11-1-2013

Journal club: role of endoscopic third ventriculostomy and ventriculoperitoneal shunt in idiopathic normal pressure hydrocephalus: preliminary results of a randomized clinical trial.

George M. Ghobrial, MD
Thomas Jefferson University, george.ghobrial@jefferson.edu

Michael J. Lang, MD
Thomas Jefferson University, Michael.Lang@jefferson.edu

As submitted to:

Neurosurgery

And later published as:

Journal Club Critical Analysis: Role of Endoscopic Third Ventriculostomy and Ventriculoperitoneal Shunt in Idiopathic Normal Pressure Hydrocephalus: Preliminary Results of a Randomized Clinical Trial

Volume 75, Issue 5, November 2013, pages: 908-910
DOI: 10.1227/NEU.0000000000000121

Journal Club Article: Pinto FCG, Saad F, de Oliveira MF, Pereira RM, de Miranda FL, Tornal JB, Lopes MIR, Ribas ESC, Valinetti EA, Teixeira MJ. Role of Endoscopic Third Ventriculostomy and Ventriculoperitoneal Shunt in Idiopathic Normal Pressure Hydrocephalus: Preliminary Results of a Randomized Clinical Trial. *Neurosurgery*. 72:845-854, 2013.

I. Significance/Context and Importance of the Study:

Idiopathic normal pressure hydrocephalus (INPH) was first defined by Hakim and colleagues in 1965[1], and its symptoms later classified by the clinical triad of gait dysfunction, urinary incontinence, and dementia. The exact pathophysiology of this disease is not well understood.[2] Surgical options for the treatment of INPH are ventriculoperitoneal shunt (VPS) placement (most commonly with a programmable valve), and endoscopic third ventriculostomy (ETV). VPS is by far the most common method used to treat INPH worldwide. Debate exists as to the superiority between the two management options. Historically, VPS placement with a programmable valve has led to improved outcomes with INPH.[3] More recent use of ETV has been reported in the form of retrospective data, demonstrating neurological improvement in up to 69% of patients.[4] However, a cited limitation of this study is the less stringent diagnostic criteria that fails to discriminate secondary NPH from INPH. This is important because of the higher success rates of treatment in secondary NPH.[2] This study by Pinto et al should be

commended for its attempt to compare ETV to VPS with a nonprogrammable valve for patients with the diagnosis of INPH prospectively. Given that the natural history of VPS carries a significant rate of shunt revision, there have been no prior attempts to provide level I evidence demonstrating equivalence or superiority of ETV to VPS placement.

II. Originality of the work

Literature pertaining to the surgical management of INPH exists largely in the form of retrospective cohort studies. Prior retrospective studies have been previously reported showing that VPS placement is beneficial in 75% of 132 patients at 18 months follow-up with INPH.[2] Likewise, there is no level I data pertaining to the use of ETV for the surgical treatment of INPH. There is however, level I data (randomized, not controlled) comparing various settings of fixed pressure valves in the setting of INPH. This present study is the first randomized clinical trial to compare therapeutic measures for INPH.

III. Appropriateness of the study design or experimental approach

The authors compare treatment of INPH with a VPS using a non-programmable valve (PS Medical, Medtronic, Minneapolis, MN) to an ETV in a randomized, parallel, open-labelled trial with enrollment in a 1:1 ratio. The selection of a non-programmable valve is due to cost and availability. Part of the inclusion criteria involves the 'tap test'(TT) where a lumbar puncture is performed and 40 mL of CSF is drained. They choose the tap test given its widely known validation and ease of use, despite its low sensitivity (<30%). More sensitive methods such as the prolonged lumbar drain (up to 100%) require higher technical expertise. The authors improve upon prior methodology of retrospective studies which only utilize the classic symptoms in better defining INPH for trial inclusion by the addition of radiographic evidence, the tap test, and excluding patients with any history of primary dementia, intracranial pathology, or medical comorbidities that may introduce bias into the diagnostic process. These stringent diagnostic criteria aim to limit the variability of results seen in the retrospective literature for surgical treatment of INPH.

The trial however is likely severely underpowered to detect a significance between the study populations. The authors calculated the study population size using Altman's nomogram and BERG score outcomes, for which they calculated 22 patients in each trial arm α=0.05 and power of 80%. The BERG scores from ETV and VPS retrospective trials used for this calculation are not explicitly cited. Recalculating the sample size using binary response rate (the primary outcome of this study being improvement of at least 2 points of the NPH score) yields significantly different results. If the response rates of the cited retrospective studies are used, with 70% and 80% response rate after ETV and VPS respectively, a standard difference of 0.23 is calculated, resulting in study arms of 350 patients required to detect significant difference at α=0.05 and power of 80%.This failure to appropriately power the study may have been even greater had the authors explicitly defined the hypothesis. Based on the stated rationale, it can be presumed that this trial is intended to be a non-inferiority trial, given the relatively similar response rates between ETV and VPS patients reported in the literature. Using the above stated response rates, with δ=0.1, α=0.05, power of 80%, each study arm would require 878 patients to detect a significant difference.

Finally, failure of the trial to demonstrate equivalence in primary outcome can be anticipated from the primary cited study justifying ETV. In the 2008 Italian study from Gangemi et al., a reponse rate of 69.1% was reported. While not reported directly in that manuscript, *post hoc* analysis of the results demonstrates a mean improvement in NPH score of 1.34 points with standard deviation of 1.4. As a result, only roughly a third of the patients in that study would have had a positive response as defined by the author's primary outcome.

IV. Adequacy of experimental techniques

While many early studies have reviewed the efficacy of CSF diversion for INPH, their inclusion criteria are usually limited to ventriculomegaly, dementia, and ataxia. More modern study criteria include clinical as well as radiographic criteria (Evans Index > 0.30), as well as lumbar CSF drainage testing in attempts to limit many of the confounding factors that cloud the diagnosis of INPH.

V. Soundness of conclusions and interpretation

The authors conclude that neurologic improvement is superior in the VPS group, specifically with gait findings at 12 months. It is difficult to reconcile that neurologic improvement is superior in the VPS group, and that it should be stressed that for this population of patients with INPH, conclusions can be made when they correlate with the specific diagnostic criteria in this study.

As previously mentioned, INPH is a disease with multiple confounding factors. Across a number of studies, inclusion and exclusion criteria differ. One of the largest series reported by Vanneste et al[5] of 131 patients found only a 31% improvement in symptoms on follow-up, contrasted with the 75% found by McGirk and colleagues.[2] These dramatically different results should illustrate to the clinician interpreting this study that the variance in methods across studies matter. For the conclusions of this study to translate over to a particular practice, ideally the diagnostic criteria for INPH should correlate between this trial and the neurosurgical practice.

The authors also state that it would be difficult to recommend ETV based off of their study. This statement is hard to reconcile given the design of the study. The small patient population, the lack of a control population, and over half of the patients diagnosed with INPH excluded (n=48) by their criteria highlight the challenge of this study, along with the trial design limitations discussed above. In addition to the large number of patients excluded prior to randomization, 5 of the 21 patients in the ETV arm were excluded due to anatomy that would add procedural risk. Four additional patients treated with ETV did not improve and underwent VPS placement, whereupon they were removed from the final analysis. The number of patients excluded from this study amounted to almost two-thirds of all patients diagnosed with INPH (57/90). Therefore, the authors rightly conclude that future multicenter studies with larger patient populations are needed.

VI. Relevance of discussion

The authors begin the discussion with its limitations. They emphasize that diagnostic criteria are important in defining INPH, a disease with symptoms that cannot be

completely controlled for. They draw on all of the prior literature and provide a more comprehensive diagnostic criteria for the study. As a result, they exclude a large number of patients (45/90). The authors use the 'tap test' as an inclusionary criteria for the study, despite its reportedly low sensitivity (26-61%). They also mention the alternatives in diagnostic criteria. Another key point raised is the type of VPS used, which is a fixed pressure valve in this study. Programmable valves are commonly used in the US, often in conjunction with anti-siphon devices that prevent overdrainage. Minor adjustments in these valves have been shown in retrospective studies to improve overall outcomes in NPH.[3] The rationale for this practice in the US is illustrated by the 20% rate of subdural hematoma all of which required a surgical evacuation.

VII. Clarity of writing, strength and organization of the paper

The strength of this manuscript is derived from this novel attempt to compare two established treatments for INPH. It is clearly written and easily understandable. The discussion is well organized, beginning with the limitations of this study which comprises roughly half of the overall discussion. The discussion then follows a logical progression of generalizability of the study and lastly interpretation.

VIII. Economy of words

This manuscript is concise and well-organized. Given the exceedingly low number of clinical series on the surgical treatment of INPH, a table listing the prior contributions would be helpful to the reader, broken down into two sections, for ETV and VPS.

IX. Relevance, accuracy and completeness of bibliography

This manuscript is well-referenced, and included all of the clinical cohort studies on surgical treatment of INPH. The first few references also include references to the original works by Hakim and Adams that discussed the early clinical symptoms of INPH.

X. Number and quality of figures, tables and illustrations

Figure 1 illustrates nicely the flow of enrollment in this study, illustrating the high number of patients excluded. Table 1 summarizes the score at various time intervals for all of the clinical outcomes measured. The scoring systems for the clinical outcomes are listed on a separate page in the methodology. The scales are not organized alike in that higher scores for all groups do not interpret as improvement or decline. It would be easier to read if the table had a legend that correlated increased numerical score correlated with clinical improvement or decline. Figure 2 shows a typical patient that underwent an ETV, pre and post intervention. This does not add much to the understanding of the study. It may be more useful to show sagittal MR imaging of the patients that were excluded, to give the author an idea of what was deemed too unsafe to perform an ETV. Excluding nearly 20% of potential candidates based off of anatomical variance alone is a high number and would be of interest to the reader. Likewise, for a typical VPS patients, a preoperative and postoperative CTH was included to demonstrate what the authors considered an adequate

cathether tip position. This does not add much clarification to the methodology and probably can be removed from the study.

XI. Future/next steps the paper logically leads to.

Despite being clinically characterized in 1965, INPH to this date does not have a clear pathophysiology, nor has there been a demonstration in the literature as to a superior form of surgical management. The authors in this study lay the groundwork for comparing surgical treatments for INPH. Future resources should be devoted to multicenter, randomized, controlled trials (RCTs) with larger patient populations. Given the considerable variation that is encountered between studies regarding diagnostic criteria for INPH, future studies should aim at standardizing this diagnostic process, in order to limit confounding variables due to disease overlap. All steps must be taken to maximize the relevance of future RCTs, which would especially be the use of programmable valves with siphon guards. Follow-up times should exceed one year to gain a better sense of the need for reoperation rate, especially in the ETV group.

References

1. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH. Symptomatic Occult Hydrocephalus with "Normal" Cerebrospinal-Fluid Pressure.A Treatable Syndrome. *The New England journal of medicine.* Jul 15 1965;273:117-126.

2. McGirt MJ, Woodworth G, Coon AL, Thomas G, Williams MA, Rigamonti D. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. *Neurosurgery.* Oct 2005;57(4):699-705; discussion 699-705.

3. Zemack G, Romner B. Adjustable valves in normal-pressure hydrocephalus: a retrospective study of 218 patients. *Neurosurgery.* Dec 2002;51(6):1392-1400; discussion 1400-1392.

4. Gangemi M, Maiuri F, Naddeo M, et al. Endoscopic third ventriculostomy in idiopathic normal pressure hydrocephalus: an Italian multicenter study. *Neurosurgery.* Jul 2008;63(1):62-67; discussion 67-69.

5. Vanneste J, Augustijn P, Dirven C, Tan WF, Goedhart ZD. Shunting normal-pressure hydrocephalus: do the benefits outweigh the risks? A multicenter study and literature review. *Neurology.* Jan 1992;42(1):54-59.