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Review

Efficacy and safety of programmable shunt valves for hydrocephalus: A meta-analysis

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HIGHLIGHTS

- Compared with Non-PV, PV did not have a statistically significant effect on one-year shunt survival rate.
- PV administration significantly reduced revision rate and over- or under-drainage complications rate.
- PV was not associated with increased rates of other adverse events: overall complications rate, infection rate, etc.

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ABSTRACT

Objectives: Shunt implantation is an option in the treatment of hydrocephalus. However, the benefits and adverse effects of programmable shunt valves have not been well assessed.
Materials and methods: Randomized controlled trials (RCTs) and observational studies assessing the efficacy and safety of programmable valves (PV) treatment for hydrocephalus were identified from electronic databases (PubMed, EMBASE, and Cochrane library). The meta-analysis was performed with the fixed-effect model or random-effect model according to heterogeneity.
Results: Three RCTs and eight observational studies met the inclusion criteria including 2622 subjects. Compared with non-PV, PV treatment did not have a statistically significant effect on one-year shunt survival rate [relative risk (RR), 1.06; 95% confidence interval (CI), 0.84–1.35], Substantial heterogeneity was observed between studies ($P = 0.09$; $I^2 = 65\%$). PV administration significantly reduced revision rate (RR, 0.56; 95% CI, 0.45–0.69; $I^2 = 29\%$; $P = 0.23$) and over- or under-drainage complications rate (RR, 0.55; 95% CI, 0.32–0.96). PV was not associated with increased rates of other adverse events, including overall complications rate, infection rate and catheter-related complications rate.
Conclusions: PV treatment is safe and may reduce the revision rate and over- or under-drainage complication rate, especially in patients aged less than 18 years with hydrocephalus. PV treatment is not associated with decreased overall complication rates in patients with hydrocephalus, but the trial sequential analysis indicate more studies are needed to confirm this result.

1. Introduction

Hydrocephalus is a disorder in which excessive volume of cerebrospinal fluid (CSF) accumulates within the cerebral ventricles, and is one of the treatable dementias [1,2]. The estimated prevalence of hydrocephalus has been reported to be as high as 1–1.5% in the general population [3]. Since the introduction of the first artificial CSF shunt in 1949, a vast number of different valves have been invented—approximately 130 different types are currently available [4]. However, the decision regarding which valve to use in the treatment of a specific patient is based mainly on clinical factors and still depends on the experience of the surgeon. Although shunt implantation is considered a routine procedure in everyday neurosurgical practice, the valve-related complications, included mechanical obstruction, infection, and subdural hematoma, still remain a major problem for the neurosurgeon [5,6]. Therefore, any valves are designed to lower the complication rate and optimize the effect of shunting are thus clearly an important priority for shunt surgery.

The most common treatment of hydrocephalus is ventriculoperitoneal shunting (VPS), which involves diversion of extra

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CSF from the ventricular system into the peritoneum, though the surgical technique through which this is achieved varies [7]. A previous systematic review of programmable shunt valves treatment for hydrocephalus including seven randomized and non-randomized controlled trials was published in 2013 [8]. The analysis demonstrated a small advantage for the programmable shunts. But this systematic review included some clinical studies which had a modest sample size. Moreover, the data from studies included in previous systematic reviews were limited to July 2012. Recently, an increasing number of studies on the efficacy and safety of programmable valves (PV) treatment for hydrocephalus have been published [9,10]. However, potential benefits and possible risks associated with PV for hydrocephalus are not fully understood. Results from studies are still controversial. Therefore, we performed an updated meta-analysis to re-evaluate and quantify the clinical advantages of PV treatment for hydrocephalus.

2. Materials and methods

The present meta-analysis was conducted according to the *Cochrane Handbook for Systematic Reviews* [11] and was reported in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) guidelines [12].

2.1. Search strategy

A systematic search of the electronic databases PubMed, EMBASE and the Cochrane Library (including Cochrane Central Register of Controlled Trials) was conducted on March 2017 using the key words: hydrocephalus, programmable valves, adjustable valves. Results were limited to human subjects. To maximize the sensitivity, we did not use any language restriction. In addition, when the same or similar patient trial was included in several publications, only the most recent report was selected for analysis. The electronic search strategies were provided in e-Appendix 1.

2.2. Study selection

Studies that met the following criteria were included: (1) RCTs or observational studies of patients who underwent a shunt surgery; (2) patients assigned to receive PV or non-programmable valve (NPV); and (3) study outcomes with report at least on one-year shunt survival time rate or catheter-related complications or overall complications or infection rate or revision rate or over- or under-drainage complications rate. Additionally, we excluded animal studies, commentaries and letters without sufficient data.

2.3. Data extraction

Two authors independently extracted data on the population under study, study type, participants' age, number of participants, follow-up time (MY, and YT OY.). Disagreement was resolved by consensus. When necessary, the original authors were contacted for supplementary information. Predefined primary outcome was the rate of one-year shunt survival time. Secondary outcomes included catheter-related complications, overall complications, infection rate, revision rate, and over- or under-drainage complications rate. A predesigned excel (Microsoft Corporation) file was used to extract relevant information.

2.4. Risk of bias assessment

The risk of bias has been assessed independently by two authors (HW, and YT OY.) according to the Cochrane risk-of-bias tool [13]. A third author was consulted if any disagreement occurred (XPY). Investigators of included studies were contacted by email when clarification on bias was needed. This scale explores the adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome, selective outcome reporting, and other potential bias. The studies that fulfilled >6, 4–6, and <4 items were defined as being of high, fair, and poor quality, respectively.

2.5. Data synthesis and statistical analysis

The statistical significant level for a two-tailed test for each primary hypothesis was 0.05. All of the statistical analyses were conducted with the Review Manager version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) and STATA version 14 (STATA Corporation, College Station, TX, USA) and TSA program version 0.9 beta. Data were analyzed separately for RCTs and observational studies. The results were expressed as relative risk (RR), with 95% confidence interval (CI) (using a fixed-effect approach) [14]. Heterogeneity across studies was assessed using a standard chi-squared test, with significance being set at $P < 0.10$. Heterogeneity across studies was also tested with the I^2 statistic, which is a quantitative measure of inconsistency across studies. I^2>50% indicates significant heterogeneity [15]. But if there was heterogeneity, the following methods were used to deal with it: (a) subgroup analysis (by study type, age, and follow-up time); (b) sensitivity analysis performed by excluding trials which potentially biased the results. If heterogeneity still potentially existed, the DerSimonian and Lair random-effects model was used. Publication bias was assessed by visually inspecting a funnel plot and also evaluated by using the Begg and Egger tests [16,17].

2.6. Trial sequential analysis

In a single RCT, repeated significance testing on accumulating data is known to inflate the overall risk of type I error [18,19]. To assess the risk of type I errors we applied trial sequential analysis (TSA) to cumulative meta-analysis. The TSA termed trial sequential monitoring boundaries, adjusts the confidence intervals and reduces type I errors [18,20]. Boundaries for concluding superiority or inferiority or futility were calculated with the O'Brien-Fleming α-spending function. When the cumulative z curve crosses the trial sequential monitoring boundary, a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed [21]. If the z curve does not cross any of the boundaries and the required information size has not been reached, evidence to reach a conclusion is insufficient [22].

Applying this method, we calculated the data on the efficacy and safety of PV treatment for hydrocephalus. Our assumptions included two-sided testing, type I error of 5%, and power of 80%. Diversity-adjusted information size was calculated based on the absolute event rate in the controls and relative risk reduction of 25% in the rate of complications. These analyses were performed using TSA program version 0.9 beta (http://www.ctu.dk/tsa).

3. Results

3.1. Literature search

The PRISMA statement flowchart shows the process of literature screening, study selection, and reasons for exclusion, as shown in Fig. 1 and e-Appendix 2. 519 relevant citations were initially identified. After duplicates removal and screening of titles and abstracts, there remained 21 studies; we further evaluated the full studies of potentially 21 publications. Of these, we excluded 10 studies. To be specific, two studies were excluded owing to lack of sufficient data,