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Diuretic therapy for newborn infants with posthemorrhagic ventricular dilatation (Review)

Whitelaw A, Brion LP, Kennedy CR, Odd D

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[Intervention Review]

Diuretic therapy for newborn infants with posthemorrhagic ventricular dilatation

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ABSTRACT

Background

Intraventricular hemorrhage remains a serious complication of premature birth and post-hemorrhagic hydrocephalus still has no satisfactory treatment. Acetazolamide and furosemide, which both reduce the production of cerebrospinal fluid, have been suggested as non-invasive therapies to reduce hydrocephalus and the need for ventriculo-peritoneal (V-P) shunting.

Objectives

To determine the effect of acetazolamide and furosemide on shunt dependence and other complications in infants developing post-hemorrhagic ventricular dilatation.

Search methods

Searches were performed of electronic databases (MEDLINE from 1966, EMBASE from 1974 and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library). PubMed was searched on April 18, 2007 and Issue 2, 2007 of The Cochrane Library was searched.

Selection criteria

Randomised, or quasi-randomised trials, of acetazolamide and/or furosemide compared with standard therapy in infants with IVH or post-hemorrhagic ventricular dilatation

Data collection and analysis

Data were extracted independently by each author and were analysed by the standard methods of the Cochrane Collaboration using relative risk (RR) and risk difference (RD), a fixed effect model and sensitivity analyses where appropriate.

Main results

There were two eligible trials: one randomized 16 infants and the other 177 infants. Neither study showed a decreased risk for V-P shunt or for V-P shunt or death associated with acetazolamide and furosemide therapy. The larger trial showed that acetazolamide and furosemide treatment resulted in a borderline increase in the risk for motor impairment at one year (RR 1.27, 95% CI 1.02 - 1.58; RD 0.16, 95% CI 0.02 - 0.31), but did not significantly affect the risk for the combined outcome of delay, disability or motor impairment among survivors, or the risk of the combined outcome of death, delay, disability or impairment at one year. The larger trial showed that diuretic treatment increased the risk for nephrocalcinosis (RR 5.31, 95% CI 1.90 - 14.84; RD 0.19, 95% CI 0.09 - 0.29); meta-analysis confirmed this result.

Authors' conclusions

Acetazolamide and furosemide therapy is neither effective nor safe in treating post-hemorrhagic ventricular dilatation. Acetazolamide and furosemide cannot be recommended as therapy for post hemorrhagic hydrocephalus.

PLAIN LANGUAGE SUMMARY

Diuretic therapy for newborn infants with posthemorrhagic ventricular dilatation

Bleeding (hemorrhage) into the fluid-producing cavities (ventricles) of the brain is a serious complication of premature birth. Large hemorrhages may result in fluid building up under pressure, progressively enlarging the brain and head. Current treatment approaches, including the insertion of a valve drainage system (shunt) are fraught with problems. Acetazolamide and furosemide, two drugs with diuretic action, reduce the production of fluid in the ventricles of the brain and have been proposed as safe treatments to treat dilatation of the ventricles after intraventricular hemorrhage in newborn infants. When compared with standard treatment, diuretic therapy was found not to reduce the need for shunt surgery. Diuretic drugs are neither safe nor effective in treating ventricular dilatation in infants with intraventricular hemorrhage.

BACKGROUND

Post-hemorrhagic hydrocephalus (PPH) is perhaps the most serious complication of intraventricular hemorrhage (IVH) in the newborn infant. Although there has been a general reduction in the percentage of small premature infants suffering IVH (du Plessis 1998), the increasing survival of babies under 28 weeks gestation over the last 10 -20 years means that there is an increased number of candidates for IVH. Therefore, PPH remains an important problem.

The mechanism of hydrocephalus is thought to be initial obstruction by blood clots followed by arachnoiditis around the brain stem (Volpe 1995). The risk of developing hydrocephalus is roughly proportional to the size of the haemorrhage. The initial phase of ventricular enlargement can be accurately documented with cranial ultrasonography (Whitelaw 1995). The majority of surviving infants have cerebral palsy with approximately one third having multiple disabilities.

The only established treatment for persistent and progressive post hemorrhagic hydrocephalus with raised pressure is the surgical placement of a ventriculoperitoneal (V-P) shunt (Volpe 1995). Unfortunately, V-P shunts are associated with frequent complications, especially blockage and infection, and the child is usually dependent on the shunt for the rest of his/her life. Thus, non-surgical treatment which avoids the need for V-P shunting is very much needed.

Early lumbar punctures or ventricular taps have been evaluated in randomised trials and reviewed in the Cochrane Library (Whitelaw 1999a). There is no reduction in the subsequent need for V-P shunt, or in neurological disability, and there is an increase in infection. Intraventricular fibrinolytic therapy has also been the subject of a Cochrane review and was found not to decrease the need for shunting (Whitelaw 1999b).

Acetazolamide, a carbonic anhydrase inhibitor, decreases the production of cerebrospinal fluid (CSF) by over 50%. Furosemide (frusemide), a loop diuretic, also decreases the production of CSF. These two drugs have been tried as therapy (acetazolamide alone or combined with furosemide) for infants developing hydrocephalus of different etiologies to avoid the need for shunt surgery (Birzis 1958; Chaplin 1980; Donat 1980; Huttenlocher 1965; Mealey 1980; Schain 1969; Shinnar 1985). Acetazolamide has also been evaluated in hydrocephalus from tuberculous meningitis (Schoeman 1991). However, diuretic therapy may not help reduce ventricular dilatation resulting from periventricular leukomalacia, which may be associated with IVH (Ment 1999; du Plessis 1998). In addition, these diuretics have several potential side effects including acid-base, fluid and electrolytes and gastrointestinal disturbances, nephrocalcinosis and lethargy.

OBJECTIVES

To determine the effect of acetazolamide and furosemide on shunt dependence and other clinical outcomes in infants developing post-hemorrhagic ventricular dilatation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Infants of less than 12 months of age with progressive ventricular dilatation or hydrocephalus following intraventricular hemorrhage

Types of interventions

Acetazolamide and/or furosemide. Either drug administered separately or both together versus neither

Types of outcome measures

Primary outcomes:

- Death at one to three years of age
- Ventriculo-peritoneal shunt surgery
- Any surgery (including external ventricular drain, ventriculostomy or reservoir placement)
- Moderate to severe long-term motor disability at one to three years of age
- Moderate to severe long-term cognitive disability at one to three years of age
- Combined outcome: death or (moderate to severe) long-term disability at one to three years of age

Secondary outcomes:

- Use of one or more therapeutic lumbar punctures after starting diuretic therapy
- Use of one or more ventricular taps after starting diuretic therapy
- Number of ventricular taps after starting diuretic therapy
- Central nervous system infection (ventriculitis, meningitis)
- Biochemical disturbance requiring discontinuation of the medication
- Nephrocalcinosis

Search methods for identification of studies

See Collaborative Review Group Strategy
MEDLINE accessed using PubMed (1966 - June 2000), EMBASE (1974- June 2000), and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, 2000, Issue 2). We examined reports in any language as long as there is an abstract in English. The following search terms were used:
#1: acetazolamide OR furosemide OR frusemide

#2: hydrocephalus OR intraventricular hemorrhage OR intraventricular haemorrhage OR post-haemorrhagic ventricular dilatation OR
post-hemorrhagic ventricular dilatation

#3 ((((#1 AND #2) AND notpubref [sb]) AND "infant " [MeSH Terms]) AND "human" [MeSH Terms])

Repeat literature searches were performed on April 18, 2007, using PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 2, 2007).

Data collection and analysis

The standard methods of the Neonatal Review Group were used. These include independent review of all candidate studies by all review authors. Each review author extracted data separately, then authors compared and resolved differences. The methodological quality of the trials was assessed by analysing the risk for four types of bias: selection, performance, attrition and detection. Standard methods of the Neonatal Review Group were used for estimating treatment effects, including relative risk (RR), risk difference (RD), number needed to treat/harm, and 95% confidence interval (CI) with a fixed effect model for meta-analyses. Data were extracted on as many randomised patients as possible, and analysed on an intent-to-treat basis, using as denominator for dichotomous variables the total number of randomised patients. For studies with possible attrition bias, a stringent sensitivity analyses was performed, assigning uniformly good outcomes to one group and bad outcomes to the other group. Additional data including those obtained after publication were requested from the authors; updated data (manuscript in press in Pediatrics) were obtained for PHVD Trial Grp 1998.

Subgroup analyses planned:
1. According to the type of patients:
1.1. Patients with mild to moderate ventricular dilatation; this group may include both patients at the very early stages of obstructive hydrocephalus and patients with periventricular leukomalacia
1.2. Patients with severe ventricular dilatation but without evidence for intracranial hypertension; this group is more likely to include patients with periventricular leukomalacia
1.3. Patients with severe ventricular dilatation and with evidence for intracranial hypertension; these patients are more likely to have an obstructive process

2. According to the medication:
2.1. Furosemide alone
2.2. Acetazolamide alone
2.3. Both together

RESULTS

Description of studies

Searching revealed only two randomised controlled trials examining the use of acetazolamide or furosemide after IVH (Libenson 1999; PHVD Trial Grp 1998). No controlled trials of acetazolamide alone or furosemide alone for this indication were identified.

Libenson et al systematically screened all infants below 1500 g birth weight or 35 weeks gestation in two hospitals during a three-year period and identified all those with IVH (Libenson 1999). Ventriculomegaly was defined as lateral ventricular width greater than 5 mm over 2 standard deviations above the mean for age. Infants were eligible for the trial if they had post-IVH ventriculomegaly and raised intracranial pressure (ICP) defined as an increase in ICP of more than 20 mm H_20 or an initial ICP greater than 90 mm H_20, measured either with the Ladd non-invasive fiberoptic monitor or by lumbar puncture. After informed consent, eligible infants were randomised to either a) treatment group: medical therapy with acetazolamide and furosemide therapy or b) control group: serial lumbar punctures. Medical therapy consisted of furosemide 1 mg/kg/day intravenously or orally and acetazolamide starting at 20 mg/kg/day increasing by 10 mg/kg/day up to 100 mg/kg/day. Sodium citrate starting at a dose of 8 mEq/kg/day was started and titrated to keep the serum bicarbonate above 18 mEq/L and serum sodium and potassium in the normal range. If ventricular measurements were stable and ICP did not rise during three months, the drugs were tapered and stopped. Criteria for lumbar punctures in the treatment group are not described in the protocol. The control group was treated with serial lumbar punctures until free flow of CSF stopped, initially every day, then on alternate days. When (if) the ventricular measurements stabilised, serial lumbar punctures were stopped. Infants with a rapidly progressive ventriculomegaly by ultrasonography, head enlargement greater than 2 cm/week and/or ICP rising by more than 20 mm H_2O/week were considered treatment outcome failures and were usually referred for V-P shunting. ICP was monitored for one year after randomisation.

The PHVD Drug Trial Group recruited infants of less than three months age with evidence of germinal layer or intraventricular hemorrhage and progressive dilatation of the lateral ventricles to more than 4 mm over the 97th centile (PHVD Trial Grp 1998). Drug therapy started with acetazolamide 25 mg/kg/day orally increasing by 25 mg/kg/day up to 100 mg/kg/day. Frusemide dosage was 1 mg/kg/day divided into two doses. Sodium bicarbonate 4 mmol/kg/day and potassium chloride 1 mmol/kg/day were started and adjusted according to plasma concentrations of sodium, potassium and bicarbonate. Drug treatment was normally for six months but weaning could be attempted if ventricular size had not increased in four weeks.

Standard therapy was at the discretion of the clinician, but guidelines advised the removal of CSF only if symptomatic raised intracranial pressure was suspected or if there had been excessive head enlargement (3 cm) over two weeks. Shunt insertion was recommended if two of the following criteria were met: head size at least 1.5 cm over the 97th centile, head growth at least 1.5 cm per week for two weeks, and the presence of any of the symptoms or signs of raised intracranial pressure (persistent reduction in level of consciousness, persistent vomiting after exclusion of other causes, or involuntary downgaze of the eyes, known as "sunsetting").

Cranial ultrasound was carried out at entry and at term. Renal ultrasonography was carried out 12 to 14 weeks after entry. Outcomes were documented at discharge from hospital and at one year. Death or shunt surgery were determined. At one year, an appropriate paediatrician, not necessarily blinded to neonatal treatment, administered the Vineland social maturity scale and a neurodevelopmental examination. Neurodevelopmental status was defined in terms of the presence or absence of neuromotor, sensory and developmental impairments and disabilities. Abnormal reflexes, tone changes, left/right asymmetry or absent pincer grasp were defined as neuromotor impairment. Neuromotor disability was based on age-equivalent standard scores for the motor skills areas of the Vineland scale. A score of 50 - 69 was a moderate neuromotor disability and a score of less than 50 was a severe neuromotor disability. The definition of sensorineural deafness was the need for a hearing aid.
The updated literature search in 2007 identified no new trials that could be included.

Risk of bias in included studies

Libenson et al gave no information on the method of randomisation and there were unequal numbers in the two groups (ten in the treatment group and six in the control group) (Libenson 1999). No statistical power calculation is given. The intervention and outcome were not blinded. Outcome variables were documented in all sixteen patients. All patients were followed for one year after randomisation, however no information on neurological follow-up at one year is given. Although nephrocalcinosis is highlighted as an outcome, the Methods section does not specify if that surveillance was carried out equally between the two groups (Libenson 1999). Another manuscript from the same authors (Stafstrom 1992) mentions that infants treated with acetazolamide and furosemide had a renal ultrasonogram at least once, although the exact timing was not specified. One patient in the treatment group received spinal taps after discontinuing diuretics. Two of the six infants in the control group were treated with acetazolamide and furosemide after worsening of hydrocephalus despite spinal taps although there is no mention of cross-over in the Methods section of the paper. There appears to have been an eight year delay between collecting data on the last randomised patient and the submission of the paper to the journal.

The PHVD Drug Trial Group concealed allocation of treatment until the infant was registered in the trial. Following parental consent, identification and clinical details of the infant were telephoned to a Randomising Centre which allocated the infant to either group using a computerised minimisation algorithm to ensure balance between the two groups with respect to referral centre and presence or absence of cerebral parenchymal lesions on ultrasonogram (PHVD Trial Grp 1998). The intervention was not blinded. Cross-over occurred but to a limited extent. In the control group only four infants (five percent) received acetazolamide for hydrocephalus and eighteen (twenty percent) received furosemide predominantly for systemic fluid balance after trial entry. In the treatment group 82 (93%) received furosemide and 87 (99%) received acetazolamide. The main end-points were death and shunt surgery, relatively immune to bias, and available in all but one patient (99.4%). However, the ascertainment of developmental outcome was not necessarily done by a paediatrician blind to treatment allocation. Of 177 babies originally randomised, 151 were analysed when the data monitoring committee stopped further recruitment; this interim analysis on 85% of the randomised patients was published in the Lancet. Information on primary outcomes selected for this systematic review is available in more than 95% of the 177 randomised patients; these data are now in press in Pediatrics. Twenty-eight of the 177 randomised infants died before one year and neurodevelopmental status at one year was known in 146 infants (98.3% of the survivors). Nearly 60% of infants in each treatment arm had a renal ultrasonogram after trial entry.

Effects of interventions

ACETAZOLAMIDE + FUROSEMIDE VS. STANDARD THERAPY (COMPARISON 01):

Death (Outcome 01.01):

In Libenson 1999 none of 16 patients died. In the PHVD Trial Grp 1998, 18/88 died in the treatment group, compared with 11/89 in the control group (NS). Meta-analysis showed no significant effect of diuretic therapy on mortality (typical RR 1.65, 95% CI 0.83, 3.30).

V-P shunt (Outcome 01.02):

In Libenson 1999, nine cases of post-hemorrhagic hydrocephalus resolved or arrested and only one infant had a V-P shunt. In the control group, three infants out of six had a V-P shunt. Two out of six control infants did not improve with serial lumbar punctures, were treated with acetazolamide and furosemide and eventually had a V-P shunt. In the PHVD Trial Grp 1998, V-P shunt was inserted in 43/88 patients in the treatment group and in 40/89 patients in the control group. Diuretic therapy did not significantly affect the risk for V-P shunt in either trial nor in the meta-analysis (typical RR 1.01, 95% CI 0.74, 1.37).

Death or V-P shunt (Outcome 01.03):

Diuretic therapy did not affect the risk for death or V-P shunt in either trial. In Libenson 1999, one of ten patients in the treatment group and three of six patients in the control group either died or had a V-P shunt. In the PHVD Trial Grp 1998, this outcome was known in all but one patient (99.4%): 56/88 patients in the treatment group and 46/89 patients in the control group either died or had a V-P shunt. Meta-analysis showed no significant difference between the two groups (typical RR 1.15, 95% CI 0.90, 1.48; typical RD 0.08, 95% CI -0.06, 0.22). Heterogeneity in RD but not RR in the meta-analysis could have resulted from small numbers in Libenson's study and possibly from bias in either trial (e.g., selection bias and cross-over in Libenson's trial, and treatment and outcome bias in both trials). Alternatively, heterogeneity could have resulted from the fact that in Libenson 1999 entry criteria included ventriculomegaly and high ICP and all patients in the control group received serial lumbar punctures, whereas in the PHVD Trial Grp 1998 entry criteria included only ventriculomegaly and patients in either group received CSF removal by lumbar puncture or other means only when needed clinically.

Other treatment for ventricular dilatation (Outcomes 01.04, 01.05, 01.10, 01.11):

In Libenson 1999, need for lumbar puncture cannot be analysed as an outcome variable because serial lumbar punctures were part of the protocol for the control group. Two out of six infants in the control group did not improve with serial lumbar punctures, were treated with acetazolamide and furosemide, and eventually needed a V-P shunt. In the PHVD Trial Grp 1998, 5/88 patients in the treatment group and 11/89 in the control group needed a CSF reservoir; 8/88 in the treatment group and 7/89 in the control group needed other surgery for hydrocephalus; 44/88 in the treatment group and 50/89 in the control group needed CSF taps of any kind, and 29/88 in the treatment group and 33/89 in the control group needed ventricular taps at any time. Diuretic therapy did not significantly affect the risk for any of these interventions in either trial. Meta-analysis could not be done because none of the variables were analysed in both trials.

Motor impairment or disability at one year among survivors (Outcome 01.06):

This outcome variable was available only in PHVD Trial Grp 1998. Motor impairment or disability was observed in 54/70 patients in the treatment group and 48/79 in the control group. Diuretic therapy significantly increased motor impairment or disability among survivors (RR 1.27, 95% CI 1.02 to 1.58; RD 0.16; 95% CI 0.02 to 0.31). Sensitivity analysis showed that the 2% attrition rate (3/149) could not have explained this effect. Nevertheless, conclusions about this outcome are fragile; if one patient in the treatment group had shifted from abnormal to normal outcome,

the RR would not have reached statistical significance (RR 1.25, 95% CI 1.00 to 1.55, z = 1.95, p = 0.05).

Delay, disability or motor impairment at one year among survivors (Outcome 01.07 and 01.08):
This outcome variable was available only in PHVD Trial Grp 1998. This combined outcome was present in 54/70 patients in the treatment group and in 52/79 patients in the control group. Diuretic therapy did not significantly increase the risk for this combined outcome among survivors (RR 1.17, 95% CI 0.96 to 1.44; RD +0.11, 95% CI -0.03, +0.26). Sensitivity analysis showed that we cannot exclude the possibility that this negative result might have been explained by the 2% attrition rate (extreme possible value of 57/70 vs 52/79, RR 1.17, 95% CI 1.02 to 1.50; RD 0.16, 95% CI 0.02 to 0.29). A secondary analysis showed a significant increased risk for delay, disability or motor impairment among survivors assessed at one year (RR 1.22, 95% CI 1.00 to 1.49, p=0.04; RD 0.15, 95% CI 0.01 to 0.29, p = 0.04).

Delay, disability or motor impairment or death (Outcome 01.09):
This outcome variable was available only in PHVD Trial Grp 1998. This combined outcome was present in 72/88 patients in the treatment group and in 62/89 patients in the control group. Diuretic therapy did not significantly affect the risk for this combined outcome (RR 1.17, 95% CI 0.99 to 1.39, RD 0.12, 95% CI 0.00 to 0.25, p = 0.06). Sensitivity analysis showed that we cannot exclude the possibility that this negative result might have been explained by the 2% attrition rate (extreme possible value of 75/88 vs. 62/89, RR 1.22, 95% CI 1.04 to 1.44; RD 0.16, 95% CI 0.03 to 0.28).

Post-hoc subgroup analysis showed significant subgroup heterogeneity between patients with a parenchymal lesion at trial entry and those without such a lesion. Among patients with parenchymal lesion at trial entry, this combined outcome was observed in 34/39 patients allocated to diuretic therapy and 35/40 patients allocated to standard therapy. In this subgroup, diuretic therapy did not have a significant effect on the risk for delay, disability, motor impairment or death (RR 1.00, 95% CI 0.84 to 1.18; RD 0.00, 95% CI -0.15 to +0.14). Sensitivity analysis showed that neither RR nor RD would have been significant even if the three patients allocated to diuretic therapy in whom outcome is unknown were assigned a poor outcome (RR 1.08; 95% CI 0.94 to 1.24; RD 0.07, 95% CI -0.05 to +0.20). In contrast, among patients without parenchymal lesion at entry, this combined outcome was observed in 38/49 patients allocated to diuretic therapy and in 27/49 patients allocated to standard therapy. In this subgroup, diuretic therapy significant increased the risk of this combined outcome (RR 1.41, 95% 95% CI 1.05 to 1.89; RD 0.22, 95% CI 0.04 to 0.41).

CNS infection (Outcome 01.12):
In the PHVD Trial Grp 1998, 13/88 patients in the treatment group and 11/89 patients in the control group developed a CNS infection (RR 1.20, 95% CI 0.57 to 2.52; RD 0.02, 95% CI -0.08 to +0.12).

Complications requiring discontinuation of diuretic therapy (Outcome 01.13):
In Libenson 1999, six out of ten infants in the treatment group had drug therapy discontinued because of side effects such as poor feeding or electrolyte disturbances. Among the two control infants who received acetazolamide and furosemide, diuretic therapy was stopped because of severe acidosis and in the other because of failure to respond to therapy. In PHVD Trial Grp 1998 drug therapy increased the risk for biochemical disturbance sufficient to discontinue treatment (RR 47.5, 95% CI 2.93 to 770.6; RD 0.26, 95% CI 0.17 to 0.35); this effect could not be attributed to attrition. Heterogeneity of the meta-analysis (RR only) may have resulted in major part from small numbers and cross-over of two of six patients in the control group in Libenson 1999.

Nephrocalcinosis (Outcome 01.14):
In Libenson 1999, three out of ten infants in the treatment group and two in the control group (both after cross-over to diuretics) developed nephrocalcinosis (NS). In the PHVD Trial Grp 1998, 21/88 patients in the treatment group and 4/89 in the control group developed nephrocalcinosis (RR 5.31, 95% CI 1.90 to 14.84; RD 0.19, 95% CI 0.09 to 0.29). These data should be interpreted cautiously because of attrition. Sensitivity analysis is not possible because the exact number of patients who received a renal ultrasonogram at the end of diuretic therapy is not provided in Libenson 1999. In the PHVD Trial Grp 1998, 51 patients in the diuretic group (58%) and 50 in the control group (56%) had a renal ultrasonography. Heterogeneity (RR only) of the meta-analysis may have resulted from cross-over of two out of six patients in the control group in Libenson 1999 and from incomplete data (possible attrition bias) in both studies.

Planned subgroup analyses:
None of the planned subgroup analyses was possible because neither randomised trial provided the data.

DISCUSSION

Only two controlled trials could be included in our review.

Results of both trials need to be interpreted with caution. The trial by Libenson 1999 had the problems of uncertain concealment of allocation, small size, unequal groups, lack of blinding, cross-over of therapy and no neurological outcome. The PHVD Drug Trial had the problems of lack of blinding. Although the follow-up rate was remarkable (97% of all surviving patients), RRs and RDs for many developmental variables were close to the limit of significance, some reaching significance and other ones not. Because of statistical heterogeneity and concerns about the methodological quality of the smaller trial, the results of the meta-analysis also need to be interpreted with caution.

Available evidence shows that acetazolamide and furosemide does not reduce the risk for V-P shunt in infants with post hemorrhagic hydrocephalus. Diuretic therapy increases nephrocalcinosis and biochemical anomalies leading to stopping of diuretic therapy. Available evidence supports the assertion that diuretic therapy increases the risk for motor impairment or disability, however, this latter result needs to be taken with caution because change in outcome of only one patient would result in lack of significance.

Known properties of this diuretic therapy include lethargy, acid-base, water and electrolytes, renal disturbances and changes in cerebral blood flow (Cammer 2000). Therapy with acetazolamide and furosemide has been used safely in children and infants while maintaining careful attention to acid-base, fluid and electrolyte balance (Shinnar 1985; Schoeman 1991; Chaplin 1980; Huttenlocher 1965; Mercuri 1994; Birzis 1958); however, diuretic therapy was less well tolerated in infants younger than two weeks of age (Shinnar 1985). In preterm infants with idiopathic apnea of prematurity administration of a single oral dose of acetazolamide

significantly decreased pH and pCO_2 without affecting apnea density (Cordoba 1994). In preterm infants with isolated post-IVH hydrocephalus, a single dose of acetazolamide did not affect pCO_2, whereas in those with hydrocephalus and chronic lung disease, acetazolamide increased pCO_2 by a median of 2.0 kPa (range 0.6 to 3.4 kPa) (Cowan 1991). In this last paper, acetazolamide produced a large increase in cerebral blood flow velocity within minutes. Small premature infants with multiple problems including hydrocephalus and chronic lung disease may be particularly vulnerable to the effects of acetazolamide. Association of hydrocephalus and chronic lung disease is frequent in this population: supplemental oxygen was administered after trial entry to 49 out of 88 infants (56%; missing data = 5) allocated to diuretic therapy and to 55 out of 89 allocated to standard therapy (62%, missing data = 3) in the PHVD Trial Grp 1998.

AUTHORS' CONCLUSIONS

Implications for practice

Acetazolamide and furosemide therapy is neither effective (no reduction in the risk for V-P shunt) nor safe (risk for nephrocalcinosis and biochemical anomalies and borderline increased risk for motor developmental anomalies at one year) in infants with post-hemorrhagic ventricular dilatation. Thus acetazolamide and furosemide cannot be recommended for these infants.

Implications for research

In view of the lack of efficacy in reducing need for V-P shunt and in view of evidence for increased risk for motor developmental anomalies and nephrocalcinosis in the drug treated group in a large trial (PHVD Trial Grp 1998), it seems unlikely that another large trial of this therapy would receive funding, ethical approval or informed parental consent. Although the proportion of premature infants suffering IVH has declined, post-hemorrhagic hydrocephalus is still a serious complication for which we do not have a satisfactory treatment. Research must focus more on the mechanisms of hydrocephalus (Whitelaw 1999c) and radically new therapeutic approaches will have to be considered. These new treatments will first need to be evaluated in animal models of post-hemorrhagic hydrocephalus.

REFERENCES

References to studies included in this review

Libenson 1999 *{published data only}*

* Libenson MH, Kaye EM, Rosman NP, Gilmore HE. Acetazolamide and furosemide for posthemorrhagic hydrocephalus of the newborn. *Pediatric Neurology* 1999;**20**:185-91.

Stafstrom CE, Gilmore HE, Kurtin PS. Nephrocalcinosis complicating medical treatment of posthemorrhagic hydrocephalus. *Pediatric Neurology* 1992;**8**:179-82.

PHVD Trial Grp 1998 *{published data only}*

* International PHVD Drug Trial Group. International randomised controlled trial of acetazolamide and frusemide in posthaemorrhagic ventricular dilatation of infancy. *Lancet* 1998;**352**:433-40.

Kennedy CR, Ayers S, Campbell MJ, Elbourne D, Hope P, Johnson A. Randomized, controlled trial of acetazolamide and furosemide in posthemorrhagic ventricular dilatation in infancy: follow-up at 1 year. *Pediatrics* 2001;**108**:597-607.

Additional references

Birzis 1958

Birzis L, Carter CH, Maren TH. The effect of acetazolamide on CSF pressure and electrolytes in hydrocephalus. *Neurology* 1958;**8**:522-8.

Cammer 2000

Cammer WB, Brion LP. Carbonic anhydrases in nervous tissue. In: WR Chegwidden, ND Carter, YH Edwards editor(s). The carbonic anhydrases: New Horizons. Basel: Birkhäuser Verlag, 2000:475-89.

Chaplin 1980

Chaplin ER, Goldstein GW, Myerberg DZ, Hunt JV, Tooley WH. Posthemorrhagic hydrocephalus in the preterm infant. *Pediatrics* 1980;**65**:901-9.

Cordoba 1994

Cordoba E, Gerhardt T, Rojas M, Duara S, Bancalari E. Comparison of the effects of acetazolamide and aminophylline on apnea incidence and on ventilatory response to CO2 in preterm infants. *Pediatric Pulmonology* 1994;**17**:291-5.

Cowan 1991

Cowan F, Whitelaw A. Acute effects of acetazolamide on cerebral blood flow velocity and pCO2 in the newborn infant. *Acta Paediatrica Scandinavia* 1991;**80**:22-7.

Donat 1980

Donat JF. Acetazolamide-induced improvement in hydrocephalus. *Archives of Neurology* 1980;**37**:376.

du Plessis 1998

du Plessis AJ. Posthemorrhagic hydrocephalus and brain injury in the preterm infant: dilemmas in diagnosis and managment. *Seminars in Pediatric Neurology* 1998;**5**:161-79.

Huttenlocher 1965

Huttenlocher PR. Treatment of hydrocephalus with acetazolamide. *The Journal of Pediatrics* 1965;**66**:1023-30.

Mealey 1980

Mealey J Jr, Barker DT. Failure of oral acetazolamide to avert hydrocephalus in infants with meningomyeocele. *The Journal of Pediatrics* 1968;**72**:257-9.

Ment 1999

Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, Makuch RW. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. *Pediatrics* 1999;**104**:243-8.

Mercuri 1994

Mercuri E, Faundez JC, Cowan F, Dubowitz L. Acetazolamide without frusemide in the treatment of post-haemorrhagic hydrocephalus. *Acta Paediatrica* 1994;**83**:1319-21.

Schain 1969

Schain RJ. Carbonic anhydrase inhibitors in chronic infantile hydrocephalus. *American Journal of Diseases of Children* 1969;**117**:621-5.

Schoeman 1991

Schoeman J, Donald P, Van Zyl L, Keet M, Wait J. Tuberculous hydrocephalus: comparison of different treatments with regard to ICP, ventricular size and clinical outcome. *Developmental Medicine and Child Neurology* 1991;**33**:396-405.

Shinnar 1985

Shinnar S, Gammon K, Bergman EW, Epstein M, Freeman JM. Management of hydrocephalus in infancy: Use of acetazolamide and furosemide to avoid cerebrospinal fluid shunts. *Journal of Pediatrics* 1985;**107**:31-7.

Volpe 1995

Volpe JJ. Neurology of the Newborn. 3rd Edition. Philadelphia: Saunders, 1995:403-63.

Whitelaw 1995

Whitelaw A. Neonatal hydrocephalus-clinical assessment and non-surgical treatment. In: Levene MI, Lilford RJ editor(s). Fetal and neonatal neurology and neurosurgery. 2nd Edition. Edinburgh: Churchill Livingstone, 1995:645-60.

Whitelaw 1999a

Whitelaw A. Repeated lumbar or ventricular punctures for preventing disability or shunt dependence in newborn infants with intraventricular hemorrhage. *Cochrane Database of Systematic Reviews* 1999, Issue 4.

Whitelaw 1999b

Whitelaw A. Intraventricular streptokinase after intraventricular hemorrhage in newborn infants. *Cochrane Database of Systematic Reviews* 1999, Issue 4.

Whitelaw 1999c

Whitelaw A, Christie S, Pople I. Transforming growth factor beta-1: a possible signal molecule for post-haemorrhagic hydrocephalus?. *Pediatric Research* 1999;**46**:576-80.

References to other published versions of this review

Whitelaw 2001

Whitelaw A, Kennedy CR, Brion LP. Diuretic therapy for newborn infants with posthemorrhagic ventricular dilatation. *Cochrane Database of Systematic Reviews* 2001, Issue 2.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Libenson 1999

Methods	Open randomised controlled trial Blinding of randomization: unclear Blinding of treatment: no Blinding of outcome: no Complete follow-up: yes
Participants	N of randomised patients = 16 (10 in treatment group, 6 in control group) Infants with birthweights < 1500 g with IVH on ultrasound followed by i) enlargement of ventricular width to 5 mm over 2 SDs and ii) raised ICP defined as either an increase in ICP of 20 mm water or an absolute ICP exceeding 90 mm water. ICP was measured either by the Ladd fiberoptic non-invasive method or by lumbar puncture.
Interventions	i) Treatment group: Acetazolamide starting at 20 mg/kg/day iv or by mouth increasing by 10 mg/kg/day to 100 mg/kg/day together with furosemide at 1 mg/kg/day. Sodium citrate was started at 8 mEq/kg/day and adjusted to keep the serum bicarbonate > 18 mEq/L. If the posthemorrhagic hydrocephalus resolved after 3 months, acetazolamide was reduced by 25 mg/kg every 3rd day and furosemide was reduced by 0.25 mg/kg/day. ii) Control group: Serial lumbar punctures initially daily then on alternate days. CSF was removed until free flow stopped.
Outcomes	Ventriculoperitoneal shunt. Nephrocalcinosis. Death
Notes	2 of the infants in the control group were treated with acetazolamide and furosemide before being shunted. Patients recruited between November 1986 and October 1989. Results published in 1992 and 1999.

Risk of bias

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

PHVD Trial Grp 1998

Methods	Open randomised controlled trial Blinding of randomization: yes Blinding of treatment: no Blinding of outcome: no Complete follow-up: no

PHVD Trial Grp 1998 *(Continued)*

Participants	N of randomised patients = 177 (88 in treatment group, 89 in control group) Infants aged < 3 months with IVH on ultrasound followed by progressive dilatation until ventricular width was > 4 mm over the 97th centile
Interventions	i) Treatment group: Acetazolamide starting at 25 mg/kg/day increased by 25 mg/kg/day up to 100 mg/kg/day. Furosemide at 1 mg/kg/day was started. Supplements of sodium bicarbonate at 4 mol/kg/day and potassium chloride at 1 mmol/kg/day were started and adjusted to give normal acid/base and electrolyte concentrations. ii) Both groups: standard therapy, i.e. CSF removed only if there was rapid head enlargement for 2 weeks or symptomatic raised ICP.
Outcomes	Death Ventriculoperitoneal shunt Disability at 1 year Vineland social maturity scale. Motor disability was defined as motor score < 70. Global delay was defined as an overall Vineland score < 70. Sensorineural deafness requiring a hearing aid. CNS infection Nephrocalcinosis Duration of hospitalisation after trial entry. Supplemental oxygen
Notes	Randomisation was given by telephone after the child was entered.

Risk of bias

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

DATA AND ANALYSES

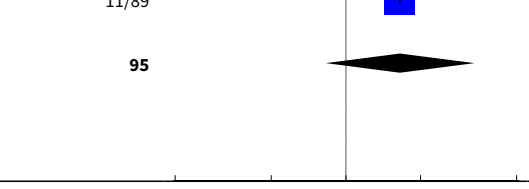
Comparison 1. Acetazolamide + furosemide vs. standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	193	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.83, 3.30]
2 Ventriculoperitoneal shunt	2	193	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.74, 1.37]
3 Death or ventriculoperitoneal shunt	2	193	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.90, 1.48]
4 CSF reservoir	1	177	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.17, 1.27]
5 Other known surgical intervention for hydrocephalus	1	177	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.44, 3.05]
6 Motor impairment or disability at one year among survivors	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.02, 1.58]

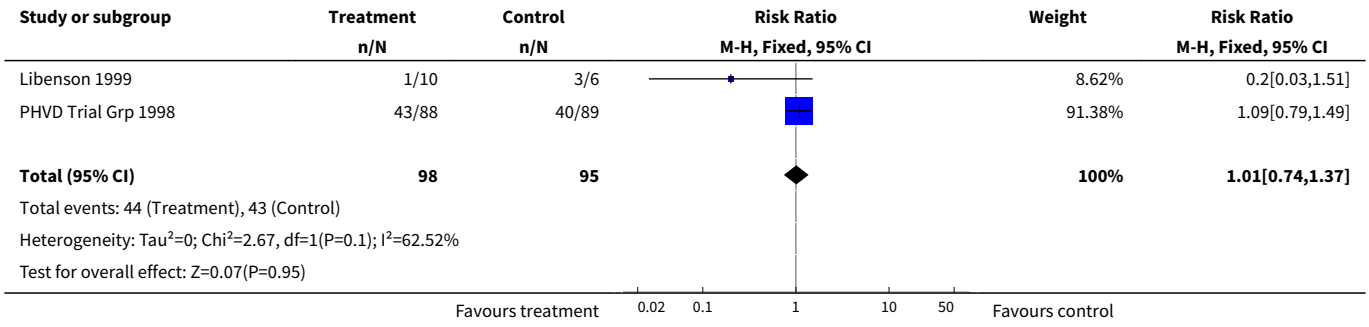
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Delay, impairment or disability at one year among survivors	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.96, 1.44]
8 Delay, impairment or disability at one year among survivors assessed	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.00, 1.49]
9 Delay, disability, motor impairment at one year or death	1	177	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [1.00, 1.39]
9.1 Parenchymal lesion present at study entry	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.18]
9.2 No parenchymal lesion at trial entry	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.05, 1.89]
10 Use of ventricular taps	1	177	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.33]
11 Use of CSF taps	1	177	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.67, 1.18]
12 CNS infection	1	177	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.57, 2.52]
13 Biochemical disorder sufficient to discontinue therapy	2	193	Risk Ratio (M-H, Fixed, 95% CI)	14.81 [3.28, 66.86]
14 Nephrocalcinosis	2	193	Risk Ratio (M-H, Fixed, 95% CI)	3.61 [1.59, 8.17]

Analysis 1.1. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 1 Death.

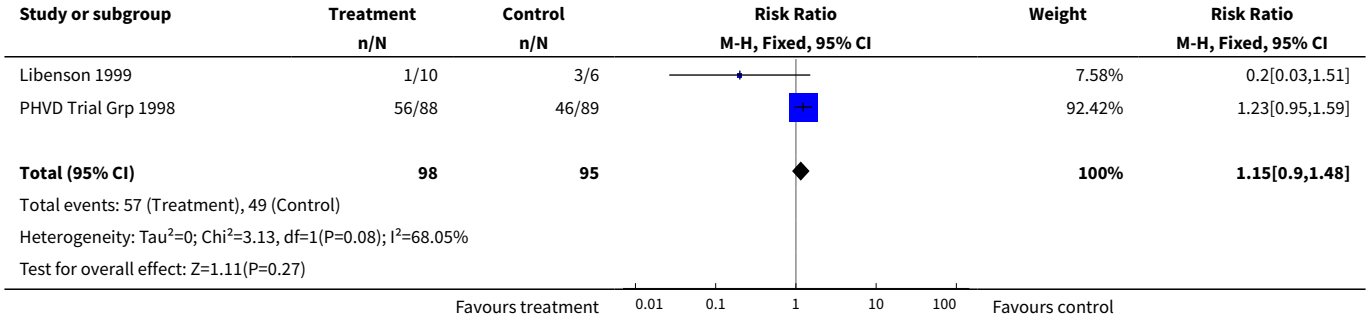
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Libenson 1999	0/10	0/6			Not estimable
PHVD Trial Grp 1998	18/88	11/89		100%	1.65[0.83,3.3]
Total (95% CI)	**98**	**95**		**100%**	**1.65[0.83,3.3]**
Total events: 18 (Treatment), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					



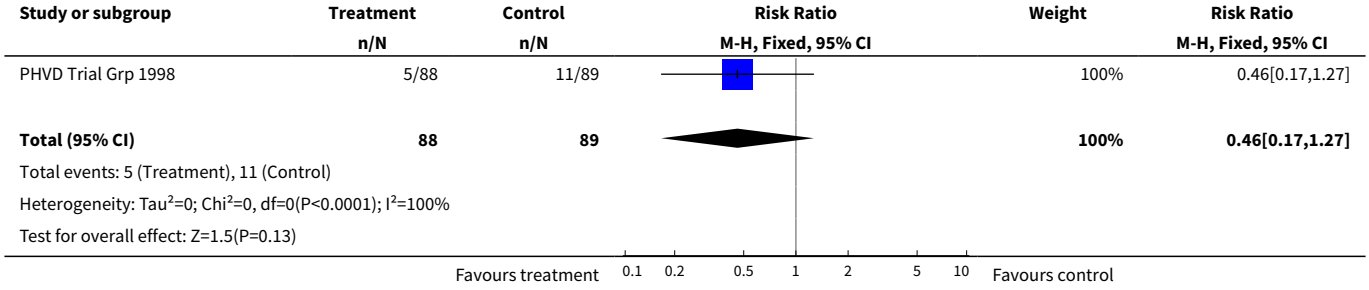
Analysis 1.2. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 2 Ventriculoperitoneal shunt.



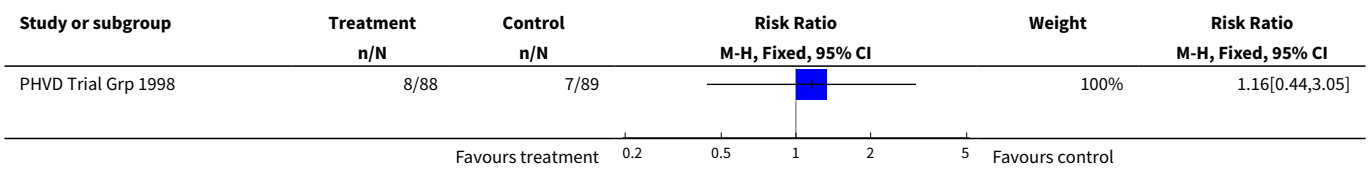
Analysis 1.3. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 3 Death or ventriculoperitoneal shunt.

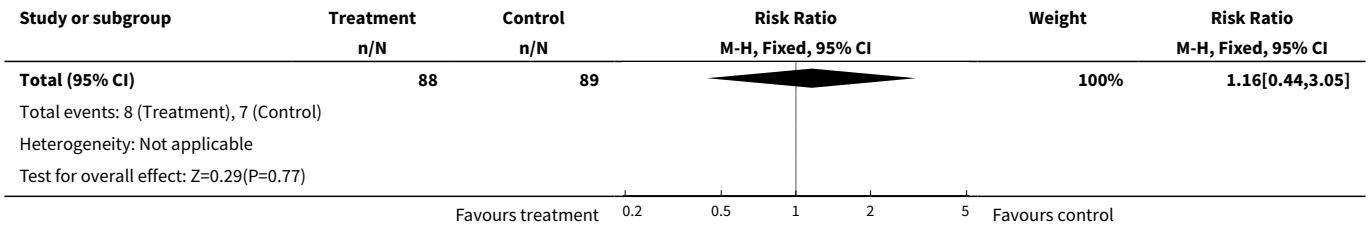


Analysis 1.4. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 4 CSF reservoir.

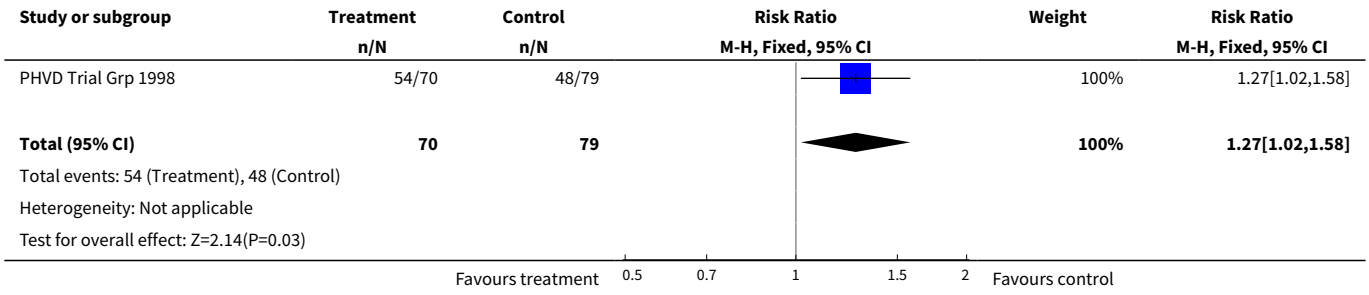


Analysis 1.5. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 5 Other known surgical intervention for hydrocephalus.

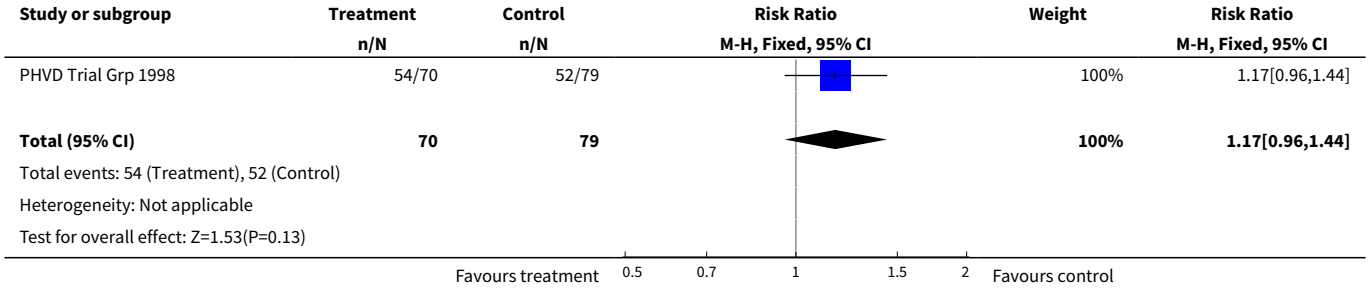




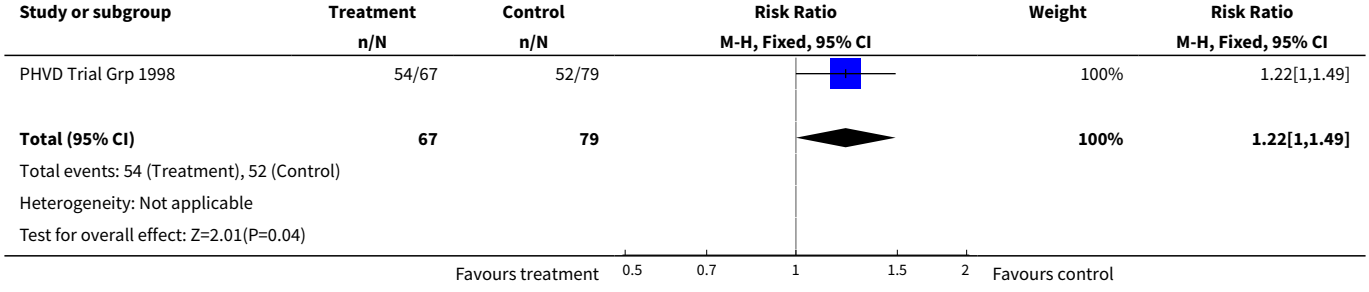
Analysis 1.6. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 6 Motor impairment or disability at one year among survivors.



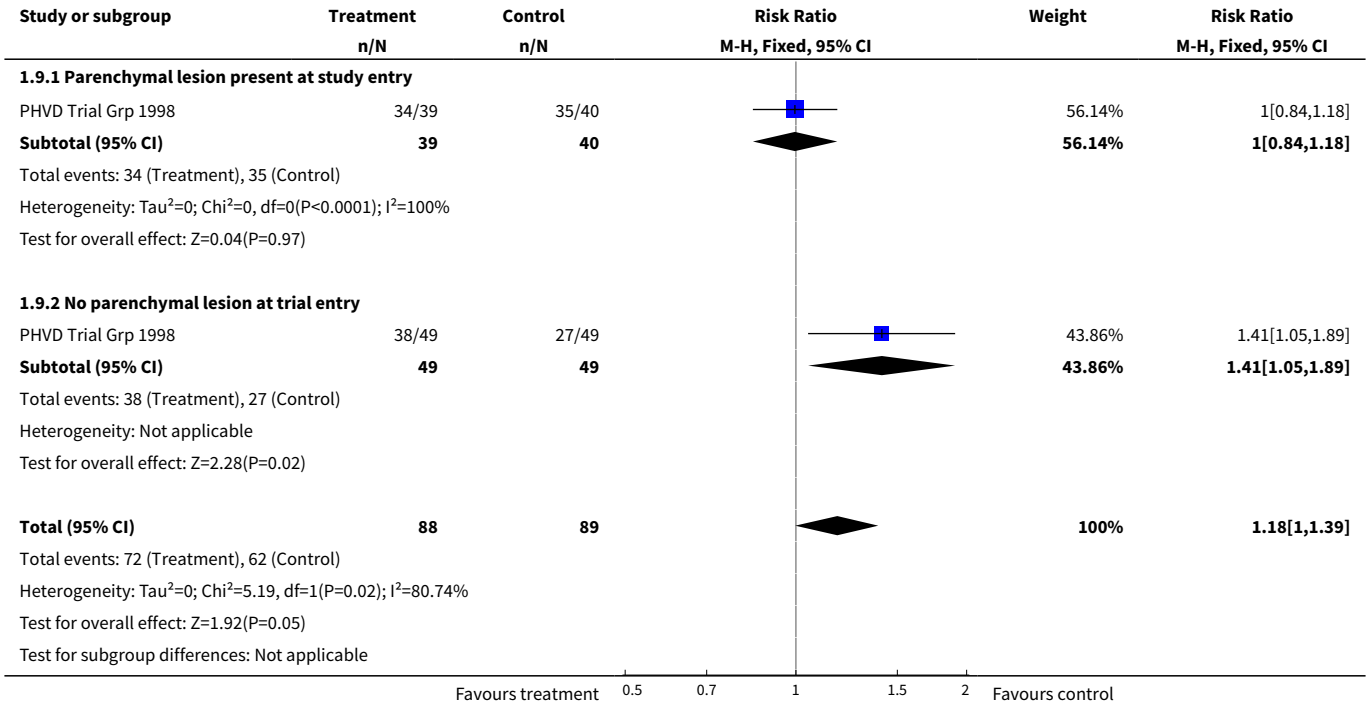
Analysis 1.7. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 7 Delay, impairment or disability at one year among survivors.



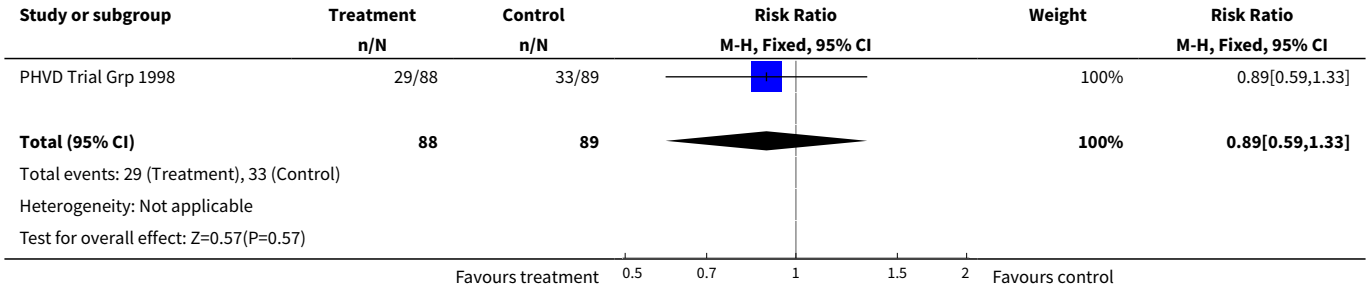
Analysis 1.8. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 8 Delay, impairment or disability at one year among survivors assessed.



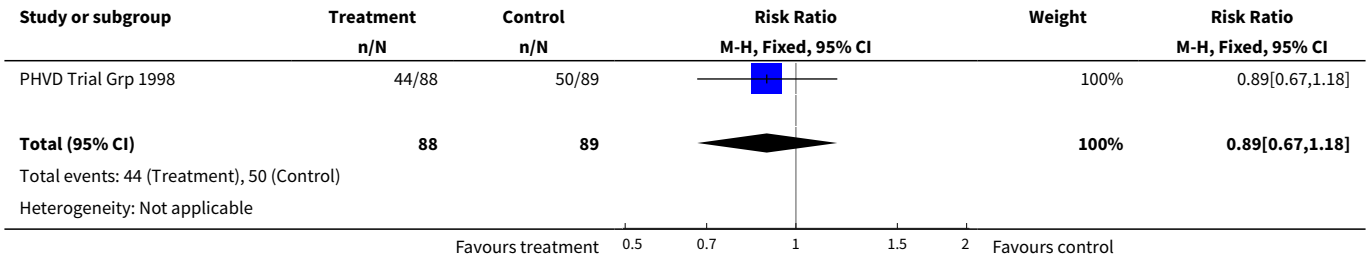
Analysis 1.9. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 9 Delay, disability, motor impairment at one year or death.

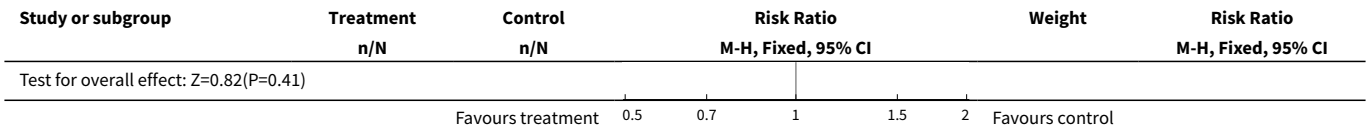


Analysis 1.10. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 10 Use of ventricular taps.

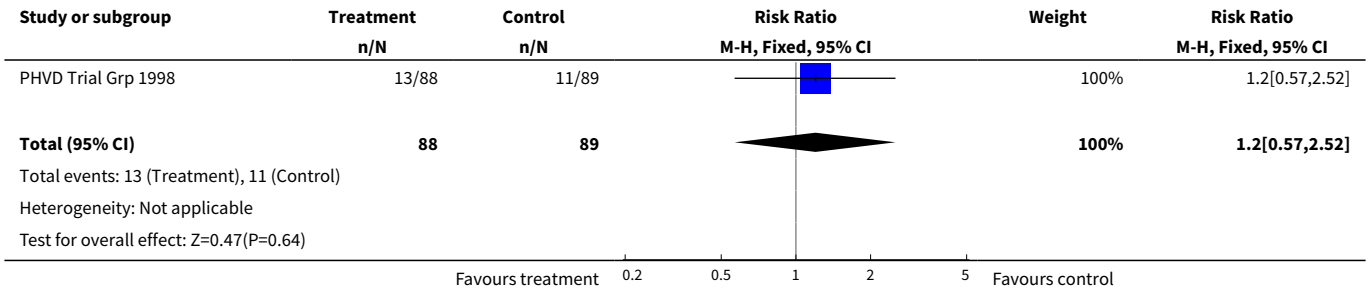


Analysis 1.11. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 11 Use of CSF taps.

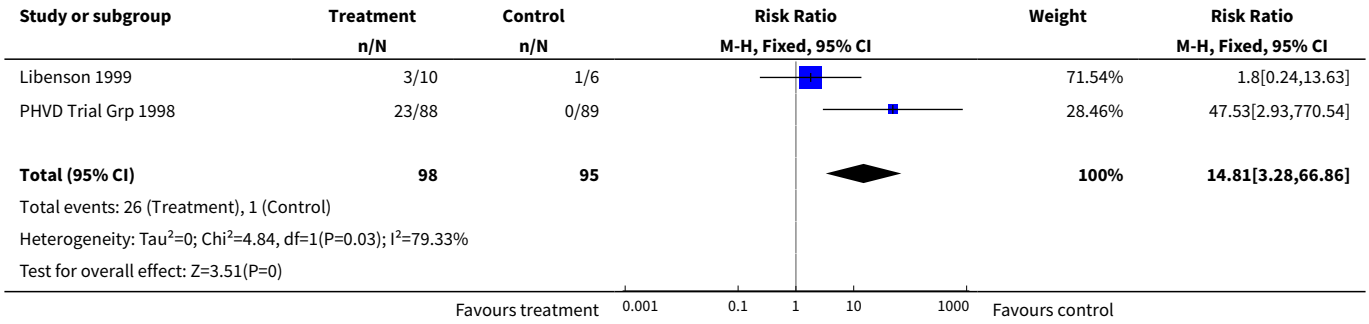




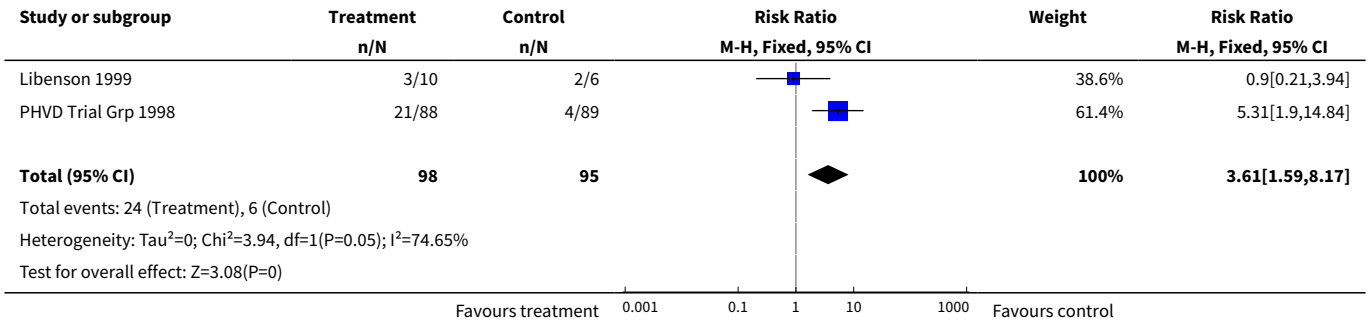
Analysis 1.12. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 12 CNS infection.



Analysis 1.13. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 13 Biochemical disorder sufficient to discontinue therapy.



Analysis 1.14. Comparison 1 Acetazolamide + furosemide vs. standard therapy, Outcome 14 Nephrocalcinosis.



WHAT'S NEW

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

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 2, 2001

Date	Event	Description
23 April 2007	New search has been performed	This review updates the existing review of "Diuretic therapy for newborn infants with posthemorrhagic ventricular dilatation" published in The Cochrane Library, Issue 2, 2001 (Whitelaw 2001). New literature searches were performed on September 29, 2003 and April 18, 2007. No additional references were identified. One of the two trials included in this review was published.
31 January 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AW carried out a literature search and wrote the first drafts of the protocol and the full review.
CK contributed unpublished data on patient outcome in the PHVD Drug Trial and contributed to drafting the full review.
LB checked the literature search independently and contributed to statistical analysis and extensive redrafting of the review.
DO carried out the update literature search independently.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- University of Bristol, UK.

External sources

- Wellcome Trust, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetazolamide [*therapeutic use]; Cerebral Hemorrhage [*complications]; Cerebral Ventricles; Dilatation, Pathologic [drug therapy] [etiology]; Diuretics [*therapeutic use]; Furosemide [*therapeutic use]; Hydrocephalus [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Ventriculoperitoneal Shunt

MeSH check words

Humans; Infant; Infant, Newborn