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Flow-regulated versus differential pressure-regulated shunt valves for adult patients with normal pressure hydrocephalus (Review)

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[Intervention Review]

Flow-regulated versus differential pressure-regulated shunt valves for adult patients with normal pressure hydrocephalus

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ABSTRACT

Background

Since 1965 many ventriculo-peritoneal shunt systems have been inserted worldwide to treat hydrocephalus. The most frequent indication in adults is normal pressure hydrocephalus (NPH), a condition that can be difficult to diagnose precisely. Surgical intervention with flow-regulated and differential pressure-regulated ventriculo-peritoneal shunts remains controversial. Knowledge about the benefits and harms of these interventions is limited.

Objectives

The objective of this review is to summarize the evidence on benefits and harms of flow-regulated versus differential pressure-regulated shunt valves for adult patients with NPH, based on reported findings of randomised clinical trials.

Search methods

The ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group Specialized Register; MEDLINE (from 1950) (Ovid SP); EMBASE (from 1980) (Ovid SP); CINAHL (from 1980) (EBSCOhost); PsycINFO (from 1806) (Ovid SP); LILACS (from 1982) (BIREME); ClinicalTrials.gov; Umin Japan Trial Register; WHO portal;*The Cochrane Library*'s Central Register of Controlled trials (CENTRAL); ISI Web of Knowledge Conference Proceedings; Index to Theses; and Australasian Digital Theses were searched until May 16, 2012.The search terms used were NPH, "normal pressure hydrocephalus," iNPH, idiopathic normal pressure hydrocephalus, sNPH, and "secondary normal pressure hydrocephalus."

Selection criteria

We planned to include randomised clinical trials comparing flow-regulated versus differential pressure-regulated shunt valves.

Data collection and analysis

Two authors with expert knowledge within the field independently reviewed studies for eligibility, assessed risk of bias, and extracted data.

Main results

No randomised clinical trials comparing flow-regulated versus differential pressure-regulated shunt valves were found.

Authors' conclusions

There is no evidence from randomised clinical trials indicates that flow-regulated and differential pressure-regulated shunt valves differ with regard to clinical outcome, shunt failure, or intervention risks. Randomised clinical trials are needed that take into account the large number of VP shunts implanted each year in patients with NPH.

PLAIN LANGUAGE SUMMARY

Flow-regulated versus differential pressure-regulated shunt valves for adult patients with normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) is a condition in which the fluid around the brain is not properly absorbed, adversely affecting brain function. It is often treated using a shunt, which drains the extra fluid from the brain into the peritoneal cavity in the abdomen, where the fluid can be absorbed (a ventriculo-peritoneal shunt). Currently about 5.5 ventriculo-peritoneal shunt implantations are performed per 100,000 inhabitants in industrial countries per year, even though evidence supporting shunting as treatment for NPH is poor. Approximately 30% to 40% of implanted shunts fail and have to be revised during the first year. To try to reduce the number of complications, many valve and shunt system designs have been developed. These valves can be classified, according to the mechanical design, into two main groups: differential pressure valves and flow-regulated valves. No randomised clinical trial so far has compared these two types of valve. Thus, there is no high-quality evidence indicating that flow-regulated and differential pressure-regulated shunt valves differ in efficacy or complication rates.

BACKGROUND

The first valve for implantation into humans to treat hydrocephalus was designed by Spitz and Holter in the 1950s (Nulsen 1951). Initially, the indication was mainly paediatric hydrocephalus. In 1965, the first valve was inserted in an adult patient with normal pressure hydrocephalus (Adams 1965), and since then many ventriculo-peritoneal shunt systems have been inserted worldwide to treat hydrocephalus in both children and adults. The most frequent indication in adults is normal pressure hydrocephalus (NPH). More recent publications estimate an incidence of VP shunt implantations of 5.5 per 100,000 inhabitants in industrial countries per year (Brean 2008), mainly for patients with NPH (Wu 2007), even though the surgical intervention remains controversial. So far, only one randomised trial has examined the effect of shunt surgery versus no shunt in NPH (Tisell 2011). This trial was very small and entailed a high risk of both type I errors and type II errors (n = 14 participants) and only found a significant difference between the two intervention groups at three months follow-up regarding psychometric performance in favour of shunt-treated participants. In practice, there is no consensus about how to identify patients who may benefit from surgery (Klassen 2011).

The probability of the outcome 'shunt failure', defined as requiring surgical revision of the shunting device (as the result of obstruction, disconnection, infection, or overdrainage), is approximately 30% to 40% during the first year after implantation for all types of indications and across patient ages (Reddy 2011; Sotelo 2005). To overcome this high proportion of complications and to improve outcomes, a variety of valve and shunt system designs have evolved over the past 30 years. Valves can be classified, according to mechanical design, into two main groups: differential pressure- and flow-regulated valves. The large number of shunts implanted and the high proportion of associated complications have prompted many publications on the subject of shunt failure. Previous multicentre randomised clinical trials have indicated that the valve design does not alter the outcome or shunt failure rate in paediatric hydrocephalus (Drake 1998).

It seems both necessary and feasible to systematically review the evidence on the relationship between valve mechanism and clinical outcome, including shunt failure rate, in adult patients with NPH.

Description of the condition

The cerebrospinal fluid, which surrounds the brain, is contained within a compartment called the *subarachnoid space*. The fluid is continually produced by the choroid plexus at a rate of approximately 0.3 ml per minute, with a total production of 450 to 700 ml a day. Approximately 150 ml is present in the subarachnoid space at any one time. From blood vessels lying in the cerebral ventricles (cavities within the brain), the cerebrospinal fluid flows through the ventricles and then over the surface of the brain, where it is finally reabsorbed into the veins through a complex and not fully understandable mechanism that involves tiny projections of the arachnoid into the veins, known as *arachnoid granulations*, and possibly molecular water channels (aqua porins) (Skjolding 2010a).

NPH is defined by a clinical triad of dementia, gait difficulties, and urinary urge incontinence coexisting with ventriculomegaly on a relevant radiological examination, such as computed tomography or magnetic resonance scan, and demonstrating ventricular enlargement disproportionate to the degree of cerebral atrophy. Other possible causes of dementia must be excluded, including the finding of an alternative neurological or medical condition or the presence of obstructive hydrocephalus (Relkin 2005). No test or imaging modality is pathognomonic for NPH, so the NPH diagnosis is not always easy.

In NPH failure of absorption of cerebrospinal fluid occurs, which has been demonstrated in the superior sagittal sinus of patients with idiopathic NPH (Bateman 2000). When NPH occurs after haemorrhage, infection, or other pathologies in the subarachnoid space, it is defined as secondary NPH. In idiopathic NPH, there is no known underlying cause. Both secondary NPH and idiopathic NPH are characterised by failure of absorption of cerebrospinal fluid. It is thought that this causes a gradual pressure gradient to slowly build up between the ventricles and the brain surface, resulting in a final new steady state in which cerebrospinal fluid formation is diminished, and the pressure is set at a slightly elevated or upper normal level. This resulting condition is thought to cause damage to nerve cells and tracts in the brain.

Description of the intervention

The mechanical function of valves in hydrocephalus shunts is defined on the basis of the flow control or differential pressure working principle.

Flow control valves are designed to keep a constant flow of cerebrospinal fluid throughout the shunt system despite physiological changes in intracranial pressure. This means that a drop in downstream or lower-end pressure when standing up should not result in increased cerebrospinal fluid flow. Flow should also be constant during physiological increases in intracranial pressure, for example, during Valsalva's manoeuvre or sneezing. The mechanical principle of this type of valve is thus aimed at removing the risk of overdrainage and 'siphoning'. This valve type contains a security overflow mechanism that allows cerebrospinal fluid flow to increase if intracranial pressure increases above acceptable levels, ensuring that intracranial pressure cannot become dangerously high.

Differential pressure valves open when the pressure difference between the front or upper end and the back or lower end of the closing mechanism exceeds its mechanical resistance; this is known as *valve opening pressure*. Differential pressure valves are designed to keep a constant intracranial pressure. They are manufactured with fixed opening pressures (high, medium, low) or with an adjustable mechanism, which can be set at a range of opening pressures by applying a magnetic adjusting device over the valve mechanism. The valve setting can be adjusted before insertion into the patient and afterwards, by applying the device over the skin covering the valve.

However, because it is not the absolute magnitude of the intracranial pressure but the pressure difference across the valve that makes the mechanism open, a reduction in pressure at the back or lower end of the valve will cause it to open at a lower intracranial pressure. Reduction in downstream or lower-end pressure typically occurs in an upright body position and in some cases results in too rapid drainage of cerebrospinal fluid through the shunt system when the patient sits or stands. This phenomenon is known as *overdrainage* or *siphoning*. To overcome this, additional position-sensitive mechanisms can be inserted into the shunt system, causing the opening pressure to be higher in

the upright position. Such anti-siphon devices can be an integrated part of the valve, or they can be an additional component that is inserted below the valve itself.

Ideally, differential pressure valves should keep a constant intracranial pressure regardless of the flow rate through the shunt system, and flow control valves should keep a constant flow regardless of intracranial pressure changes. However, all shunts contain tubing with flow resistance, and in all valves a mechanical resistance has to be overcome for the mechanism to open. This means that, in reality, all valve types and all shunt systems have a combination of differential pressure and flow control properties. Differential pressure valves are made so that pressure difference is the major determinant of their function; conversely maintenance of constant flow is the major determinant of function in flow control valves (Sgouros 2010).

How the intervention might work

Surgical intervention for NPH is based on the presumption that provision of a device to divert cerebrospinal fluid from the ventricles will lead to normalisation of the pressure difference, and thereby to stability or improvement in symptoms and signs. The cerebrospinal fluid is drained through a tube (shunt) from the brain ventricles to an absorption site outside the cranial cavity. The system is divided into three functional units. The first unit, the intraventricular catheter, is inserted into the brain ventricles through a burr hole in the skull. This is followed by the second unit, a valve, which is placed subcutaneously on the head; and finally the third unit, which consists of a tube from the valve to the extracranial absorption site. The preferred distal placement for extracranial absorption of cerebrospinal fluid is the peritoneal cavity, in which case the system is termed a ventriculo-peritoneal, or VP, shunt. Much less frequently, the distal catheter is placed in the right atrium, and rarely in other sites.

Why it is important to do this review

To the best of our knowledge, no systematic review comparing shunt types for NPH has previously been conducted. It is important for the surgeon to choose the shunt valve with the best outcomes, if such a shunt exists, and with this result to explore the cost benefit of shunt implementation in NPH patients. Also if a superior shunt system can be identified, this knowledge may help in understanding the cerebrospinal dynamics of NPH.

OBJECTIVES

The objective of this systematic review is to summarise the evidence on benefits and harms of flow-regulated versus differential pressure-regulated shunt valves for adult patients with NPH, on the basis of findings of randomised clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials comparing flow-regulated versus differential pressure-regulated shunt valves.

Types of participants

Surgical NPH patients aged 18 years or older participated. Patients with both idiopathic and secondary NPH were included.

Types of interventions

Surgical ventriculo-peritoneal shunt insertion in patients with NPH.

Comparison: flow-regulated valve type versus differential-pressure valve type.

Types of outcome measures

Primary outcomes

- Death from any cause.
- Participants with one or more serious adverse events (SAEs) including and excluding all-cause mortality, defined according to International Conference of Harmonization of Good Clinical Practice (ICH-GCP) for devices. Additionally, we will include complications and adverse events specific for hydrocephalus shunt systems, such as (1) clinical and radiological signs of shunt obstruction; (2) computed tomography (CT)- or x-ray—confirmed shunt disconnection; and (3) clinical and radiological signs of overdrainage including subdural hematoma.
- Worsening of clinical symptoms of NPH (triad of gait disturbance, urinary incontinence, and subcortical cognitive problems (dementia)).
- Quality of life (QOL), measured with any score.

Secondary outcomes

- Participants with shunt failure, defined as proportion of shunt re-interventions (surgical shunt interventions for any reason) within the longest follow-up in each trial.
- Changes in the Evans ratio (radiological ventriculomegaly).
- Cost benefit of either intervention.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group Specialized Register. The search terms were NPH, "normal pressure hydrocephalus," iNPH (idiopathic normal pressure hydrocephalus), and sNPH (secondary normal pressure hydrocephalus).

ALOIS is maintained by the Trials Search Co-ordinator for the Cochrane Dementia and Cognitive Improvement Group and contains planned, ongoing, and completed dementia and cognitive improvement studies identified from the following:

- Monthly searches of a number of major healthcare databases: MEDLINE (1950 to date) (Ovid SP), EMBASE (1980 to date) (Ovid SP), CINAHL (1980 to date) (EBSCOhost), PsycINFO (1806 to date) (Ovid SP), and LILACS (1982 to date) (BIREME).
- Monthly searches of a number of trial registers: ClinicalTrials.gov; Umin Japan Trial Register; WHO portal (which covers ClinicalTrials.gov; ISRCTN; Chinese Clinical Trials Register; German Clinical trials register; Iranian Registry of Clinical Trials; and the Netherlands National Trials Register, plus others).
- Quarterly search of *The Cochrane Library*'s Central Register of Controlled trials (CENTRAL).

- Monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; and Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see About ALOIS on the ALOIS Website.

Additional separate searches were run in many of the above sources plus additional sources (such as the Chinese Biomedical Literature Database and BIOSIS Previews) to ensure that the most up-to-date results were retrieved. The search strategies that were used for retrieval of reports of trials from MEDLINE (via the Ovid SP platform) can be seen in Appendix 1.

Searches were performed without language or date restrictions.

Searching other resources

We contacted manufacturers and companies associated with producing the devices or sponsoring the trials where the valves are used, including the following companies: GE Healthcare; Codman and Shurtleff; Transonic Systems Inc.; Johnson & Johnson; Nihon Medi-Physics Co Ltd.; and Daiichi Pharmaceuticals.

We handsearched the reference list of reviews, randomised and non-randomised studies, and editorials for additional studies. We contacted the main authors of studies and experts in this field to ask about any missed, unreported, or ongoing trials.

Data collection and analysis

Selection of studies

Two authors (MZ and MJ) independently evaluated all relevant publications for eligibility. There were no disagreements. No eligible studies were identified for inclusion. We provide a detailed description of the excluded articles in the section Characteristics of excluded studies. We also provide a detailed description of our search results.

Data extraction and management

We screened the titles and abstracts to identify studies that are eligible. MZ and MJ independently extracted and collected the data on a standardised paper form (Appendix 2). MZ and MJ were not blinded to the author, institution, or publication source of trials. MZ and MJ resolved disagreements by discussion. We approached all corresponding authors of included trials for additional information relevant to the review's outcomes measures and risk of bias components. For more specific information, please see the section Contributions of authors.

Dealing with missing data

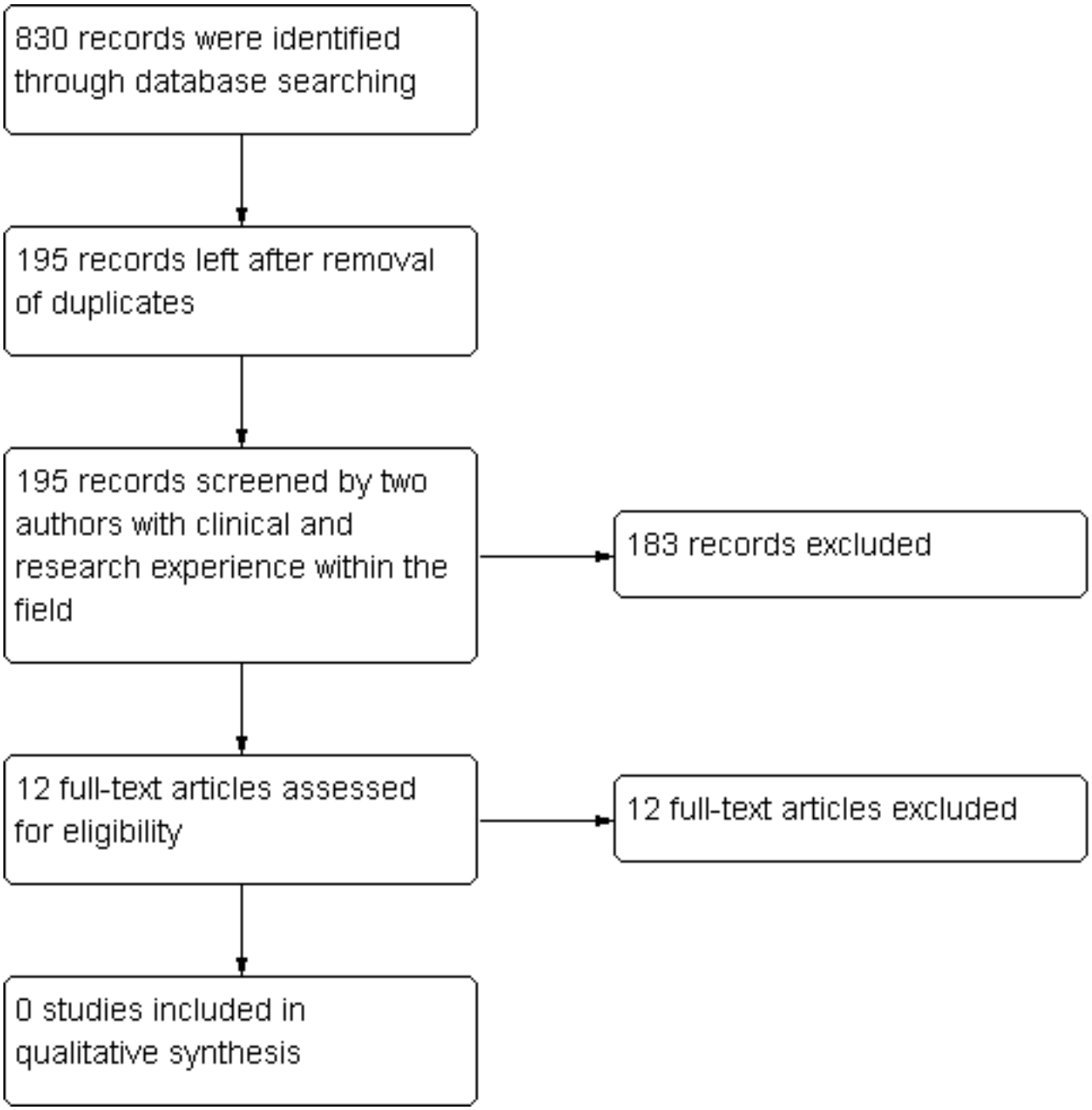
We contacted all first authors and contact persons of trials with missing data to retrieve the relevant data.

RESULTS

Description of studies

Figure 1 reviews the process of how studies were identified for inclusion in the review; also see Characteristics of excluded studies.

Figure 1. Flow diagram of study selection. For additional details, please see Characteristics of excluded studies.



The studies identified for the review did not include any randomised clinical trials of flow-regulated versus differential pressure-regulated shunt valves for adult participants with normal pressure hydrocephalus. No published evidence indicates that such a trial has been performed. Randomised clinical trials related to shunting in adult NPH participants are restricted to those in which differential pressure-regulated shunt valves with different pressure settings are compared.

Results of the search

The search was performed by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group by the 17th of May 2012.

Included studies

No randomised clinical trials are included in this review. (Please see protocol for intentional approach if studies were found Ziebell 2012)

Excluded studies

See Characteristics of excluded studies. The following studies have been excluded from the review: Boon 1997; Boon 1998; Farahmand 2009; Lund-Johansen 1994; Meier 2006a; Meier 2006b; Meier 2010; Meier 2011; Pollack 1999; Weiner 1995; Lemcke 2012; Toma 2011.

Risk of bias in included studies

There are no included studies comparing flow-regulated versus differential pressure-regulated shunt valves.

Effects of interventions

Presently, no published trials have compared flow-regulated versus differential pressure-regulated shunt valves.

We found only one study, by Weiner 1995, with the specified purpose of comparing flow-regulated versus differential pressure-regulated shunt valves. This was a retrospective study in which the selection criteria reduced the included number of participants to 37 from the initial unselected number of 1500 shunt participants. In this study, the distribution between shunt types was approximately 50/50, and the authors found no statistically significant difference in shunt survival. Another retrospective study by Lund-Johansen 1994 used wider clinical inclusion criteria to report on a group of 95 participants, amongst whom 25 participants with NPH were included. In the entire group of 95 participants, 40 had a flow-regulated and 55 a differential pressure-regulated valve. Investigators found no statistically significant differences in failure, complications, or time to first revision. Farahmand 2009 also conducted a non-randomised controlled study on 450 participants with various types of hydrocephalus including NPH. In this retrospectively analysed material, only six flow-regulated valves were compared with 443 differential pressure-regulated valves, and no statistically significant difference in revision rate was noted.

DISCUSSION

Shunting as an intervention for normal pressure hydrocephalus remains controversial, and so far only one randomised controlled study of shunt versus no shunt has been reported (Tisell 2011). The trial was very small (n = 14 participants), entailing high risks of both type I and type II errors, and found a significant difference between the two intervention groups only on psychometric test performance at three months' follow-up, favouring participants in the intervention group who had undergone surgery. No statistically significant difference was noted between the two intervention groups in terms of gait or overall clinical performance (perceptual speed and accuracy, reaction time, manual dexterity, verbal learning and memory, motor speed, speed, response selection, and inhibition). All of these tests have been used in individuals with iNPH and have been shown to be valid and sensitive to postoperative results. We identified one ongoing randomised trial that aims to compare conservative versus surgical management of idiopathic NPH (Toma 2011). Although the trial was planned to end during 2011, results so far are not available.

A few small retrospective studies included participants with either differential pressure-regulated or flow-regulated shunts as the intervention (Farahmand 2009; Lund-Johansen 1994; Weiner 1995), but only one of these studies specifically compared the two valve types (Weiner 1995). None of these studies showed statistically significant differences in shunt failure between the two shunt types. However, comparisons based on small, retrospective, non-randomised controlled studies should be assessed with utmost caution because observational studies can never take into consideration unmeasured confounding, especially confounding by indication.

Of the remaining studies, we identified none that addressed the review question (see Characteristics of excluded studies).

In general, the number of randomised clinical trials in the field of neurosurgery is limited. There seems to be an obvious reason for the lack of high-quality evidence regarding optimum treatment of NPH. Diagnosis of NPH is still controversial, and no test or imaging modality is pathognomonic for NPH. Therefore, it is still problematic to identify with a high degree of certainty which patients will benefit from a ventriculo-peritoneal shunt, and which will not.

Finally (even though it is beyond the scope of this review), it is notable that a few multicenter trials comparing valve designs conducted in paediatric hydrocephalus populations have been performed, which found no difference in outcome when comparing different valve types (Drake 1998; Kestle 2000). However, hydrocephalus in children is a different condition. Child hydrocephalus is extremely seldom described as normal pressure, but rather is described as high-pressure, hydrocephalus. Additionally, child hydrocephalus requires a slightly different surgical technique, and different kinds of complications are observed because of the level of physical activity, lack of compliance with having a shunt implanted, and 'out-growing' of the device. Thus, evidence derived from studies of children cannot be applied to adults. However, these publications support the need for similar randomised trials in adult hydrocephalus, and they show how similar randomised trials on NPH can be conducted in adults.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomised clinical trials exploring the benefits and harms of flow-regulated versus differential pressure-regulated shunt valves in adult patients with normal pressure hydrocephalus.

Implications for research

Randomised clinical trials exploring the benefits and harms of flow-regulated versus differential pressure-regulated shunt valves for adult patients with normal pressure hydrocephalus are needed. Even though this is not the topic of this review, it seems to be in line with the lack of evidence comparing shunts versus no shunts. Clearly, additional randomised clinical trials are warranted, preferably undertaken to compare open shunts versus no shunts. Only in this way can we obtain both short- and long-term knowledge about the benefits and harms.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Boon 1997	Randomised clinical trial comparing low-pressure versus medium-pressure shunts in 101 normal pressure hydrocephalus participants. Boths systems are differential-pressure valves.
Boon 1998	Same trial as Boon 1997, although reporting on only 96 participants.
Farahmand 2009	Not a randomised trial. A prospective study on 450 participants with hydrocephalus in any form. Six flow-regulated valve participants were compared with 443 differential-pressure valve participants. No statistically significant difference in revision was noted.
Lund-Johansen 1994	Retrospective study of 95 mixed hydrocephalus participants (25 normal pressure hydrocephalus). 40 flow-regulated valve participants compared with 55 differential-pressure valve participants. No statistically significant difference in revision.
Meier 2006a	An open prospective trial to determine the optimal opening pressure for pressure-relief valves used in shunts for normal pressure hydrocephalus.
Meier 2006b	Same trial as Meier 2006a.
Meier 2010	Randomised multicentre trial comparing programmable differential-pressure valves with and without anti-gravity unit in 152 participants with idiopathic normal pressure hydrocephalus.
Meier 2011	Same trial as Meier 2010, although only 133 participants were described.

Study	Reason for exclusion
Pollack 1999	Randomised clinical trial to assess safety of a specific differential-pressure programmable shunt (experimental) versus differential-pressure and flow-regulated shunt valves (control). Included 377 participants with varying causes of hydrocephalus; separate results for those with NPH not given. No randomisation between differential-pressure (n = 178) and flow-regulated shunt valves (n = 5) in control group.
Weiner 1995	Retrospective study of 37 idiopathic normal pressure hydrocephalus participants comparing differential-pressure programmable shunt versus differential-pressure and flow-regulated shunt valves. Not a randomised trial.

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

Lemcke 2012

Trial name or title	On the method of a randomised comparison of programmable valves with and without anti-gravitational units: The SVASONA trial.
Methods	Randomised clinical trial.
Participants	Normal pressure hydrocephalus.
Interventions	Programable shunt with and without gravitational unit.
Outcomes	Clinical outcome.
Starting date	
Contact information	
Notes	

Toma 2011

Trial name or title	Conservative versus surgical management of idiopathic normal pressure hydrocephalus: a prospective double-blind randomised clinical trial: trial protocol.
Methods	RCT.
Participants	Idiopathic normal pressure hydrocephalus.
Interventions	Conservative versus surgical management of idiopathic normal pressure hydrocephalus.
Outcomes	Primary is clinical outcome (improvement in gait).
Starting date	
Contact information	
Notes	

APPENDICES

Appendix 1. Search strategy: MEDLINE

Source	Search strategy
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. Hydrocephalus, NormalPressure/ 2. normal pressure hydrocephalus.ti,ab. 3. NPH.ti,ab. 4. sNPH.ti,ab. 5. iNPH.ti,ab. 6. or/1-5 7. valve*.ti,ab. 8. shunt*.ti,ab. 9. (flow adj2 (control or regulat*)).ti,ab. 10. differential pressure.ti,ab. 11. Ventriculoperitoneal Shunt/ or Peritoneovenous Shunt/ 12. ("pressure sensitive" adj5 shunt*).ti,ab. 13. or/7-12 14. 6 and 13 15. randomized controlled trial.pt. 16. controlled clinical trial.pt. 17. randomi?ed.ab. 18. placebo.ab. 19. randomly.ab. 20. trial.ab. 21. groups.ab. 22. or/15-21 23. (animals not (humans and animals)).sh. 24. 22 not 23 25. 14 and 24

Appendix 2. Data extraction form

Flow-regulated versus differential pressure-regulated shunt valves for adult patients with normal pressure hydrocephalus

Study Selection, Quality Assessment and Data Extraction Form

First author	Journal/Conference Proceedings etc	Year

Study eligibility

RCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No* / Unclear

***Issue relates to selective reporting when authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Reviewers should contact trialists for information on possible non-reported outcomes & reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should then be excluded.**

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.

Freehand space for comments on study design and treatment:

References to trial

Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	Author(s)	Journal/Conference Proceedings etc	Year
A	*The paper listed above*		
B	*Further papers*		
C			
D			
E			

Participants and trial characteristics

Participant characteristics	
Covariate	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Disease status / type, iNPH, sNPH or both	

Trial characteristics

Methodological quality

Allocation of intervention	
State here method used to generate allocation and reasons for grading	Grade (circle)
	Low risk of bias (Random)
	High risk of bias (e.g. alternate)
	Unclear

Concealment of allocation **Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding**	
State here method used to conceal allocation and reasons for grading	Grade (circle)
	Low risk of bias
	High risk of bias
	Unclear

Blinding	
Person responsible for participants' care	Yes / No
Participant	Yes / No
Outcome assessor	Yes / No
Other (please specify)	Yes / No
Incomplete outcome data	
Low risk of bias, if the numbers and reasons for dropouts and withdrawals in the intervention groups were described, or if it was specified that there were no dropouts or withdrawals.	Yes / No
High risk of bias, if the number or reasons for dropouts and withdrawals were not described.	Yes / No
Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.	Yes / No
Selective outcome reporting	
Low risk of bias, if predefined or clinically relevant and reasonably expected outcomes are reported on.	Yes / No
High risk of bias, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.	Yes / No
Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.	Yes / No
Baseline imbalance	

(Continued)

Low risk of bias, if there was no baseline imbalance in important characteristics.	Yes / No
High risk of bias, if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.	Yes / No
Unclear, if the baseline characteristics were not reported.	Yes / No
Early stopping	
Low risk of bias, if sample size calculation was reported and the trial was not stopped, or the trial was stopped early by formal stopping rules at a point where the likelihood of observing an extreme intervention effect due to chance was low.	Yes / No
High risk of bias, if the trial was stopped early due to informal stopping rules or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high.	Yes / No
Unclear, if sample size calculation was not reported and it is not clear whether the trial was stopped early or not.	Yes / No

Other bias	
No risk of other bias, the trial appears to be free of other components that could put it at risk of bias.	Yes / No
Risk of other bias, there are other factors in the trial that could put it at risk of bias, e.g., 'for-profit' involvement, authors have conducted trials on the same topic, etc.	Yes / No
Unclear, the trial may or may not be free of other components that could put it at risk of bias.	Yes / No
Modified intention-to-treat A modified intention-to-treat analysis is one in which all the participants in a trial are operated and analysed according to the intervention to which they were allocated, whether they received it or not.	
All participants entering trial after surgery.	
15% or fewer excluded.	
More than 15% excluded.	
Not analysed as modified 'intention-to-treat'.	
Unclear.	

Were withdrawals described? Yes ? No ? not clear ?

Discuss if appropriate

Trial characteristics	
	Further details
Single centre / Multicentre	
Country / Countries	
How was participant eligibility defined?	
How many participants were randomised?	
Number of participants in each intervention group	
Number of participants who received intended intervention (per protocol population)	
Number of participants who were analysed	
Duration of surgery in minutes	
Antibiotic regime used	
Time of antibiotic administration	
Administration of oxygen, type of face mask ?	
Duration of supplemental oxygen intervention including postoperative period or not ?	
Mean temperature and range during anaesthesia	
Mean fluid volume and range management during anaesthesia	
Fraction of patients with epidural anaesthesia	
Fraction of patients administered vasopressors	
Median (range) length of follow-up reported in this paper (state weeks, months, or years or if not stated)	
Time-points within which SSI were diagnosed during the trial ?	
Time-points reported in the trial ?	
Time-points you are using in RevMan	
Trial design (e.g. parallel / cross-over*)	
Other	

* If cross-over design, please refer to the Cochrane Editorial Office for further advice on how to analyse these data

Other design characteristics of the trial

1. The trial used clinical history criteria to NPH **Yes ? No ?**

2. The trial used brain imaging criteria **Yes ? No ?**

3. The trial used physical criteria **Yes ? No ?**

4. The trial used physiological criteria **Yes ? No ?**

5. The trial included only sNPH or iNPH or both **Yes ? No ?**

Data extraction

Outcomes	Available for the trial
1.1 Overall mortality. We will use the longest follow-up data from each trial regardless of the period of follow-up.	Yes/No
1.2 Serious adverse events including and excluding all-cause mortality defined according to International Conference of Harmonization of Good Clinical Practice (ICH-GCP) for devices and in addition: Subdural Haematoma, CT/x-ray or MR confirmed shunt disconnection, clinical signs of over-drainage, and clinical measure of non-drainage into abdomen.	Yes/No
1.3 Re-occurrence of clinical signs to NPH (triad of gait disturbance, urinary incontinence, and sub-cortical cognitive problems (dementia).	Yes/No
1.4 Quality of life measured with any score.	Yes/No
2.1 Shunt failure defined as proportion of shunt re-interventions (surgical shunt interventions for any reason) within the longest follow-up in each trial.	Yes/No
2.2 Changes in the Evans ratio (radiology sign of hydrocephalus).	Yes/No

For Continuous data							
Code of paper	Outcomes (rename)	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (SD)	n	Mean (SD)	
A etc.	**2.3 Duration of postoperative hospitalisation.**	**Days**					
A etc.	**2.4 Quality of life**	**Score (any)**					

For Dichotomous data			
Code of paper	Outcomes	Intervention group E/N E = number of events N = number of participants	Control group E/N E = number of events n = number of participants
A	1.1 Overall mortality.		
	1.2 Re-occurrence of clinical signs to NPH (triad of gait disturbance, urinary incontinence, and sub-cortical cognitive problems (dementia).		
	2.1 Shunt-failure defined as proportion of shunt re-interventions (surgical shunt interventions for any reason) within the longest follow-up in each trial.		
	2.2 Serious adverse events including and excluding all-cause mortality defined according to International Conference of Harmonization of Good Clinical Practice (ICH-GCP) for devices and, in addition, Subdural Haematoma, CT/x-ray or MR confirmed shunt disconnection, clinical signs of over-drainage, and clinical measure of non-drainage into abdomen.		

Other information which you feel is relevant to the results

Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports of potentially eligible trials not already identified for this review?		
First author	Journal / Conference	Year of publication

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list contact name and details

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Securing funding for the review: MZ, MJ.
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DECLARATIONS OF INTEREST

None known for any author.

INDEX TERMS

Medical Subject Headings (MeSH)

Hydrocephalus, Normal Pressure [*surgery]; Pressure; Ventriculoperitoneal Shunt [*instrumentation] [methods]

MeSH check words

Adult; Humans