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Editorial

# Impact of ventricular-peritoneal shunt valve design on clinical outcome of pediatric patients with hydrocephalus: Lessons learned from randomized controlled trials

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## Abstract

Hydrocephalus is one of the most common diseases managed by pediatric neurosurgeons. Cerebrospinal fluid (CSF) shunting has been the mainstay of durable treatment for hydrocephalus for many decades. There are two main categories of shunt designs for regulating the extent of CSF diversion: (1) Fixed-parameter valves and (2) adjustable valves. Furthermore, these valves can also function with and without an anti-siphon device. Here, we review randomized controlled trials (RCTs) that examined the impact of these valve designs on the clinical outcome of pediatric patients afflicted with hydrocephalus. All three RCTs suggested no significant differences in clinical outcome as a function of shunt design. Implications of these findings are discussed.

**Key Words:** Hydrocephalus, pediatrics, shunt

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## BACKGROUND

Hydrocephalus has been recognized as a disease entity since as early as 400 BC by Hippocrates.[1] His observations of children with clinical symptoms of headache, vomiting, and visual disturbances were first thought of as being related to liquefaction of the brain secondary to seizure activity.[1] It was not until 1774 when Le Cat placed a wick within the ventricular system, which was the earliest known technology for external ventricular drainage.[1] In 1893, Mikulicz implanted this wick within the subgaleal space, documenting this first internalized ventricular shunting system. In 1907, Payre anastamosed a saphenous vein graft with preserved venous flaps from the ventricular system to the superior sagittal sinus, thereby making the first valved ventricular shunting system, laying the groundwork for the modern shunt. Since the introduction of the mechanical shunt valve, a plethora of shunt designs have emerged such that by the mid-1990s, there were 127 distinct commercially available shunt valves.[8]

Despite a large variation in design, shunt valve construction generally falls into two main categories: (1) Fixed-parameter valves and (2) adjustable valves. Fixed-parameter valves are valves designed to maintain



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the ventricular system at a preset pressure (fixed-pressure) or at a preset flow (fixed-flow). In contrast, adjustable pressure shunts are engineered to allow modulation of the resistive force, thereby allowing the clinician to adjust the pressure threshold of the valve based on clinical indications.[5] The benefit of fixed-parameter valves is that there are less "moving parts" within the valve, conceptually reducing mechanical failures of the valve system. On the other hand, the adjustable valves allow pressure modulation without the need for a surgical valve-swap.

These valves can also have the addition of an anti-siphon device. Anti-siphon devices allow CSF to flow safely, without worry of aggressive shunting by sudden positional changes. When included in a shunt, the anti-siphon device, in principle, prevents "dumping" of CSF as the patient sits up from a recumbent position as a result of a negative pressure differential between the compartments of the proximal and distal catheters.[3,6] A typical design of anti-siphon involves the use of flexible diaphragms. In the recumbent position, the diaphragm is open and allows CSF to flow. However, when the patient sits up, the induced negative pressure forces the flexible diaphragms to close over the CSF outlet, blocking it from siphoning out CSF.[3] The goal of the device is to prevent postural intracranial hypotension and over-drainage.

We performed an exhaustive search of the literature and identified three published RCTs that examined the impact of shunt valve design (fixed-pressure versus adjustable-pressure) and the use of an anti-siphon device on the clinical outcome of pediatric patients with hydrocephalus. The PubMed online database was searched from January 1st 1980 through June 25th 2016 using the following queries "shunt valve," "hydrocephalus," and "randomized controlled trial." Three articles were identified and reviewed by RH. Three RCTs were identified that compared the clinical outcomes of different shunt designs. Here, we review the findings of these three RCTs and discuss the implications of these findings.

## RANDOMIZED CONTROLLED TRIALS

### Design of fixed-pressure valves with anti-siphon devices and a fixed pressure valve without an anti-siphon device

The effects of a fixed pressure valve with an anti-siphon device and a fixed-flow valve with an anti-siphon device were compared to a fixed pressure valve without an anti-siphon device by Drake *et al.*[4] The authors enrolled 344 pediatric patients across 12 different pediatric centers to compare hydrocephalic patients randomized to treatment between fixed-pressure valve with an anti-siphon device (Medtronic Delta), fixed-flow valve with an anti-siphon device (Orbis-Sigma), or a fixed-pressure valve without an anti-siphon device (no branding was reported). It was left up to the surgeon's clinical judgment to select the opening pressure of the valve once the patient was randomized. Each surgeon was allowed to perform the shunt procedure based on his/her standard practice. Primary outcomes included the incidence of shunt malfunction defined as shunt obstruction, overdrainage, loculated ventricles, and shunt infection. Secondary outcomes included death, surgical complications, type of shunt malfunction, and hospital stay. Clinical and radiographic measurements were recorded at 3, 12, 24, and 36 months following surgery.

There were no differences between the baseline characteristics or the cause of hydrocephalus for the three groups, suggesting that randomization was successfully achieved. Overall, 67% of patients were failure-free at 1 year and 47% of patients were failure-free at 2 years. In terms of primary outcome, there were no significant differences between the three groups in terms of shunt failure (27% for the Orbis-Sigma, 33% for the Delta valve, and 34% for the valve without an anti-siphon device). When qualitatively analyzed by the specific type of shunt failure, the Orbis-Sigma valve was less likely to fail from proximal failure and less likely to incur overdrainage. No formal statistical testing was provided in this comparison. A long-term follow-up study revealed that the clinical outcomes remained comparable among the three groups,[7] with a 3-year failure rate of 54% and a 4-year failure rate of 59%. The authors conclude that there does not appear to be one valve that is clearly superior for the initial treatment of pediatric hydrocephalus.

### Fixed versus adjustable valves

A multi-institutional RCT conducted by Pollack *et al.*[2,9] compared the clinical performance of shunts harboring an adjustable valve (Codman-Hakim) to those with a fixed-pressure valve. A total of 377 pediatric patients were enrolled, of which 194 were randomized to a programmable valve and 183 randomized to a fixed-pressure valve. It was left up to the surgeon's clinical judgment to select the valve brand and setting (if randomized to the adjustable valve cohort) once the patient was randomized, and each surgeon was allowed to perform the shunt procedure and include an anti-siphon device based on his/her standard practice. The primary end-point was re-operation for valve replacement after 24 months. Follow-up was performed at regular intervals at 1, 3, 6, 12, 18, and 24 months postoperatively. Imaging studies were obtained at 3, 12, and 24 month visits.

There were no differences between the baseline characteristics or the cause of hydrocephalus for the two groups, suggesting that randomization was successfully achieved. In terms of primary outcome, there were no significant differences between the two groups in terms of

re-operation (43% vs. 43%). Patients with programmable valves underwent, on average, 2.78 instances of re-programming within their 24 month observational period. Post-hoc analysis showed no statistical difference in the incidence of subdural hygromas, subdural hematomas, or underdrainage between the two groups (~6%). Despite the similar incidence of subdural hygromas and hematomas, resolution of subdural fluid collections was achieved by adjusting pressure setting in 7 of the 12 occurrences. A surgical procedure was required to address these collections in 4 of the 11 patients in the fixed-pressure group, compared to 1 of the 12 patients in the adjustable-valve group. While these differences did not reach statistical significance, the authors concluded that, though the overall safety and efficacy of the adjustable pressure valve were comparable to those of fixed-pressure valves, there exists a therapeutic advantage of the former in the management of subdural hygromas and hematomas.

### Fixed valves set at different pressures

Sinha *et al.*[10] performed a single institution RCT enrolling 40 pediatric patients with hydrocephalus randomized fixed-pressure valve set at low pressure (5 cm $H_2O$) and medium pressure (10 cm $H_2O$).[10] Both valves were without an anti-siphon device. These valves were from the same manufacturer and functioned with the same mechanism of pressure regulation. No clear primary end-point was indicated in the study. The clinical variables studied were: (1) Decrease in ventricle size, as assessed by measuring ventricle-hemispheric ratio (VHR) pre- and postoperatively (at 3 months) and (2) complications as a result of the shunt procedure.

No statistical comparison was made between the two randomized groups in terms of baseline characteristics. Myelomeningoceles were the indication for shunting in majority of the patients, and there were no differences in indication between the two groups. The improvement in VHR was comparable between the two groups (15.05% mean decrease in the low-pressure system and 15.71% mean decrease in the medium pressure system). Complication rates were comparable between these two groups (21% for the low pressure system and 19% for the medium pressure system). The authors conclude that the clinical performance of low pressure or medium pressure fixed pressure valves were comparable.

## EXPERT OPINIONS

"Programmable valves offer a potential non-invasive response to the development of symptomatic subdural hematoma after ventriculoperitoneal shunt placement" Hal S. Meltzer, Rady Children's Hospital.

There is likely no procedure in the neurosurgical armamentarium which achieves more "bang for the buck" than the humble insertion of ventriculoperitoneal shunt. A uniformly fatal condition is converted to a uniformly survivable one, although at the cost of shortened life span (20% mortality over 20 years in one myelomeningocele outcome study) and innumerable potential complications. While no one step in this procedure is considered technically daunting, taken as a whole, the procedure is a veritable "house of cards." Any issue with any one of the steps involved usually will result in collapse of the goal of an optimal surgical result. Since valve selection represents only one of the myriad steps involved in this procedure, it is not surprising that none of the above reviewed studies were able to demonstrate a statistically significant difference in major outcome measures. The value of shunt valve selection resides, however, in the nuanced potential for a reduction in a few of the many possible complications of this procedure. Anti-siphon valves (ex. Delta valve) or flow controlled valves (ex. Orbis-sigma) theoretically reduce chronic CSF overdrainage and may prevent development of the extremely pernicious complication of symptoms of high ICP in patients with shunts and normal neuroimaging (slit ventricle syndrome). This has been our personal observation since we adopted their use 15 years ago. Programmable valves offer a potential noninvasive response to the development of symptomatic subdural hematoma after ventriculoperitoneal shunt placement. We have also used these valves as a treatment for the perplexing symptoms experienced by patients with the theoretically markedly reduced brain compliance seen in slit ventricle syndrome. While the observed benefits conferred to select patients by these valves may never reach the level of statistical significance in large, unfiltered randomized trials, it does not diminish their value.

"To take away the conclusion that shunt valve type has no importance would be a gross error as any practicing neurosurgeon can attest who has had to combat hydrocephalus" David Gonda, M.D, University of California, San Diego.

To take away the conclusion that shunt valve type has no importance would be a gross error as any practicing neurosurgeon can attest who has had to combat hydrocephalus in a complex patient by adding or removing anti-siphon devices or changing valve pressure resistances to optimize CSF outflow. Hydrocephalus is too varied in its etiologies, presentation, and severities to be treated as a single entity, as has been done in the randomized controlled valve study trials to date. Any trial hoping to demonstrate a superiority of one valve type over another will have to be designed around more specified subgroups hydrocephalus patients. Its not surprising that no superior valve has been identified when all subtypes of hydrocephalus are treated indifferently.

Dozens of differing valve types have been engineered with the primary aim of improving CSF flow dynamics.

However, identifying outcome measures to capture potential benefits related to differences in flow dynamics has been challenging. Early complications related directly to flow dynamics, such as overdrainage, occur in only 3–4% of patients, which is dwarfed by other causes of shunt failure seemingly unrelated to CSF flow dynamics such as obstruction (>30%) and infection (8–10%). It is still unknown how the different valve-induced CSF flow dynamics affected long-term brain development and the occurrence of dreaded late complications such as craniocerebral disproportion and slit ventricle syndrome. Future valve design studies will need to look beyond the outcomes of mere shunt revision.

"The key to future RCTs will require larger collaborative experienced groups well trained in the practice of human investigations research in order to obtain sufficient numbers, with clearly defined populations and clinically relevant primary outcomes measured." Daniel Guillaume, M.D., University of Minnesota School of Medicine.

It is not surprising that randomized clinical trials comparing shunt valve designs for the treatment of hydrocephalus have not shown a significant difference in clinical outcomes. Several factors create challenges in focusing solely on the valve design. First, hydrocephalus is not a distinct disease entity but rather a common term used to describe the end result of many different conditions. Even pediatric types of hydrocephalus are quite diverse. Second, the physiology of normal and pathologic CSF circulation is poorly understood. Thus, a clearly defined treatment population is difficult when dealing with a heterogeneous group of poorly understood conditions. Third, even if the overall complication rate is not affected by valve design and choice, there may be specific complications for certain populations that are better managed with a particular type of valve. For example, although there was no statistical difference in subdural fluid collections in the study comparing adjustable to fixed pressure valves, these collections were successfully treated with valve adjustment in more than half of those with adjustable valves (7 of 12), but required a surgical procedure in those with fixed pressure valves (4 of 11), indicating that adjustable valves, while not inferior to fixed pressure valves, can eliminate need for additional surgeries aimed at changing shunt resistance. Fourth, the valve is only one component of the VP shunt system, all of which regulate flow. Distal catheter length and inner diameter contribute to shunt resistance and changing either, for example by trimming a peritoneal catheter, can dramatically alter flow. Moreover, ventricular catheter placement, which can be optimized by use of image guidance, is thought to play an important role in shunt function and malfunction. None of these technical placement variables were controlled in the studies reviewed.

There is no "home run" in shunt design. More nuanced study of particular subsets of patients and better defined protocols will be required to identify the singles and doubles that improve the care of children with shunted hydrocephalus. The key to future RCTs will require larger collaborative experienced groups well trained in the practice of human investigations research to obtain sufficient numbers, with clearly defined populations and clinically relevant primary outcomes measured. The Hydrocephalus Clinical Research Network was developed and is well poised to continue answering these questions for this difficult-to-treat group of conditions.

## Editorial comments

Arguably, treatment of hydrocephalus through insertion of a catheter system with a preset flow rate or pressure is one of the most blatant examples of a simpleton response to a complex, multidimensional problem. The statement is not meant to cheapen the value of this life-preserving measure. The intent, instead, is to illuminate CSF hydrodynamics as a living, homeostatic system where flow, pressure, and composition are dynamically regulated by intricate interactions between multitudes of complex physiologic variables, including metabolic states of the brain (e.g., sleep, anxiety, etc.), cerebral compliance, and cardiac output. When taken in this context, it is not surprising that some of the most interesting neurosurgical phenomenon and challenging clinical issues occur in patient shunted as treatment for altered CSF hydrodynamics.

Given the complexity of the matter, the investigators involved in the above reviewed RCTs should be noted for their intellectual courage and the rigor of their landmark studies. Beyond the general conclusions of these RCTs, what have we learned from these studies? When CT images from Drake study[4] were analyzed, the positions of the ventricular catheters accounted for three-quarters of the variability in shunt failure, suggesting that the impact of valve design cannot be studied without controlling for this variable. Another key lesson gleamed through the Drake study[4] as well as the Sinha study[10] is that the steady state ventricular size reached after resolution of hydrocephalus were comparable, despite significant differences in valve design or setting. These findings suggest the capacity of the cerebrum to accommodate differential perturbations to achieve a common range of ventricular volumes. The end-steady state ventricular volume after shunt placement is, thus, unlikely an informative outcome measure for future clinical trials. If physical laws apply, maintenance of constant volume despite differing resistive pressure imply altered cerebral compliance. How this altered compliance impacts neurocognitive function remains an open question.

Technologies that afford continuous transmission of physiologic measurements from a sensor inserted into the

CSF space to a remote recording system should afford opportunities for better modeling of CSF hydrodynamics. There is no doubt that, with as our understanding of CSF hydrodynamic improves, novel shunt designs will emerge, including "smart" valves that self-adjust to select parameters. It is essential that the efficacy of such shunts be rigorous scrutinized through statistically sound RCTs, with meaningful clinical variables, including neuro-cognitive and quality of life measures. Given the complexity of CSF hydrodynamics, unsubstantiated assertions based on theoretical speculation, case reports, or single-arm case series should be greeted with healthy skepticism.

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### Conflicts of interest
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