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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	4
AUTHORS' CONCLUSIONS	4
REFERENCES	5
CHARACTERISTICS OF STUDIES	6
DATA AND ANALYSES	6
Analysis 1.1. Comparison 1 Intraventricular streptokinase vs control, Outcome 1 Hydrocephalus shunt.	7
Analysis 1.2. Comparison 1 Intraventricular streptokinase vs control, Outcome 2 Death.	7
Analysis 1.3. Comparison 1 Intraventricular streptokinase vs control, Outcome 3 Meningitis.	7
Analysis 1.4. Comparison 1 Intraventricular streptokinase vs control, Outcome 4 Secondary IVH.	8
WHAT'S NEW	8
HISTORY	8
CONTRIBUTIONS OF AUTHORS	9
DECLARATIONS OF INTEREST	9
SOURCES OF SUPPORT	9
INDEX TERMS	9

[Intervention Review]

Intraventricular streptokinase after intraventricular hemorrhage in newborn infants

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ABSTRACT

Background

Hydrocephalus following intraventricular hemorrhage (IVH) is still one of the most serious complications of premature birth. Ventriculoperitoneal shunt surgery cannot be carried out early and permanent dependence on a shunt is associated with several serious complications. Streptokinase could be useful in the treatment of post-hemorrhagic hydrocephalus. This form of therapy is based on the hypothesis that multiple blood clots in the cerebrospinal fluid (CSF) are the initial cause of post-hemorrhagic ventricular dilatation and lysis of clots could reopen the pathways of circulation and re-absorption of CSF.

Objectives

To determine the effect of intraventricular streptokinase after intraventricular hemorrhage on the risk of permanent shunt dependence, neurodevelopmental disability or death in neonates at risk for, or actually developing post-hemorrhagic hydrocephalus (PHH).

Search methods

Pediatric, Neurosurgical and General Medical Journals were handsearched from 1976 until October 2000, as well as the MEDLINE database (via PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library) up to April 2007. Personal contacts were used.

Selection criteria

Randomized controlled trials and quasi-randomized controlled trials evaluating the use of injection of streptokinase into the CSF in infants having or at risk for post-hemorrhagic hydrocephalus.

Data collection and analysis

Details of patient selection, patient allocation and the interventions were extracted. The end-points examined were: ventriculoperitoneal shunt, death, meningitis, and secondary hemorrhage.

Main results

Two randomized trials evaluated intraventricular streptokinase in infants developing post-hemorrhagic ventricular dilatation were identified. When intraventricular streptokinase was compared with conservative management of post-hemorrhagic ventricular dilatation, the numbers of deaths and babies with shunt dependence were similar in both groups.

No information on the effect of intraventricular streptokinase on disability is available. There is cause for concern about meningitis and secondary intraventricular hemorrhage, but numbers are insufficient to quantify the risks.

Authors' conclusions

Intraventricular fibrinolytic therapy with streptokinase, given when post-hemorrhagic ventricular dilatation is established, cannot be recommended for neonates following IVH. A conservative approach with CSF drainage applied only to symptomatic raised intracranial pressure seems appropriate.

PLAIN LANGUAGE SUMMARY

Intraventricular streptokinase after intraventricular hemorrhage in newborn infants

There is no evidence of benefit from giving streptokinase to newborn babies after brain haemorrhage. Bleeding (hemorrhage) into the ventricles of the brain is a serious complication of premature birth and large hemorrhages often lead to hydrocephalus, the process by which fluid accumulates under pressure inside the brain, expanding the head excessively and damaging the brain tissue. The insertion of a valve and drainage system (ventriculoperitoneal shunt) is fraught with problems in this patient group and alternatives to this therapy are needed. A possible approach is to try to dissolve the blood clots initially blocking the reabsorption of fluid in the brain. Streptokinase is a "clot-busting" agent that has been successfully used to unblock coronary arteries. The review found no good evidence that intraventricular injection of streptokinase to infants with large intraventricular hemorrhage or post-hemorrhagic ventricular enlargement reduces the need for ventriculoperitoneal shunt or improves outcome.

BACKGROUND

Although many interventions have been shown to reduce the risk of intraventricular hemorrhage (IVH), it is still a common consequence of premature birth. post-hemorrhagic hydrocephalus (PHH) is the most serious complication of IVH. The risk of PHH is related to the size of the original hemorrhage and the initial mechanism is thought to be blockage of the channels of CSF reabsorption by multiple small blood clots (Hill 1984). Permanent hydrocephalus is thought to result from inward migration of fibroblasts and collagen deposition in the CSF pathways. Early insertion of a ventriculoperitoneal shunt is fraught with complications and delayed shunt operations in small prematures have a high rate of blockage and infection (Punt 1995). Furthermore, these infants are nearly always shunt-dependent for the rest of their lives and require several later operations even if no other problems occur. Therefore, it would be a great advantage if treatment could reduce the risk of permanent hydrocephalus after established IVH.

Neurodevelopmental outcome is poor in infants with PHH. Although part of this is because of parenchymal brain lesions present before PHH developed, it is likely that some of the dysfunction is the result of prolonged periods with raised intracranial pressure with periventricular edema and distortion of the developing axonal pathways and their myelination.

It has been postulated that early removal of bloody CSF by lumbar or ventricular tap might improve the prognosis of infants at risk of, or actually developing, PHH and this is the subject of another Cochrane review which concluded that early tapping after IVH could not be recommended.

It has been suggested that increasing the lysis of blood clots in the CSF by intraventricular injection of plasminogen activator might restore the circulation of CSF and prevent permanent hydrocephalus. Five small open non-randomized (phase 1) studies with streptokinase, urokinase or tissue plasminogen activator have been carried out, looking at measurable acute changes, drug delivery methods, pharmacokinetics and short term outcome (Whitelaw 1992; Hudgins 1994; Whitelaw 1996; Hansen b 1997; Hudgins 1997; Nowak 1999). The number of infants included is small and the results vary from 100% success (Hudgins 1994) to 100% failure (Hansen b 1997) in terms of avoiding shunt surgery.

Another therapeutic approach is to use drugs which reduce the production of CSF. Both acetazolamide and furosemide produce substantial reductions in CSF production and these two drugs in combination have been used in an uncontrolled open trial of infants developing post-hemorrhagic hydrocephalus (Shinnar 1985). This treatment strategy has now been tested in a large multicentre randomized trial, the PHVD Trial 1998, which found that the risk of death or shunt surgery was increased in the infants treated with acetazolamide and furosemide.

OBJECTIVES

The objectives of this review are to examine the effect of intraventricular treatment with streptokinase after IVH or early PHH on:

- the need for a permanent shunt
- neurodevelopmental outcome or survival
- adverse effects such as meningitis or secondary bleeding

METHODS

Criteria for considering studies for this review

Types of studies

All controlled trials whether truly randomized or quasi-randomized in which intraventricular fibrinolytic therapy was compared to standard (control) treatment in newborn infants with IVH or early PHH were to be identified. Treatment by injection of plasminogen activator cannot be done 'blind' by the neonatologist but the assessment of outcome could be carried out by individuals blind to early treatment allocation.

Types of participants

Infants of less than three months of age with a) IVH demonstrated by ultrasound or CT scan (at risk of PHH) or b) infants with IVH followed by progressive ventricular dilatation were included. Infants with other causes of hydrocephalus (e.g. infection, congenital aqueduct stenosis, tumour) were excluded.

Types of interventions

Injection of streptokinase into the CSF

Types of outcome measures

The main outcomes of interest are the number of children

- acquiring permanent shunts
- dying during follow-up
- meningitis during treatment
- secondary intraventricular hemorrhage during treatment

Search methods for identification of studies

The reviewer has been an active trialist in this area and has personal contact with many groups in this field. Journals handsearched from January 1976 (when CT scanning of neonates started) to October 2000 include: Pediatrics, J Pediatrics, Archives of Disease in Childhood, Pediatric Research, Developmental Medicine and Child Neurology, Acta Paediatrica Scandinavica, Child's Nervous System, European J of Pediatrics, Neuropediatrics, Neurosurgery, J Neurosurgery, Pediatric Neurosurgery, Biology of the Neonate, New England J Medicine, Lancet, British Medical Journal. The MEDLINE database (via PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library) were searched from January 1976 to April 2007 using the MeSH terms streptokinase, intraventricular hemorrhage, hydrocephalus, newborn infant. Proceedings of the Society for Pediatric Research, European Society for Pediatric Research, Neonatal Society and Royal College of Paediatrics and Child Health were searched by hand from 1988 to 2006.

Data collection and analysis

Each identified trial was assessed for methodological quality with respect to

- adequate allocation concealment
 - method of allocation
 - performance bias
 - exclusion bias
 - bias in outcome assessment.
- Trials without a simultaneous control group (e.g. those with historical controls) were rejected.

Inclusion criteria and therapeutic interventions for each trial were reviewed to see how they differed between trials. The outcomes in each trial were examined to see how comparable they were between studies.

Statistics: 2 X 2 tables were made from each trial for each important outcome and odds ratio, relative risk and risk difference with 95% confidence intervals were used in the meta-analysis.

Heterogeneity was examined using the I^2 statistic.

RESULTS

Description of studies

See Table, Characteristics of Included Studies.

Risk of bias in included studies

Searching yielded only two trials that qualified for inclusion.

Assessment of validity:

[Luciano 1997](#)

Method of randomization - unclear

Blinding of caretakers - no

Almost all subjects analyses - yes

Blinding of observers - no

[Yapicioglu 2003](#)

Method of randomization - unclear

Blinding of caretakers - no

Almost all subjects analyses - yes

Blinding of observers - no

Effects of interventions

INTRAVENTRICULAR STREPTOKINASE AFTER INTRAVENTRICULAR HEMORRHAGE IN NEWBORN INFANTS (COMPARISON 01):

Hydrocephalus shunt (Outcome 01.01):

Only two small randomized trials of intraventricular fibrinolytic therapy (streptokinase) were found. The numbers of infants dying or requiring a peritoneal shunt for hydrocephalus were similar in the two groups. Both studies reported on the need for a shunt for hydrocephalus. No difference was noted in the meta-analysis (typical RR 1.33, 95% CI 0.67, 2.67; typical RD 0.17 95% CI -0.21, 0.59).

Side effects of interventions:

The group of infants who received intraventricular streptokinase had one case of meningitis and one case of secondary intraventricular bleeding, both being likely side-effects of the intervention. However, these differences were not statistically significant.

DISCUSSION

The major outcomes (death or shunt) were similar when the two groups were compared, although there is a suggestion that infants receiving streptokinase may have a higher risk for shunt insertion. However the trials of streptokinase were so small that their power to detect a therapeutic effect was limited.

AUTHORS' CONCLUSIONS

Implications for practice

Intraventricular fibrinolytic therapy with streptokinase starting before one month of age in infants developing post-hemorrhagic ventricular dilatation cannot be recommended.

Implications for research

As ventriculoperitoneal shunting is still a treatment with many problems in preterm infants with PHH, alternative therapies are very much needed. Neither early tapping of CSF nor acetazolamide and furosemide are effective in reducing the need for shunting and both forms of therapy have adverse effects.

It may be that the results to date of intraventricular fibrinolytic therapy are negative because the treatment (starting nearly two weeks after birth) has been given too late. Fibrosis, desposition of extracellular matrix proteins and chronic inflammatory changes may already have become irreversible. Furthermore, very low levels of plasminogen ([Whitelaw 1995](#)) and the presence of Plasminogen Activator Inhibitor-1 (PAI-1) ([Hansen a 1997](#)) would be expected to limit the fibrinolytic effect of intraventricular streptokinase. There is now considerable evidence that the cytokine, Transforming Growth Factor Beta-1 (TGF beta-1), plays a major role in the development of hydrocephalus after intraventricular haemorrhage and that intraventricular injection of tissue plasminogen activator, on its own, increases the concentration of TGF beta-1 in ventricular CSF ([Whitelaw 1999](#)). This could help to explain the failure of intraventricular injection of fibrinolytic agents to prevent hydrocephalus. Therapeutic strategies need to consider ways of removing, blocking or preventing release of this, and perhaps other, cytokines.

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Whitelaw A, Mowinckel M-C, Abildgaard U. Low levels of plasminogen in cerebrospinal fluid after intraventricular haemorrhage: a limiting factor for clot lysis?. *Acta Paediatrica* 1995;**84**:933-6.

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Whitelaw A, Saliba E, Fellman V, Mowinckel M-C, Acolet D, Marlow N. Phase 1 study of intraventricular recombinant tissue plasminogen activator for treatment of posthaemorrhagic hydrocephalus. *Archives of Disease in Childhood* 1996;**74**:F20-6.

Whitelaw 1999

Whitelaw A, Christie S, Pople I. Transforming Growth Factor Beta-1: A possible signal molecule for posthemorrhagic hydrocephalus. *Pediatric Research* 1999;**46**:576-80.

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A Whitelaw. Intraventricular streptokinase after intraventricular hemorrhage in newborn infants. *Cochrane Database of Systematic Reviews* 2000, Issue 1. [DOI: [10.1002/14651858.CD000498](https://doi.org/10.1002/14651858.CD000498)]

Whitelaw 2001

A Whitelaw. Intraventricular streptokinase after intraventricular hemorrhage in newborn infants. *Cochrane Database of Systematic Reviews* 2001, Issue 1. [DOI: [10.1002/14651858.CD000498](https://doi.org/10.1002/14651858.CD000498)]

CHARACTERISTICS OF STUDIES

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

Luciano 1997

Methods	Open randomised trial
Participants	12 newborn infants who were shown by ultrasound to have intraventricular hemorrhage followed by progressive enlargement to 4 mm over the 97th centile for ventricular width
Interventions	Insertion of a percutaneous ventricular catheter via the anterior fontanelle. Streptokinase 20,000 units/day was given intraventricularly for 96 hours. CSF drainage was performed several times a day to prevent raised intracranial pressure.
Outcomes	Death, insertion of a ventriculoperitoneal shunt, meningitis and secondary intraventricular bleeding.
Notes	

Risk of bias

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

Yapicioglu 2003

Methods	Open randomised trial
Participants	12 newborn infants who developed posthaemorrhagic hydrocephalus.
Interventions	Lumber puncture to remove 5-10ml of CSF, followed by insertion of a percutaneous ventricular catheter via the anterior fontanelle, and removal of a further 5ml of CSF. Streptokinase 25,000 units over 3 days at 0.5ml/h was given intraventricularly. CSF drainage of 5-10ml of CSF was performed once a day. Intraventricular vancomycin (1mg/day) for infection prophylaxis.
Outcomes	Third ventricular size, death, insertion of a ventriculoperitoneal shunt, meningitis and secondary intraventricular bleeding.
Notes	

Risk of bias

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

DATA AND ANALYSES

Comparison 1. Intraventricular streptokinase vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hydrocephalus shunt	2	24	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.67, 2.67]
2 Death	2	24	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.17, 5.98]
3 Meningitis	2	24	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.15, 61.74]
4 Secondary IVH	2	24	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.15, 61.74]

Analysis 1.1. Comparison 1 Intraventricular streptokinase vs control, Outcome 1 Hydrocephalus shunt.

Analysis 1.2. Comparison 1 Intraventricular streptokinase vs control, Outcome 2 Death.

Analysis 1.3. Comparison 1 Intraventricular streptokinase vs control, Outcome 3 Meningitis.

Analysis 1.4. Comparison 1 Intraventricular streptokinase vs control, Outcome 4 Secondary IVH.

WHAT'S NEW

Date	Event	Description
10 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 3, 1997

Date	Event	Description
31 May 2007	New citation required but conclusions have not changed	Substantive amendment
31 May 2007	New search has been performed	<p>This review updates the existing review "Intraventricular streptokinase after intraventricular hemorrhage in newborn infants" published in The Cochrane Library, Issue 1, 2001 (Whitelaw 2001).</p> <p>That review concluded that treatment with intraventricular streptokinase cannot be recommended for established post-hemorrhagic ventricular dilatation.</p>

Date	Event	Description
		Our updated search identified one new randomized trial for inclusion in the review. The updated results and consequently the conclusions remain similar.

CONTRIBUTIONS OF AUTHORS

DO carried out the updated literature search and wrote the first drafts of the updated review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- University of Bristol, UK.

External sources

- Wellcome Trust, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cerebral Ventricles; Cerebral Hemorrhage [complications] [*drug therapy]; Fibrinolytic Agents [administration & dosage] [*therapeutic use]; Hydrocephalus [etiology] [prevention & control]; Injections, Intraventricular; Randomized Controlled Trials as Topic; Streptokinase [administration & dosage] [*therapeutic use]

MeSH check words

Humans; Infant, Newborn