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Whitelaw A, Lee-Kelland R

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[Intervention Review]

Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage

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ABSTRACT

Background

Although in recent years the percentage of preterm infants who suffer intraventricular haemorrhage (IVH) has reduced, posthaemorrhagic hydrocephalus (PHH) remains a serious problem with a high rate of cerebral palsy and no evidence-based treatment. Survivors often have to undergo ventriculoperitoneal shunt (VPS) surgery, which makes the child permanently dependent on a valve and catheter system. This carries a significant risk of infection and the need for surgical revision of the shunt. Repeated removal of cerebrospinal fluid (CSF) by either lumbar puncture, ventricular puncture, or from a ventricular reservoir in preterm babies with IVH has been suggested as a treatment to reduce the risk of PHH development.

Objectives

To determine the effect of repeated cerebrospinal fluid (CSF) removal (by lumbar/ventricular puncture or removal from a ventricular reservoir) compared to conservative management, where removal is limited to when there are signs of raised intracranial pressure (ICP), on reduction in the risk of permanent shunt dependence, neurodevelopmental disability, and death in neonates with or at risk of developing posthaemorrhagic hydrocephalus (PHH).

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3), MEDLINE via PubMed (1966 to 24 March 2016), Embase (1980 to 24 March 2016), and CINAHL (1982 to 24 March 2016). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-RCTs.

Selection criteria

RCTs and quasi-RCTs that compared serial removal of CSF (via lumbar puncture, ventricular puncture, or from a ventricular reservoir) with conservative management (removing CSF only when there were symptoms of raised ICP). Trials also had to report on at least one of the specified outcomes of death, disability, or shunt insertion.

Data collection and analysis

We extracted details of the participant selection, participant allocation and the interventions. We assessed the following outcomes: VPS, death, death or shunt, disability, multiple disability, death or disability, and CSF infection. We assessed the quality of the evidence using the GRADE approach.

Main results

Four trials (five articles) met the inclusion criteria of this review; three were RCTs and one was a quasi-RCT; and included a total of 280 participants treated in neonatal intensive care units in the UK. The trials were published between 1980 and 1990. The studies were sufficiently similar regarding the research question they asked and the interventions that we could combine the trials to assess the effect of the intervention.

Meta-analysis showed that the intervention produced no significant difference when compared to conservative management for the outcomes of: placement of hydrocephalus shunt (typical risk ratio (RR) 0.96, 95% confidence interval (CI) 0.73 to 1.26; 3 trials, 233 infants; I^2 statistic = 0%; moderate quality evidence), death (RR 0.88, 95% CI 0.53 to 1.44; 4 trials, 280 infants; I^2 statistic = 0%; low quality evidence), major disability in survivors (RR 0.98, 95% CI 0.81 to 1.18; 2 trials, 141 infants; I^2 statistic = 11%; high quality evidence), multiple disability in survivors (RR 0.9, 95% CI 0.66 to 1.24; 2 trials, 141 infants; I^2 statistic = 0%; high quality evidence), death or disability (RR 0.99, 95% CI 0.86 to 1.14; 2 trials, 180 infants; I^2 statistic = 0%; high quality evidence), death or shunt (RR 0.91, 95% CI 0.75 to 1.11; 3 trials, 233 infants; I^2 statistic = 0%; moderate quality evidence), and infection of CSF presurgery (RR 1.73, 95% CI 0.53 to 5.67; 2 trials, 195 infants; low quality evidence).

We assessed the quality of the evidence as high for the outcomes of major disability, multiple disability, and disability or death. We rated the evidence for the outcomes of shunt insertion, and death or shunt insertion as of moderate quality as one included trial used an alternation method of randomisation. For the outcomes of death and infection of CSF presurgery, the quality of the evidence was low as one trial used an alternation method, the number of participants was too low to assess the objectives with sufficient precision, and there was inconsistency regarding the findings in the included trials regarding the outcome of infection of CSF presurgery.

Authors' conclusions

There was no evidence that repeated removal of CSF via lumbar puncture, ventricular puncture or from a ventricular reservoir produces any benefit over conservative management in neonates with or at risk for developing PHH in terms of reduction of disability, death, or need for placement of a permanent shunt.

PLAIN LANGUAGE SUMMARY

Repeated lumbar or ventricular taps in newborns with intraventricular haemorrhage

Review question

Cochrane researchers reviewed the evidence about the effect of removal of cerebrospinal fluid (CSF) via lumbar or ventricular puncture and draining CSF via a needle inserted into the base of the spine or into a fluid-filled cavity in the brain on improving rates of disability, death, and the need for a permanent surgical procedure in preterm infants who have had bleeding inside the cavities of the brain (intraventricular haemorrhage (IVH)).

Background

Babies that are born preterm are at risk of developing IVH. IVH can cause an excess of CSF to build up on the brain. The risk of this happening might be reduced by the removal of blood in the CSF via lumbar or ventricular taps. This might reduce the need for a permanent surgical procedure called a ventriculoperitoneal shunt (VPS). VPS is problematic as it can easily become infected and often has to be replaced or repaired, which requires an operation.

Study characteristics

We searched for trials up to 24 March 2016 that compared removing CSF via lumbar or ventricular taps in all babies at risk of developing a build-up of fluid on the brain against a conservative approach where this was only done if there was evidence that the build-up of fluid was causing an excess of pressure in the brain. We included four trials that included a total of 280 preterm infants treated in neonatal intensive care units in the UK. The trials were published between 1980 and 1990.

Key results

We found no evidence that removal of CSF by lumbar or ventricular taps reduces the need for a permanent shunt to be inserted. There was also no evidence that it reduced the risk of major disability, multiple disability, or death. There was insufficient evidence to determine if this approach can lead to an increased risk of developing an infection in the CSF.

Quality of the evidence

We assessed the outcomes of major disability, multiple disability, and disability or death as high quality evidence.

We recorded the quality of the evidence for the outcomes of shunt insertion, and death or shunt insertion as low quality evidence, as there was an issue with the random allocation method in one included trial that reported on this outcome.

For the outcomes of death and infection of CSF presurgery, the quality of the evidence was moderate due to the previously mentioned problem with allocation. In addition these studies did not have enough patients to sufficiently answer the question. In the case of the outcome infection of CSF presurgery, the results were inconsistent between the included trials.

Summary of findings for the main comparison. Repeated lumbar or ventricular punctures compared to conservative treatment in newborns with intraventricular haemorrhage

Repeated lumbar or ventricular punctures compared to conservative management for infants with intraventricular haemorrhage (IVH)

Population: preterm infants less than three months of age with either: a) IVH demonstrated by ultrasound or computed tomography (CT) scan; or b) infants with IVH followed by progressive ventricular dilatation.

Settings: neonatal intensive care units.

Intervention: serial lumbar puncture, ventricular puncture, or tapping from a subcutaneous reservoir.

Comparison: conservative management.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with conservative treatment	Risk with serial lumbar or ventricular punctures			
Hydrocephalus shunt	Study population		RR 0.96 (0.73 to 1.26)	233 (3 RCTs)	⊕⊕⊕⊖ moderate[1]
	469 per 1000	450 per 1000 (342 to 591)			
Death	Study population		RR 0.88 (0.53 to 1.44)	280 (4 RCTs)	⊕⊕⊖⊖ low[1,2]
	199 per 1000	175 per 1000 (105 to 286)			
Major disability in survivors	Study population		RR 0.98 (0.81 to 1.18)	141 (2 RCTs)	⊕⊕⊕⊕ high
	761 per 1000	746 per 1000 (617 to 898)			
Multiple disability in survivors	Study population		RR 0.90 (0.66 to 1.24)	141 (2 RCTs)	⊕⊕⊕⊕ high
	537 per 1000	484 per 1000 (355 to 666)			
Death or disability	Study population		RR 0.99 (0.86 to 1.14)	180 (2 RCTs)	⊕⊕⊕⊕ high
	814 per 1000	806 per 1000			

		(700 to 928)			
Death or shunt	Study population		RR 0.91 (0.75 to 1.11)	233 (3 RCTs)	⊕⊕⊕⊖ moderate[1]
	646 per 1000	588 per 1000 (485 to 717)			
Infection of CSF presurgery	Study population		RR 1.73 (0.53 to 5.67)	195 (2 RCTs)	⊕⊕⊖⊖ low[2,3]
	43 per 1000	74 per 1000 (23 to 241)			

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; CSF: cerebrospinal fluid; CT: computed tomography; IVH: intraventricular haemorrhage; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded by 1 as Mantovani 1980 used an alternation method for random sequence generation.
[2]Downgraded by 1 due to imprecision, which is present because the width of the CI is consistent with both important benefit and harm.
[3]Downgraded by 1 due to inconsistency between studies. Dykes 1989 reported no cases of CSF infection. Ventriculomegaly 1990 reported infection in 10/157 cases.

BACKGROUND

Description of the condition

Although many interventions can reduce the risk of intraventricular haemorrhage (IVH), it is still a common consequence of preterm birth. Posthaemorrhagic hydrocephalus (PHH) is the most serious complication of IVH.

PHH is thought to result from the deposition of extracellular matrix proteins, such as fibronectin and laminin, in the channels necessary for circulation and reabsorption of cerebrospinal fluid (CSF) (Cherian 2004). Ventriculoperitoneal shunt (VPS) surgery is the conventional approach for treatment of established hydrocephalus. However, treatment of PHH is more difficult than other types of hydrocephalus because the large amount of blood in the ventricles, combined with the small size and instability of the patient, make an early VPS operation a very high risk procedure. In one series of 19 infants with PHH requiring shunt surgery, there were 29 shunt blockages and 12 infections (Hislop 1988). The risk of shunt blockage was increased if the CSF protein was over 1.5 g/L at shunt insertion. In a series of 36 infants shunt-operated for PHH, shunt blockage and infection occurred only in those operated on before 35 days of age (Taylor 2001). Repeated shunt revisions and infection are associated with worsening of neurological outcome (Tuli 2003). Furthermore, these infants are nearly always shunt-dependent for the rest of their lives and will require several later operations even if no other problems occur. Thus it would be advantageous if a treatment could reduce the risk of permanent hydrocephalus after established IVH.

Neurodevelopmental outcome is poor in infants with PHH. Although this is due in part to 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 (ICP) with periventricular oedema and distortion of the developing axonal pathways and their myelination. It is also likely that some of the dysfunction is the result of injury from free radicals and inflammation as free iron, a source of free radicals, has been demonstrated in the CSF of infants with PHH (Savman 2001), as have pro-inflammatory cytokines (Sävman 2002).

A treatment for PHH remains elusive. A Cochrane Review that assessed drug treatment for reduction of CSF production (acetazolamide and furosemide) found no evidence of benefit (Whitelaw 2001b).

The Drainage, Irrigation and Fibrinolytic therapy (DRIFT) trial was stopped before completion due to an increase in secondary intraventricular bleeding in participants. However, DRIFT reduced severe cognitive disability, severe disability, and overall death in survivors (Whitelaw 2010). A 10-year follow-up study is currently in place.

There is now a separate Cochrane Review on intraventricular streptokinase after IVH (Whitelaw 2007). The available evidence suggests that fibrinolytic intervention relatively late (two to four weeks after the IVH) is ineffective.

Further randomised control trials (RCTs) are needed to evaluate the timing of external ventricular drainage, as a retrospective review has suggested that early (less than 25 days) placement is associated with improved cognition (Bassan 2012). Endoscopic choroid plexus cauterisation and ventriculosubgaleal shunt insertion also require investigation as potential treatments.

Description of the intervention

Lumbar punctures (also known as a spinal tap) remove CSF via insertion of a needle into the lower back to drain CSF from the lumbar cistern. In a ventricular puncture the CSF is externally drained directly from the lateral ventricles via a needle. If a ventricular reservoir has been placed (this consists of a catheter leading to the lateral ventricle attached to a reservoir implanted under the scalp), CSF can also be tapped directly from the reservoir without the need for a direct ventricular puncture.

A ventricular or lumbar puncture is indicated in the context of PHH if there is evidence of significant raised ICP. Evidence may include: direct measurement of a CSF pressure over 12 mmHg, decreasing diastolic velocities on cerebral artery Doppler waveforms, deteriorating sensory evoked potentials, and clinical signs of raised ICP. Recently amplitude integrated electroencephalography (aEEG) has been identified as another method that may indicate that increasing pressure is affecting the functioning of the brain. The aEEG trace is described as becoming more discontinuous, followed by a return to a normal pattern after drainage (Olischar 2009; Klebermass-Schrehof 2013).

In this Cochrane Review we assessed the use of serial lumbar ventricular punctures in infants with, or at risk of, developing PHH but without any signs of raised ICP. We compared this to conservative management, wherein the use of lumbar or ventricular punctures was restricted to where there are signs of raised ICP only.

How the intervention might work

It has been postulated that removal of bloody CSF by serial lumbar or ventricular punctures might improve the prognosis of infants at risk of, or actually developing, PHH. The physical removal of CSF that contains blood and protein might reduce the inflammatory reaction, decrease deposition of extracellular matrix proteins, and re-establish normal CSF drainage. The infants might benefit in terms of better neurological function because of reduced ICP and less periventricular oedema. Removal of blood and protein might also reduce the need for a permanent shunt.

Why it is important to do this review

There is a clear need to reduce mortality and the burden of disability that arises from this condition. Several trials have attempted to answer the question of whether this approach could produce a clear benefit. A systematic review is required to assess the evidence.

This is an update of the original Cochrane Review, Whitelaw 2001a, in which randomised trials failed to show any benefit of routine removal of CSF via lumbar or ventricular puncture. However, since then a retrospective review of infants with PHH in the Netherlands indicated that infants who received a lumbar puncture or subcutaneous ventricular reservoir “early” (defined as infants who at the decision to remove CSF via lumbar or ventricular puncture had a ventricular width above the 97th centile but below the 97th centile + 4 mm or 2 standard deviations of the mean (Levene 1981)) were less likely to receive a shunt when compared to

the "late" group (odds ratio 0.22, 95% confidence interval (CI) 0.08 to 0.62) (de Vries 2002).

This has led to some questioning whether a benefit could be found if CSF removal for infants where there was rapidly increasing ventricular size was completed at an earlier time than is currently used. Subsequently, a RCT that prospectively compares low threshold versus high threshold intervention has started (ISRCTN43171322).

Given the renewed interest in this topic, it was necessary to revise the review and confirm that the assessment of the literature was current and the conclusions still valid.

OBJECTIVES

To determine the effect of repeated cerebrospinal fluid (CSF) removal (by lumbar/ventricular puncture or removal from a ventricular reservoir), compared to conservative management, where removal is limited to when there are signs of raised intracranial pressure (ICP), on reduction in the risk of permanent shunt dependence, neurodevelopmental disability, and death in neonates with or at risk of developing posthaemorrhagic hydrocephalus (PHH).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs that compared repeated CSF removal to standard (control) treatment in newborn infants with intraventricular haemorrhage (IVH) or early posthaemorrhagic hydrocephalus (PHH) were to be identified. We defined RCTs as studies that assigned the participants prospectively to one of two (or more) forms of healthcare by using random allocation. A quasi-RCT was one in which it appeared that the study participants were assigned prospectively to one of two (or more) alternative forms of healthcare by using some quasi-random method of allocation (such as by alternation, date of birth, or case record number). We excluded trials that did not have a simultaneous control group (for example, those without historical controls).

Types of participants

We included infants younger than three months of age who had either of the following.

- IVH demonstrated by ultrasound or computed tomography (CT) scan (at risk of PHH).
- IVH followed by progressive ventricular dilatation.

We excluded infants who had other causes of hydrocephalus (for example, infection, congenital aqueduct stenosis, and tumour).

Types of interventions

Repeated removal of CSF by repeated lumbar puncture, ventricular punctures, or from a subcutaneous ventricular reservoir.

Types of outcome measures

Primary outcomes

- Placement of a hydrocephalus shunt.
- Death prior to 12-month follow-up.
- Major disability in survivors.
- Multiple disability in survivors.
- Death or disability.
- Death or shunt.

Secondary outcomes

- Infection of CSF presurgery.

Search methods for identification of studies

Electronic searches

For the search update in 2016, we used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register). We conducted a comprehensive search that included the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3) in the Cochrane Library; MEDLINE via PubMed (1966 to 24 March 2016); Embase (1980 to 24 March 2016); and CINAHL (1982 to 24 March 2016). See Appendix 1 for the full search strategy. We did not apply any language restrictions.

We searched the following clinical trials registries for ongoing or recently completed trials: ClinicalTrials.gov (clinicaltrials.gov); the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.whoint/ictrp/search/en/); the National Institute for Health Research (NIHR) (www.ukctg.nihr.ac.uk/default.aspx); and the ISRCTN Registry (www.isrctn.com/).

Searching other resources

We searched for conference abstracts of the Pediatric Academic Societies (PAS) and the European Society for Paediatric Research (ESPR) from 2009 to 2015, and we searched the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-RCTs.

Previous version of this review

For the previous version of this Cochrane Review, Whitelaw 2001a, we handsearched the following journals from January 1976 (when CT scanning of neonates started) to October 2000: Pediatrics; Journal of Pediatrics; Archives of Disease in Childhood; Pediatric Research; Developmental Medicine and Child Neurology; Acta Paediatrica Scandinavica; European Journal of Pediatrics; Neuropediatrics; Neurosurgery; Journal of Neurosurgery; Pediatric Neurosurgery; Biology of the Neonate; New England Journal of Medicine; The Lancet; and the British Medical Journal (BMJ). We searched MEDLINE (via PubMed), CINAHL, Embase, and the Cochrane Library from 1976 to 2000, and updated the searches in April 2009 using the following MeSH terms: intraventricular haemorrhage, hydrocephalus, lumbar puncture, newborn infant. We handsearched the following conference proceedings from 1988 to October 2000: the Proceedings of the Society for Pediatric Research; the European Society for Pediatric Research; the Neonatal Society; and the British Paediatric Association.

Data collection and analysis

Selection of studies

We employed the standard methods of Cochrane Neonatal. We screened the literature search results by title and abstract, and coded them as either 'retrieve' or 'do not retrieve'. Articles in the 'do not retrieve' category did not fulfil the inclusion criteria. Articles in the 'retrieve' category were articles that either potentially fulfilled the inclusion criteria or articles that we were unsure whether they fulfilled the inclusion criteria or not. We retrieved the full-text articles of all studies in the 'retrieve' category and assessed them against the inclusion criteria. We listed all studies that we excluded after full-text assessment and their reasons for exclusion in the 'Characteristics of excluded studies' table. We presented the study selection process in a PRISMA diagram.

Data extraction and management

One review author (RLK) extracted, assessed, and coded all data from the included trials. The second review author, AW, repeated this process to check consistency. We resolved disagreements by discussion. We entered the data into Review Manager 5 (RevMan 5) for analysis and storage (Review Manager 2014).

We extracted data on the following: the number of participants, number of participants allocated to intervention, and primary and secondary outcomes.

We checked the inclusion criteria and therapeutic interventions of each included trial to see how they differed between trials. We examined the outcomes in each trial to see how comparable they were between studies.

We assessed the methodological quality and risk of bias of each included trial.

Assessment of risk of bias in included studies

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We excluded trials that did not have a simultaneous control group (for example, those with historical controls). If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

For this review update, we assessed the included studies using the following key domains for assessing risk of bias (Higgins 2011).

Random sequence generation

- Low risk of bias: if, for example, the trial used a table of random numbers or computer-generated random numbers.
- High risk of bias: if, for example, the trial used alternation, date of birth, day of the week, or case record number.
- Unclear risk of bias: if insufficient information was provided.

Allocation concealment

- Low risk of bias: if, for example, numbered or coded identical containers were administered sequentially, by an onsite computer system that could only be accessed after entering the characteristics of an enrolled participant; or serially numbered, opaque, sealed envelopes, were used; or sealed envelopes that were not sequentially numbered or opaque were used.
- High risk of bias: if, for example, the trial used an open table of random numbers.
- Unclear risk of bias: if insufficient information was provided.

Blinding

Treatment by removal of CSF through lumbar puncture, ventricular puncture, or from a ventricular reservoir cannot be done 'blind' by the neonatologist but the assessment of outcome could be carried out by individuals blinded to early treatment allocation.

- Low risk of bias: if there was adequate blinding of outcome assessors to treatment allocation.
- High risk of bias: if there was no blinding.
- Unclear risk of bias: if insufficient information was provided.

Incomplete outcome data

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether the study reported attrition and exclusions, the number of participants included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where the trial authors provided sufficient information, we re-included missing data in the analyses. We categorised the methods as follows.

- Low risk of bias: no missing data or the proportion of missing data compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate.
- High risk of bias: when the proportion of missing data compared with observed event risk was large enough to induce clinically relevant bias in the intervention effect estimate.
- Unclear risk of bias: if insufficient information was provided.

Selective reporting

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as follows.

- Low risk: it was clear that the study authors reported all of the study's prespecified outcomes and all expected outcomes of interest to the review.
- High risk: not all the study's prespecified outcomes were reported, one or more reported primary outcomes were not prespecified, outcomes of interest were reported incompletely and so we could not use them; or the study failed to include results of a key outcome that we would have expected to have been reported.
- Unclear risk: insufficient information is provided.

Other sources of bias

Any other source of bias identified but not part of the previous headings.

Measures of treatment effect

We performed statistical analyses using RevMan 5 (Review Manager 2014). We analysed categorical data using risk ration (RR), risk difference (RD), and the number needed to treat for an additional beneficial outcome (NNTB) for outcomes 1.1 to 1.6, and number needed to treat for an additional harmful outcome (NNTH) for outcome 1.7. For continuous data, we analysed these using weighted mean difference (WMD) values. We reported the 95% confidence interval (CI) on all estimates.

Unit of analysis issues

We made a consideration if an included trial randomised groups of individuals together or if there were repeated observations for the same outcome. In this review we required that the number of observations matched the number of randomised participants.

Dealing with missing data

Where data was missing we attempted to contact the study authors for the original data.

Where the trial authors reported or supplied sufficient information, we re-included missing data in the analyses. When we were unable to obtain this data, we stated this.

Assessment of heterogeneity

We examined heterogeneity between included trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If noted, we explored the possible causes of statistical heterogeneity using prespecified subgroup analysis (for example, differences in study quality, participants, intervention regimens, or outcome assessments).

Assessment of reporting biases

We tried to obtain the study protocols of all included studies to compare outcomes reported in the protocol versus those reported in the findings for each of the included studies.

When we suspected reporting bias, we intended to contact study authors to ask them to provide missing outcome data. When this was not possible and we suspected that missing data might introduce serious bias, we intended to explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis.

Data synthesis

We constructed 2 x 2 tables for each trial for each important outcome, and risk ratio and risk difference with 95% CIs.

We performed meta-analysis using RevMan 5 (Review Manager 2014). For estimates of typical risk ratio and risk difference, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. We performed all meta-analyses using a fixed-effect model.

Quality of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: insertion of hydrocephalus shunt, death, presence of major disability in survivors, presence of multiple disability in survivors, death or disability, and death or shunt.

Two review authors independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro Guideline Development Tool (GDT) to create a 'Summary of findings' table to report the quality of the evidence (GRADEpro GDT 2014).

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

No subgroup analysis was undertaken as part of the review. No subset of participants (i.e. males or females) or studies (i.e. by geographical location) were identified before the review as being heterogenous enough to require a subgroup analysis.

Sensitivity analysis

A sensitivity analysis was not undertaken as the outcome measures of the review were thought to be clearly objective and non-contentious.

A sensitivity analysis could be performed if missing data was identified during the review and thought sufficient enough to influence the overall assessment of outcomes.

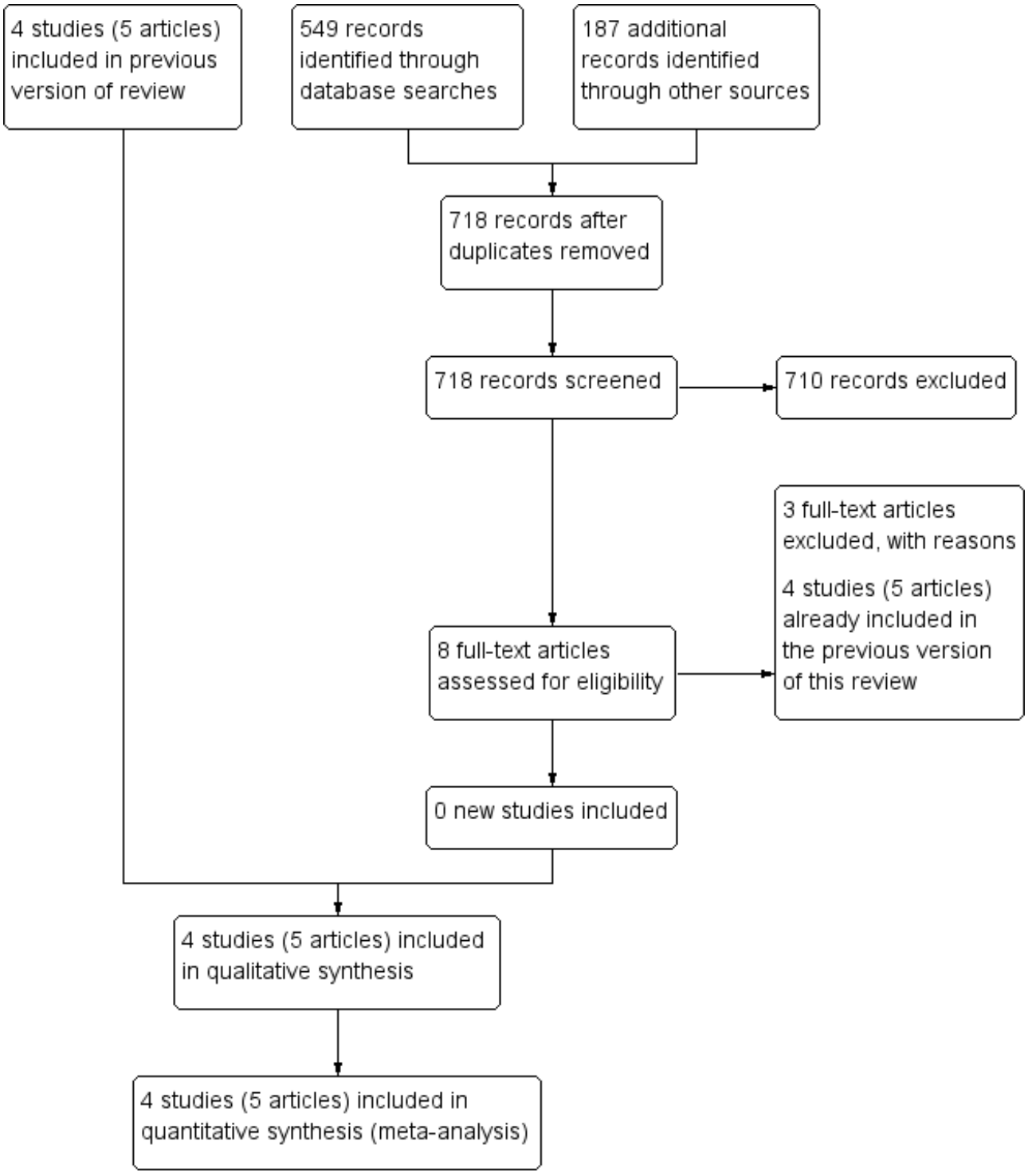
RESULTS

Description of studies

Results of the search

The previous version of this review, Whitelaw 2001a, included four trials (reported in five articles). For this Cochrane Review update, we updated the literature searches without date limit as the search terms were expanded. The searched yielded 771 results, but we did not identify any new studies that satisfied the inclusion criteria of the review (Figure 1). Therefore this Cochrane Review included four trials including 280 preterm infants treated in neonatal intensive care units in the UK. The trials were published between 1980 and 1990.

Figure 1. Study flow diagram: review update



Included studies

See the 'Characteristics of included studies' table.

An important issue is the heterogeneity of the populations or intervention, or both, in the included trials. Two trials, Mantovani 1980 and Anwar 1985, enrolled infants with IVH and examined the effect of repeated lumbar puncture in preventing the development of permanent hydrocephalus (as defined by ventriculoperitoneal shunt (VPS) placement). Two trials enrolled neonates with IVH who then went on to show progressive ventricular dilatation (Dykes 1989; Ventriculomegaly 1990). They examined the effect of lumbar punctures (Dykes 1989), or lumbar punctures or ventricular punctures (Ventriculomegaly 1990). The first approach is non-selective and allows earlier intervention (which might, in theory, offer a better chance of success). The second approach is selective but still means that some babies are treated who would have

resolved without shunting anyway. The second approach usually means later treatment because one has to wait and see which IVH infants will show progressive dilatation. A further point is that Ventriculomegaly 1990 used ventricular as well as lumbar puncture to achieve CSF drainage, whereas the other three included trials used only lumbar puncture. Larger volumes of cerebrospinal fluid (CSF) could be taken each time by ventricular puncture than by lumbar puncture but the potential for trauma and infection in the brain is probably greater by the ventricular route. All four included trials tackled the same question: does repeated removal of CSF reduce the risk of hydrocephalus? All four trials attempted in their interventions to drain as much CSF as was practical. For these reasons, we have examined them.

In Dykes 1989, paediatric neurologists and a psychologist assessed developmental outcome at different ages. The study authors did not state whether or not these people were blinded to early treatment allocation. The study classified the children into 'major handicap' and "no major handicap". The study then subdivided those who had major handicap into those with a) 'single system disability'; and b) those with 'multiple handicaps'. We extracted the number of children a) without major disability; b) with a single disability; and c) with multiple disability.

In Ventriculomegaly 1990, one developmental paediatrician who was blinded to early treatment allocation examined virtually all the included children. Children were examined at 12-months post-term and at 30-months post-term. We extracted the number of children with single-system disability and those with multiple impairments.

Impairments, disabilities, and handicaps

The term 'handicap' may, in retrospect, have been used in rather an imprecise way and we have avoided it in the analyses. We took disability to mean a disturbance of function severe enough to prevent the child functioning at an age appropriate level. Single-system disability meant that the findings were confined to one system of the nervous system, for example, a) hemiplegia without mental retardation; or b) sensorineural hearing loss.

We interpreted the terms 'multiple handicap', 'multiple disability', or 'multiple impairments' to mean clinically significant disturbances of function in different domains of the nervous system, for example, the combination of mental retardation, spastic diplegia, cortical blindness, and epilepsy. When we calculated the figures for death or disability, we subtracted the number of infants randomised but lost to follow-up from the totals originally entered. Death or disability were mutually exclusive and thus we could aggregate them.

Update

For this review update we noted that Anwar 1985 reported the outcome as VPS or placement of ventricular reservoir. As the placement of a reservoir is a much milder outcome than a shunt we were unable to include this data for two outcomes: outcome 1.1 acquiring permanent shunt, or outcome 1.6 death or shunt. We contacted the study authors for the original data in order to obtain information on the number of infants who had only a shunt placement. However, we were unable to obtain this data.

We also combined the outcomes of death and shunt as a new outcome: outcome 1.6 death or shunt. Two trials, Ventriculomegaly 1990 and Anwar 1985, did not report on the breakdown of data to make this analysis in the paper, i.e. they did not provide the number of VPS placements that also died. For Ventriculomegaly 1990 we were able to access the original data to make the new analysis. For Anwar 1985 we contacted the original authors but were unable to obtain the original data. As such, we excluded Anwar 1985 from the analysis of outcome 1.6.

Finally, we added a new outcome: outcome 1.7 presence of CSF infection before surgery. CSF infection (meningitis/ventriculitis) is a serious adverse outcome and repeated lumbar or ventricular punctures in preterm infants carries a theoretical risk of introducing infection. Two trials, Dykes 1989 and Ventriculomegaly 1990, reported incidence of CSF infection prior to surgery and we assessed this as a secondary outcome.

Excluded studies

In this review update we assessed eight full-text articles. The previous version of this review, Whitelaw 2001a, already included four of these studies. The other three studies were ineligible based on study design (see the 'Characteristics of excluded studies' table).

Risk of bias in included studies

We assessed all included studies for risk of bias and presented the results in 'Risk of bias' tables (Figure 2; Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies

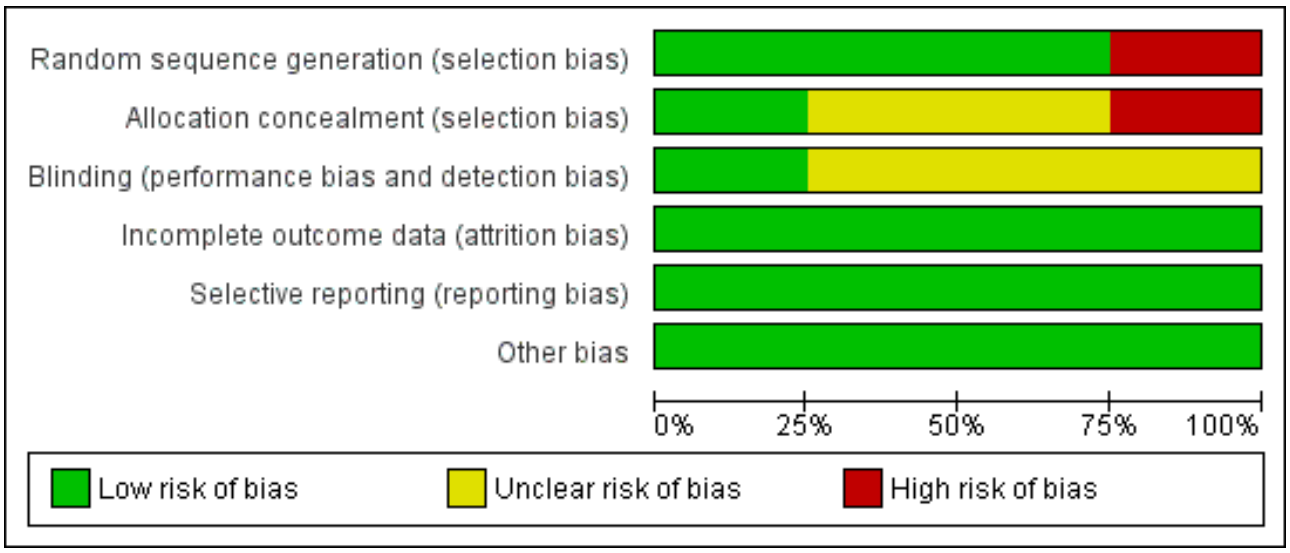
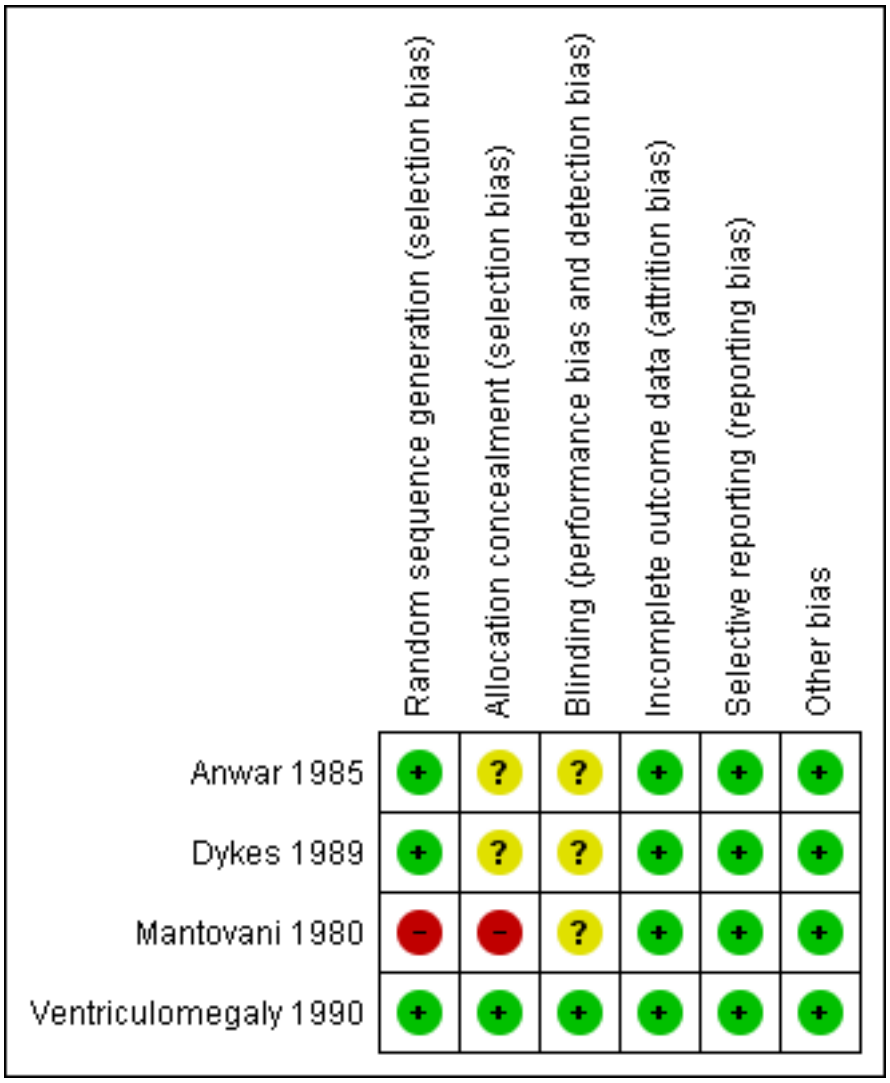


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study



Allocation

We judged Mantovani 1980 to be at high risk of selection bias, as this trial used an alternation method for random sequence generation. All other included studies randomised participants by using a low risk method (random number table or telephone method) and were at low risk.

In Anwar 1985 and Dykes 1989, it was unclear whether or not there was concealment of allocation, another potential source of selection bias. We considered these trials to be at unclear risk of bias.

Blinding

Assessors of neurodevelopmental outcome were blinded to allocation in Ventriculomegaly 1990, but it is unclear if this was the case in Dykes 1989 and Mantovani 1980. For Anwar 1985, the trial authors reported that the ultrasonographers were blinded to study classification. However, the trial defined hydrocephalus as an outcome by ultrasound and clinical signs of raised ICP. The trial authors did not give any information as to whether the assessors of the clinical signs of raised ICP were blinded to treatment allocation.

Incomplete outcome data

Across all included trials there was minimal attrition bias due to loss to follow-up.

Selective reporting

There was low risk of selective reporting as all included trials reported major outcomes of interest and there was no unexpected omission of key outcomes.

Other potential sources of bias

No other sources of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** Repeated lumbar or ventricular punctures compared to conservative treatment in newborns with intraventricular haemorrhage

The four trials included a total of 280 infants, with 157 from the Ventriculomegaly 1990 trial alone. There was no evidence of benefit

in the treatment group for any of the outcomes (see 'Summary of findings' table 1: Summary of findings for the main comparison).

Primary outcomes

Placement of a hydrocephalus shunt (outcome 1.1)

Three trials (233 participants) reported on acquiring permanent shunt (Mantovani 1980; Dykes 1989; Ventriculomegaly 1990). These trials showed no benefit to intervention (typical risk ratio 0.96, 95% confidence interval (CI) 0.73 to 1.26; typical risk difference −0.02, 95% CI −0.15 to 0.11; Analysis 1.1).

Death prior to 12-month follow-up (outcome 1.2)

All four included trials reported on death prior to 12-month follow-up with a total of 280 participants and found no benefit to intervention (typical risk ratio 0.88, 95% CI 0.53 to 1.44; typical risk difference −0.02, 95% CI −0.11 to 0.06; Analysis 1.2).

Major disability in survivors (outcome 1.3) and multiple disability in survivors (outcome 1.4)

Two trials (141 participants) reported on major disability in survivors and multiple disability in survivors (Dykes 1989; Ventriculomegaly 1990). These trials showed no benefit to the treatment group regarding major disability in survivors: typical risk ratio 0.98, 0.81 to 1.18; typical risk difference −0.02 (95% CI −0.16 to 0.12); Analysis 1.3) and multiple disability in survivors (typical risk ratio 0.90, 95% CI 0.66 to 1.24; typical risk difference −0.05, 95% CI −0.21 to 0.11; Analysis 1.4).

Death or disability (outcome 1.5)

Two trial (180 participants) reported on combined death or disability (Dykes 1989; Ventriculomegaly 1990). These trials showed no benefit to the treatment group (typical risk ratio 0.99, 95% CI 0.86 to 1.14; typical risk difference −0.01, 95% CI −0.12 to 0.10; Analysis 1.5).

Death or shunt (outcome 1.6)

Three trials (233 participants) reported on death or shunt (Mantovani 1980; Dykes 1989; Ventriculomegaly 1990). These trials found no benefit to the treatment group (typical risk ratio 0.91, 95% CI 0.75 to 1.11; typical risk difference −0.06, 95% CI −0.19 to 0.06; Analysis 1.6).

Secondary outcome

Infection of CSF presurgery (outcome 1.7)

Two trials (195 participants) reported on the secondary outcome of infection of CSF presurgery (Dykes 1989; Ventriculomegaly 1990). These trials found no significant difference between the treatment groups (typical risk ratio 1.73, 95% CI 0.53 to 5.67; typical risk difference 0.03, 95% CI −0.04 to 0.10; Analysis 1.7).

DISCUSSION

Summary of main results

Although it was a reasonable hypothesis that removal of protein and blood by repeated cerebrospinal fluid (CSF) removal would improve outcome in infants with intraventricular haemorrhage (IVH) but without signs of symptoms of raised intracranial pressure (ICP), meta-analysis of four included trials did not demonstrate any evidence of benefit in any of the outcome measures assessed (see 'Summary of findings' table 1: Summary of findings for the main comparison).

For the outcomes of death (Analysis 1.2) and infection of CSF presurgery (Analysis 1.7), the confidence interval (CI) for risk ratio was particularly wide: 0.88 (0.53 to 1.44) and 1.73 (0.53 to 5.67) respectively. This indicates that imprecision is present because the width of CI is consistent with both important benefit and harm. This indicates that the total sample size was insufficiently large for a precise estimate of this outcome.

For the outcome of infection of CSF presurgery (Analysis 1.7), there was inconsistency between the results of the two trials. Dykes 1989 reported no cases of CSF infection and Ventriculomegaly 1990 reported infection in 10/157 cases.

Overall completeness and applicability of evidence

For this Cochrane Review update we re-conducted the search for completeness. The included randomised controlled trials (RCTs) have outcome measures that are applicable to the review question. We found no ongoing trials that examined this review's question. However, there are ongoing trials that are comparing the timing of CSF removal in response to increasing ventricular size (ISRCTN43171322).

Quality of the evidence

Four RCTs including 208 preterm infants met the inclusion criteria of this review. We downgraded the quality of the evidence due to selection bias, namely the use of a alternation method for randomisation in one trial (Mantovani 1980). Also, it was unclear as to whether there was allocation concealment in two trials (Anwar 1985; Dykes 1989). Other sources of bias were likely to be minimal. In particular there were very low numbers of participants lost to follow-up and no evidence of selective reporting. There is some evidence that there was insufficient precision to assess the outcomes of death (Analysis 1.2) and infection of CSF presurgery (Analysis 1.7). There were inconsistent results between studies for infection of CSF presurgery (Analysis 1.7). The quality of the evidence was low for the outcomes of death and infection of CSF presurgery; moderate for the outcomes of acquiring permanent shunt, and death or acquiring permanent shunt; and high for the outcomes of major disability in survivors, multiple disability in survivors, and death or disability.

Potential biases in the review process

We were unable to identify any clear sources of bias in the review process. As stated in the declarations of interest, Professor Andrew Whitelaw was an author of one of the included trials (Ventriculomegaly 1990).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the routine use of repeated CSF removal by lumbar or ventricular puncture or from a ventricular reservoir, for infants at risk of, or actually developing, posthaemorrhagic hydrocephalus (PHH); where there are no signs of raised ICP.

Implications for research

Further research is required to ascertain the optimal timing of CSF removal in response to signs of increasing ICP.

ACKNOWLEDGEMENTS

We are very grateful to Colleen Ovelman, Managing Editor Cochrane Neonatal, for her assistance in completing this review update.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anwar 1985

Methods	Open randomised clinical trial
Participants	Preterm infants with grade 3 or 4 intraventricular haemorrhage (IVH) on ultrasound scan
Interventions	Daily lumbar puncture starting at 7 to 10 days. Cerebrospinal fluid (CSF) was drained until flow stopped. Lumbar punctures were continued until the ventricular size decreased, remained unchanged for 2 consecutive weeks, or if the infant developed hydrocephalus requiring a ventricular drain or shunt.
Outcomes	• Hydrocephalus, defined as a progressive increase in ventricular size as measured by ultrasound, in association with either signs of increased intracranial pressure (ICP) or an increase in head circumference > 2 cm/week for at least 2 weeks. • Shunt or ventricular reservoir. • Death before discharge from hospital. • Death.
Notes	This trial used a random number table for treatment allocation.

Anwar 1985 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used a random number table to allocate participants to treatment.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not give any information regarding allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial authors reported that the ultrasonographers were blinded to study classification. However, the trial defined hydrocephalus as an outcome by ultrasound and clinical signs of raised ICP. The trial authors did not give any information as to whether the assessors of the clinical signs of raised ICP were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial included almost all participants to the end of the trial.
Selective reporting (reporting bias)	Low risk	The trial authors reported on the main outcomes of hydrocephalus, death, and shunt placement. The trial did not test the neurodevelopmental outcome.
Other bias	Low risk	No other sources of bias identified

Dykes 1989

Methods	Open randomised clinical trial using random number tables
Participants	Neonates with asymptomatic severe posthaemorrhagic hydrocephalus (PHH)
Interventions	Daily lumbar punctures, taking enough CSF to lower the CSF pressure by half. Volumes ranged from 2 to 21 mL. Duration 1 to 3 weeks.
Outcomes	• Hydrocephalus management failure, defined as increasing head circumference, progressive decrease in cortical mantle (for example, occipital cortical mantle < 1 cm), signs of raised ICP. • Placement of ventriculoperitoneal shunt (VPS). • Death during follow-up. • Assessment at 3 to 6 years into no major handicap, single system disability, and multiple disability.
Notes	The trial authors did not state whether the paediatric neurologists and the psychologist were blind to early treatment allocation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used a random number table to allocate participants to treatment.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not give any information regarding allocation concealment.

Dykes 1989 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial authors did not give any information regarding whether or not the observers of outcomes (neurologists and psychologist) were blinded to treatment group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial included all children for the outcome of hydrocephalus management failure. Regarding neurodevelopmental follow-up, 1/15 children in the close observation group were lost to follow-up at 1 to 2 years. None of the 16 children in the LP group were lost to follow-up. At 3 to 6 years, 1/15 children in the close observation group and 1/16 children in the LP group were lost to follow-up. This small proportion of missing data is unlikely to have a significant bias to the outcome.
Selective reporting (reporting bias)	Low risk	The trial reported the main outcomes of death, hydrocephalus, shunt placement, and disability.
Other bias	Low risk	No other sources of bias identified

Mantovani 1980

Methods	Open clinical trial with alternation of treatment
Participants	Infants weighing less than 2000 g with grade 2 or 3 IVH on computed tomography (CT) scan
Interventions	Daily lumbar punctures starting 24 hours after diagnosis of IVH. 3 to 5 mL CSF was removed daily. Lumbar punctures were continued until the CSF was clear and protein concentration was < 180 mg/dL.
Outcomes	• Hydrocephalus was defined as 2 CT scans with progressively enlarging ventricles. • Placement of VPS. • Death before discharge from hospital.
Notes	Not true randomisation. The trial authors did not state whether or not the observers of outcomes were blinded to early treatment allocation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The trial used an alternation method to assign participants to treatment.
Allocation concealment (selection bias)	High risk	Alternation method, allocation method not concealed to researchers.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial authors did not state whether or not the outcome observers were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial authors analysed almost all participants recruited to the trial.
Selective reporting (reporting bias)	Low risk	The trial authors commented on the main outcomes of hydrocephalus, shunt placement, and death. The trial did not test neurodevelopmental outcomes.
Other bias	Low risk	No other sources of bias identified

Ventriculomegaly 1990

Methods	Open randomised multicentre clinical trial at 15 neonatal intensive care units in England, Ireland, and Switzerland. Randomisation by telephoning and registering the infant before hearing the allocation.
Participants	Neonates with IVH, with progressive increase in ventricular size and whose ventricular width had increased to 4 mm over the 97th centile.
Interventions	Repeated lumbar puncture taking as much CSF as possible, maximum 2% body weight, carried out daily or less frequently to prevent further increases in ventricular size. If not more than 2 mL of CSF could be obtained, ventricular tapping was carried out in the same way and often enough to hold the ventricular width constant.
Outcomes	• Permanent shunting if there was failure to control head size despite medical management or if repeated tapping was necessary for more than 4 weeks. • Death. • Placement of VPS. • Neurodevelopmental assessment at 12 months post-term. • Neurodevelopmental status at 30 months by a developmental paediatrician.
Notes	The developmental paediatrician that assessed the survivors at 12 and 30 months was blinded to early treatment allocation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used a telephone method to allocate participants to treatment.
Allocation concealment (selection bias)	Low risk	The trial used a telephone method to allocate participants to treatment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The developmental paediatrician that assessed survivors was blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 12 months follow-up, 3/79 children in the early tapping group and 3/78 children in the conservative group were lost to follow-up. By 30 months, a further 3 in the early tapping group and 4 in the conservative management group were lost to follow-up. This small proportion of missing data is unlikely to have significantly biased the outcome.
Selective reporting (reporting bias)	Low risk	The trial authors reported the main outcomes of interest: death, hydrocephalus, shunt placement, and disability.
Other bias	Low risk	No other sources of bias identified

Abbreviations: CT: computed tomography; ICP: intracranial pressure; IVH: intraventricular haemorrhage; PHH: posthaemorrhagic hydrocephalus; RCT: randomised controlled trial; VPS: ventriculoperitoneal shunt.

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

Study	Reason for exclusion
Kreusser 1985	Not a randomised controlled trial (RCT).
Lipscomb 1983	Not a RCT.
Papile 1980	Not a RCT.

Abbreviations: RCT: randomised controlled trial.

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

ISRCTN43171322

Trial name or title	A multicentre randomised controlled trial of low versus high threshold treatment in preterm infants with progressive posthaemorrhagic ventricular dilatation (PHVD)
Methods	The infants are randomly allocated to the low threshold group or the high threshold group. Those in the low threshold group are treated when the ventricles reach a lower size threshold compared with the high threshold group. Treatment consists of lumbar punctures, where a needle is inserted into the lower part of the spine to drain fluid. If lumbar punctures are still needed over 28 days after the first one, a shunt is inserted into the brain to drain fluid. The two groups are compared with regard to how many infants need a shunt and their brain development at two years of age.
Participants	Premature infants with: 1. A gestational age equal to or below 34 weeks 2. An intraventricular haemorrhage grade III according to Volpe (>50% of the ventricle) and grade IV haemorrhage 3. A progressive posthaemorrhagic ventricular enlargement above the 97th centile for gestational age according to Levene and a diagonal width enlargement of the frontal horn above 6 mm according to Davies
Interventions	Comparison: low threshold versus high threshold intervention. Low threshold: intervention when an increase in ventricular width according to Levene above the 97th centile towards the P97 + 4 but without crossing the >P97 + 4 and an increase in diagonal width according to Davies above 6 mm towards 10 mm, but not above 10 mm. High threshold: intervention after an increase in ventricular width according to Levene above the P97 + 4 and an increase in diagonal width according to Davies above 10 mm. Intervention: Lumbar punctures (LP; 10 ml/kg) on 2 days. Cranial ultrasound is repeated daily. If on the third day a LP is still required, a subcutaneous reservoir will be inserted. Daily 10 cc/kg will be drained in 2 taps a day. Punctures from the reservoir will be continued over the next days or weeks. The amount of CSF drained will be increased or decreased in order to reach and keep the ventricular index according to Levene <P97 and diagonal anterior horn width <6 mm. If punctures are still necessary exceeding 28 days after the first LP, a ventriculoperitoneal shunt is inserted. If the bodyweight of the infant is less than 2.5 kg, the insertion of the shunt will be postponed until the bodyweight is over 2.5 kg, if CSF drainage is still needed then.
Outcomes	Primary: Need for ventriculoperitoneal shunt Secondary: 1. Neurodevelopmental outcome on the Bayley Scales of Infant Development at 24 months corrected age, assessed by a 'blinded' developmental psychologist

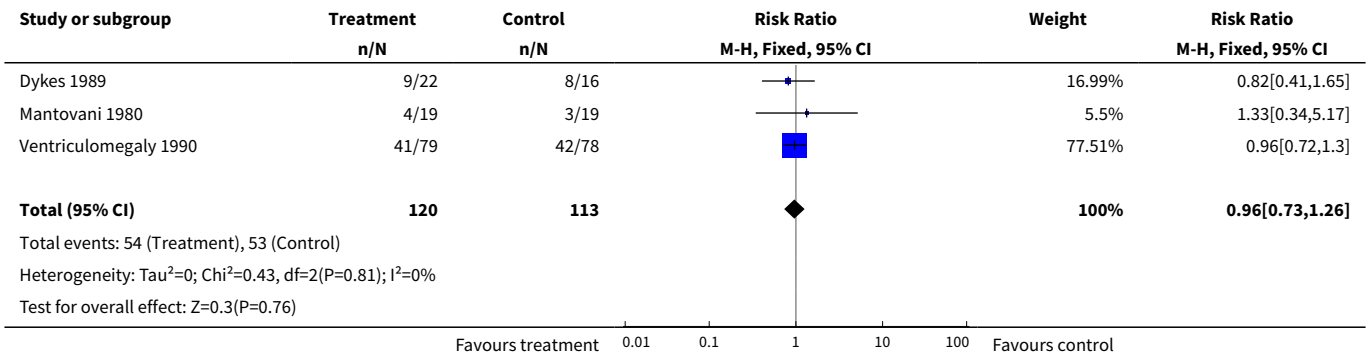
ISRCTN43171322 *(Continued)*	2. Number of (lumbar) punctures, reservoirs, reservoir dysfunctions, reservoir infections and reservoir revisions, drains, drain dysfunctions, drain infections and drain revisions
Starting date	January 27, 2006
Contact information	LS de Vries MD, PhD, l.s.devries@umcutrecht.nl
Notes	

DATA AND ANALYSES

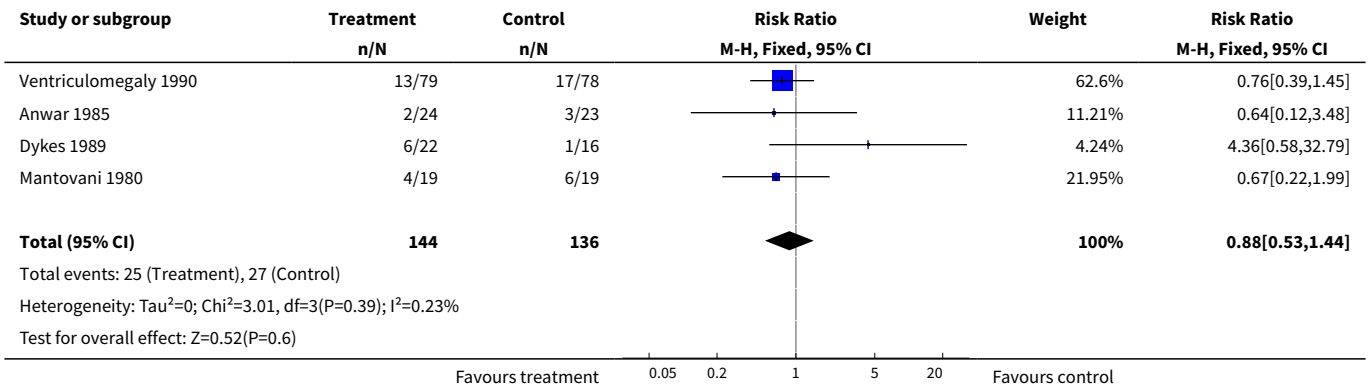
Comparison 1. Lumbar punctures or ventricular punctures versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Placement of a hydrocephalus shunt	3	233	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.26]
2 Death prior to 12-month follow-up	4	280	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.53, 1.44]
3 Major disability in survivors	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.18]
4 Multiple disability in survivors	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.66, 1.24]
5 Death or disability	2	180	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.14]
6 Death or shunt	3	233	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.11]
7 Infection of CSF presurgery	2	195	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.53, 5.67]

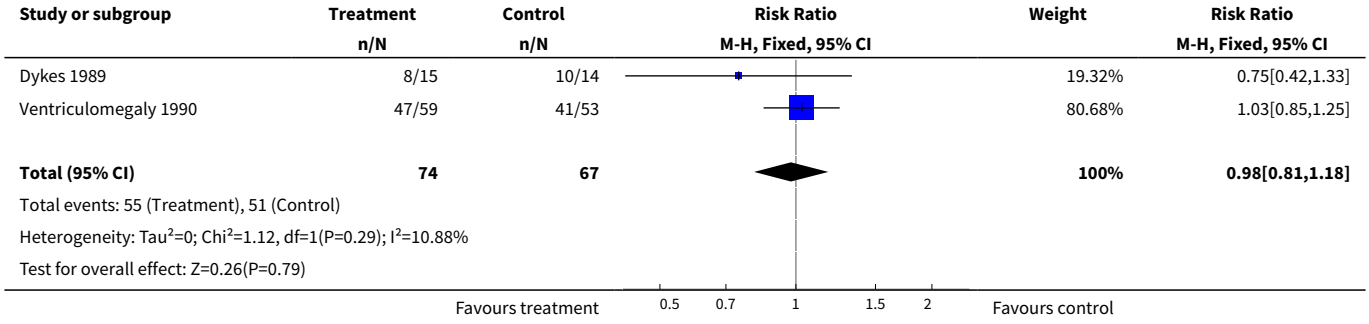
Analysis 1.1. Comparison 1 Lumbar punctures or ventricular punctures versus control, Outcome 1 Placement of a hydrocephalus shunt.



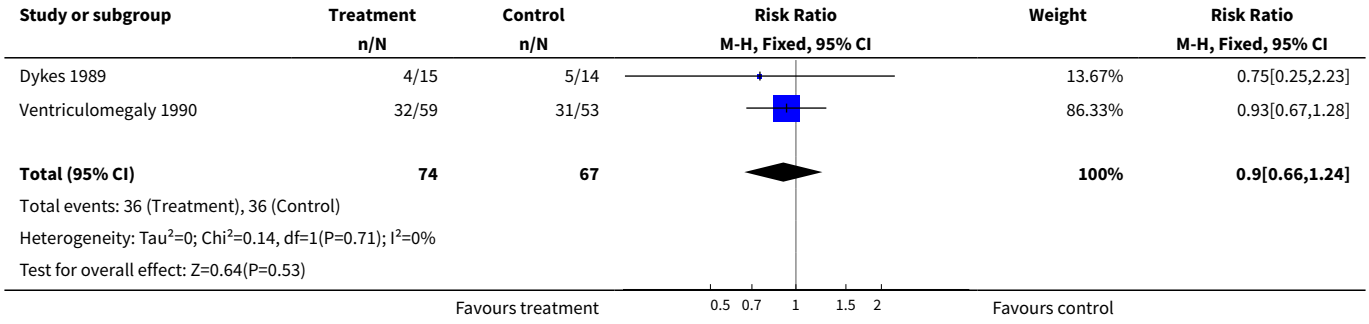
Analysis 1.2. Comparison 1 Lumbar punctures or ventricular punctures versus control, Outcome 2 Death prior to 12-month follow-up.



Analysis 1.3. Comparison 1 Lumbar punctures or ventricular punctures versus control, Outcome 3 Major disability in survivors.

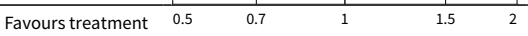


Analysis 1.4. Comparison 1 Lumbar punctures or ventricular punctures versus control, Outcome 4 Multiple disability in survivors.



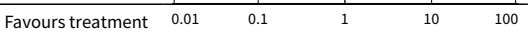
Analysis 1.5. Comparison 1 Lumbar punctures or ventricular punctures versus control, Outcome 5 Death or disability.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dykes 1989	14/21	11/15		17.66%	0.91[0.59,1.4]
Ventriculomegaly 1990	61/73	59/71		82.34%	1.01[0.87,1.16]
Total (95% CI)	**94**	**86**		**100%**	**0.99[0.86,1.14]**
Total events: 75 (Treatment), 70 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=0.16(P=0.87)					



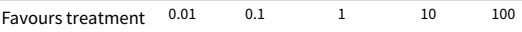
Analysis 1.6. Comparison 1 Lumbar punctures or ventricular punctures versus control, Outcome 6 Death or shunt.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dykes 1989	10/22	8/16		12.41%	0.91[0.46,1.78]
Mantovani 1980	8/19	9/19		12.06%	0.89[0.44,1.81]
Ventriculomegaly 1990	52/79	56/78		75.53%	0.92[0.74,1.13]
Total (95% CI)	**120**	**113**		**100%**	**0.91[0.75,1.11]**
Total events: 70 (Treatment), 73 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=2(P=1); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					



Analysis 1.7. Comparison 1 Lumbar punctures or ventricular punctures versus control, Outcome 7 Infection of CSF presurgery.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dykes 1989	0/22	0/16			Not estimable
Ventriculomegaly 1990	7/79	4/78		100%	1.73[0.53,5.67]
Total (95% CI)	**101**	**94**		**100%**	**1.73[0.53,5.67]**
Total events: 7 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.9(P=0.37)					



APPENDICES

Appendix 1. Search methodology

We used the following search terms ((intracranial hemorrhage OR intraventricular hemorrhage OR hydrocephalus) OR (posthaemorrhagic OR posthemorrhagic OR hemorrhag* OR haemorrhag* OR bleed* OR IVH OR intracranial OR intraventricul* OR ventricul* OR perventricul*

OR hydrocephalus OR PHVD OR PVD OR dilatati*)) AND (tap* OR puncture* OR drain* Or Lumbar* OR LP) plus the following database-specific terms:

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

WHAT'S NEW

Date	Event	Description
24 March 2016	New citation required but conclusions have not changed	We included a new analysis, but there were no other changes to the conclusions.
24 March 2016	New search has been performed	This is an update of the review 'Repeated lumbar or ventricular punctures in newborns with intraventricular hemorrhage' (Whitelaw 2001a). We reviewed and updated the search strategy, updated the review text and analyses, and included new outcomes (1.6 Death or shunt and 1.7 Infection of cerebrospinal fluid). We did not find any new eligible studies.

HISTORY

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

Date	Event	Description
28 October 2008	Amended	Converted to new review format.
2 November 2000	New search has been performed	This review updates the review "Repeated lumbar or ventricular punctures in newborns with intraventricular hemorrhage" which was published in The Cochrane Library, Disk Issue 3, 1998. Searching has not revealed any new randomised trials. There is no evidence that this intervention improves outcome.
2 November 2000	New citation required but conclusions have not changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Andrew Whitelaw (AW) performed the original literature search, extracted data, and conducted the original Cochrane Review (Whitelaw 2001a). Yolanda Montagne, former Cochrane Neonatal Trials Search Coordinator, updated the search in 2009 and AW screened articles for potential inclusion. For this update, Richard Lee-Kelland (RLK) updated the literature search, text, and analyses, and included a new analysis of outcomes 1.6 and 1.7. AW reviewed the updated search, text, and analyses.

DECLARATIONS OF INTEREST

AW is an author of one of the included trials (Ventriculomegaly 1990).
RLK has no known conflicts of interest.

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- University of Bristol, UK.

External sources

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- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the methodology and plan for the 'Summary of findings' tables and GRADE recommendations, which were not in the original protocol or previous version of the review (Whitelaw 1998; Whitelaw 2001a).

For the 2016 review update, we did not include VPS or placement of ventricular reservoir as part of outcome 1.1 acquiring permanent shunt, or outcome 1.6 death or shunt, as the placement of a reservoir is a much milder outcome than a shunt.

We combined the outcomes of death and shunt as a new outcome: outcome 1.6 death or shunt.

Finally, we added a new outcome: outcome 1.7 presence of CSF infection before surgery. CSF infection (meningitis/ventriculitis) is a serious adverse outcome and repeated lumbar or ventricular punctures in preterm infants carries a theoretical risk of introducing infection.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cerebral Ventricles; *Punctures [adverse effects]; *Spinal Puncture [adverse effects]; Cerebral Hemorrhage [complications] [mortality] [*therapy]; Conservative Treatment [adverse effects]; Controlled Clinical Trials as Topic; Hydrocephalus [etiology] [*prevention & control]; Infant, Premature; Non-Randomized Controlled Trials as Topic; Randomized Controlled Trials as Topic; Retreatment; Ventriculoperitoneal Shunt [adverse effects]

MeSH check words

Humans; Infant; Infant, Newborn