taking place. It will be updated if relevant information becomes available, e.g. on completion of an appropriate study.</p>

CONTRIBUTIONS OF AUTHORS

Philip Bath: conceived and designed the review, developed the search strategy, interpreted the data, wrote and updated the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Wolfson Foundation, UK.
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- Stroke Association, UK.

NOTES

NOTE: This review covers an area where no active research is taking place. It will be updated if relevant information becomes available, e.g. on completion of an appropriate study.

INDEX TERMS

Medical Subject Headings (MeSH)

Brain Ischemia [drug therapy]; Epoprostenol [*therapeutic use]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [*drug therapy]

MeSH check words

Humans