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

BACKGROUND: Currently, the most common treatment for idiopathic normal pressure hydrocephalus (INPH) is a ventriculoperitoneal shunt (VPS), generally with programmable valve implantation. Endoscopic third ventriculostomy (ETV) is another treatment option, and it does not require prosthesis implantation.

OBJECTIVE: To compare the functional neurological outcome in patients after 12 months of treatment with INPH by using 2 different techniques: ETV or VPS.

METHODS: Randomized, parallel, open-label trial involving the study of 42 patients with INPH and a positive response to the tap test, from January 2009 to January 2012. ETV was performed with a rigid endoscope with a 30° lens (Minop, Aesculap), and VPS was performed with a fixed-pressure valve (PS Medical, Medtronic). The outcome was assessed 12 months after surgery. The neurological function outcomes were based on the results of 6 clinical scales: mini-mental, Berg balance, dynamic gait index, functional independence measure, timed up and go, and normal pressure hydrocephalus.

RESULTS: There was a statistically significant difference between the 2 groups after 12 months of follow-ups, and the VPS group showed better improvement results (ETV = 50%, VPS = 76.9%).

CONCLUSION: Compared with ETV, VPS is a superior method because it had better functional neurological outcomes 12 months after surgery.

KEY WORDS: Cerebrospinal fluid shunts, Endoscopic third ventriculostomy, Idiopathic normal pressure hydrocephalus

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Idiopathic normal pressure hydrocephalus (INPH) is characterized by progressive gait apraxia, cognitive dysfunction, and urinary incontinence (Hakim-Adams syndrome). INPH is associated with communicating hydrocephalus (as demonstrated by brain computed tomography [CT] or magnetic resonance imaging [MRI]) and cerebrospinal fluid (CSF) pressure within the normal range (7–24 cm H₂O). The clinical triad of

Hakim-Adams syndrome is present in approximately 50% of cases; however, only 1 or a combination of 2 symptoms should be considered for diagnostic investigation.^{1–3}

Currently, there are 2 main therapeutic options: ventriculoperitoneal shunt (VPS) and endoscopic third ventriculostomy (ETV). The most widely accepted and performed option is the VPS with programmable valve implantation. Nevertheless, it is widely accepted that surgical treatment of patients with INPH is necessary, because surgery has been associated with a positive impact on the course of the disease.^{4,5}

In 2008, an Italian multicenter study reported the benefits of ETV in the treatment of 110 patients with INPH. After a 24-month follow-up period, it was reported that 69.1% of the patients had improved.⁶ This therapeutic success rate is

ABBREVIATIONS: BERG, Berg balance scale; DGI, dynamic gait index; EI, Evans index; ETV, endoscopic third ventriculostomy; FIM, functional independence measure; INPH, idiopathic normal pressure hydrocephalus; MMSE, Mini-Mental State Examination; NPH Scale, NPH Japanese Scale; TT, tap test; TUG, timed up and go; VPS, ventriculoperitoneal shunt

consistent with the results obtained with the VPS, ranging from 69% to 90%.⁷⁻¹³ However, that was a retrospective study, and the patients were not submitted to predictive functional tests, such as the tap test (TT), which is a test that is common in the literature.¹⁴

By performing a prospective randomized study, our objective is to compare the functional neurological outcomes of patients with INPH who have been treated with 2 different techniques: VPS or ETV.

PATIENTS AND METHODS

Trial Design

The study was a randomized clinical trial with a parallel design. The allocation ratio was 1:1. The patients were users of the medical facility and met the eligibility criteria.

Participants

The adopted diagnostic criteria for probable INPH¹⁵ were as follows:

- Clinical:** progressive clinical picture of gait apraxia, cognitive impairment (mainly recent memory and executive functions), and sphincter incontinence (urinary and/or fecal). The presence of only 1 or a combination of 2 symptoms is also seen as a suggestive criterion of the diagnosis. No personal history of subarachnoid hemorrhage, head trauma, cranial neurosurgery for any reason, or central nervous system infection.
- Radiological:** ventricular dilation, confirmed by brain CT and MRI, showing only the communicating hydrocephalus and an Evans index (EI) of >30%.
- Manometric:** CSF pressure within the normal range, as demonstrated by the opening pressure on lumbar CSF puncture between 7 and 24 cm H₂O.

Inclusion criteria included the diagnosis of probable INPH, age 55 to 75 years, duration of symptoms <24 months, preserved ambulation even with 2 supports, absence of other dementia syndromes, absence of malignant disease, compensated clinical comorbidities (hypertension, diabetes mellitus, hormonal disorders), positive TT result, and free and informed consent signed by patients and family members.

Exclusion criteria included the diagnosis of secondary normal pressure hydrocephalus (NPH), age <55 or >75 years, duration of symptoms >24 months, other associated dementia syndromes, incapacity to walk, malignancy, uncontrolled clinical comorbidities, negative TT result, or refusal to participate in the study by a family member or the patient.

This is a prospective randomized study conducted from January 2009 to January 2012 in patients with INPH at the Institute of Psychiatry, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, after approval by the ethics committee (CAPPESQ 0348/09).

Interventions

The TT was performed in the preoperative period to determine the CSF pressure and therapeutic prognosis by withdrawing 40 mL of CSF.^{16,17} Clinical evaluation was performed by a multidisciplinary team consisting of a neurosurgeon, a neurologist, and a physiotherapist. Two pre-TT evaluations were performed with a 1-week interval. Two additional evaluations were performed 3 and 72 hours after lumbar puncture. Each evaluation consisted of 6 clinical scales, and the TT was considered positive when the patient scored at least 2 points higher on the NPH Japanese Scale. The other scales were considered to be secondary outcomes, and, in general, they were related to changes in the NPH Japanese Scale. The best result of the 2 pre-TT evaluations and the 2 post-TT assessments was taken into account for comparison.

Scales Used

- Mini-Mental Status Examination^{18,19} (MMSE)**
Objective: to evaluate cognitive alterations.
Score: 0 to 30 (higher is better).
- The Berg Balance Scale^{20,21} (BERG)**
Objective: to evaluate the functional balance capacity in the following positions: sitting, standing, and leg support.
Score: 0 to 56 (higher is better).
- Functional Independence Measure²² (FIM)**
Objective: to assess the degree of dependence for the functional activities of daily living.
Score: 18 to 126 (higher is better; 18-36 total dependence, 37-90 moderate dependence, and 91-126 independent).
- Dynamic Gait Index²³ (DGI)**
Objective: to assess the disorders of gait dynamics. The individual is submitted to a walking test that consists of walking 6 m while making acceleration and deceleration movements and going through obstacles.
Score: 0 to 24 (higher is better).
- NPH Japanese Scale⁹ (NPH Scale)**
Objective: to score the patients according to the clinical characteristics of the NPH triad.
Score: 0 to 12 (higher is worse).

Gait Disorder

- 0 Absent
- 1 Unstable gait, but independent
- 2 Walks with 1 support
- 3 Walks with 2 supports or a walker
- 4 Cannot walk

Dementia

- 0 Absent
- 1 No apparent dementia, but apathetic
- 2 Socially dependent, but independent at home
- 3 Partially dependent at home
- 4 Totally dependent

Urinary Incontinence

- 0 Absent
- 1 Absent, but has polyuria or urinary urgency
- 2 Sometimes, only at night
- 3 Sometimes, even during the day
- 4 Frequent

6. Timed Up and Go²⁴ (TUG)

Objective: to assess mobility and balance. The test quantifies functional mobility in seconds by using the time during which the individual performs a task. The time it takes for the individual to rise from the chair, walk for 3 m up to a predetermined point, return to the chair, and sit down is measured.

Normal performance for healthy adults: 10 to 12 seconds.

Normal for impaired adults: 12.01 to 20 seconds.
Functional impairment: >20.01 seconds.

ETV was performed via a right precoronal burr hole (Kocher point) with a rigid ventricular neuroendoscope containing a 30° lens (Minop, Aesculap). The floor of the third ventricle was bluntly perforated in the midline halfway between the mammillary bodies and the infundibular recess. The fenestration was subsequently enlarged by inflating the balloon of a 4F Fogarty catheter. The ventriculostomy size was approximately 4 to 6 mm.

VPS was performed via a right precoronal burr hole (Kocher point). The chosen valve pressure (PS Medical, Medtronic) was based on the final manometry value at the TT. After the removal of 40 mL, a final pressure of <4 cm H₂O resulted in the selection of a low-pressure valve; a final pressure between 4 and 10 cm H₂O resulted in the selection of a medium-pressure valve; and a final pressure >10 cm H₂O resulted in the selection of a high-pressure valve.

Outcomes

Our hypothesis is that INPH treatment with the VPS is a superior option in comparison with ETV. To test this hypothesis, a complete evaluation was performed with the validated scales to quantify and compare the clinical profiles before and after surgery. The BERG Scale, DGI, FIM, MMSE, NPH Scale, and TUG were compared between the 2 groups. All patients were followed for 12 months, with prescheduled consultations at 3, 6, and 12 months after surgery. The patients were evaluated according to the 6 scales at 3 and 12 months.

Primary Outcome

After 1 year, the late postoperative result was classified as positive if the patient had at least a 2 points higher score on the NPH Scale.

Secondary Outcomes

The other scales, which were generally related to changes in the NPH Scale, were considered secondary outcomes. Surgical complications were also quantified in both groups to analyze safety and efficiency profiles.

Sample Size

The sample size was calculated according to a specific formula. The Altman normogram was performed to test the difference between the means in the BERG Scale²⁵ (before and after surgery) in both treatment groups.

Assuming that variances were equal in both groups, the difference between means was given as 85% (taking into consideration the differences in BERG) of the standard deviation, which contained a significance level of 5% and a power of 80%. The minimum sample size was 22 patients for each group. Because 10% of the patients did not perform follow-ups, each group comprised 25 patients. Randomization was performed in blocks of 10 patients to ensure that equal numbers of participants were in each group.²⁶

In our sample, 21 patients were randomly assigned to the ETV group and 21 were randomly assigned to the VPS group, totaling 42 patients. This number of patients is clearly less than the hypothetical number of patients, which is 50.

Randomization

The assignment of participants was performed in the operating room after the patients had been anesthetized. An independent physician from

the surgical ward of the hospital randomly chose between 2 equally sized and opaque white sealed envelopes that were placed side to side over a table. Each envelope contained a white sheet of paper with the name of a procedure on it (either VPS or ETV), thus choosing the intervention to be performed. All of the material needed for both procedures was present in the operating room. At this point, there was no blinding.

The patients were divided into 2 groups: group 1, ETV, and group 2, VPS.

Complications such as CSF leak, infection, shunt malfunction, or hyperdrainage were strictly observed, treated, and recorded for the later comparisons between the groups.

In the immediate postoperative period, and at 6 months postoperation, as well, all of the patients underwent a brain CT. An MRI with CSF flow study was performed on patients who underwent ETV but did not show clinical improvement for 3 months. This procedure was performed to determine the patency of the orifice on the third ventricle floor. The patient then underwent a VPS with a fixed-pressure valve. These patients were considered ETV failures. The results after the second procedure (VPS) were not used for statistical calculations, because we strongly believe that a patient who undergoes VPS after an unsuccessful previous ETV has a very different clinical profile than a patient who has not undergone ETV. Because of hydrodynamic alterations, we believe that these patients represent 2 different groups.

Statistical Methods

In this study, numerical data are presented as the mean with the range. Categorical data are presented as percentages. To determine the distribution of our data, the Kolmogorov-Smirnov test was performed. Statistical analysis of the clinical results 12 months after surgery was performed by using the Student *t* test for the paired and unpaired groups. The significance level was established as $P < .05$. All tests were corrected for multiple comparisons.

After 1 year, the late postoperative result was classified as positive when the patient scored at least 2 points higher on the NPH Scale. The other scales, which were generally related to changes in the NPH Scale, were considered to be secondary outcomes.

All of the scales were directly compared. However, if a particular scale was limited for a specific symptom of INPH, then the NPH Scale was considered the main outcome after it had been validated and designed to evaluate each of the 3 elements of the classic triad. Thus, improvement or an unchanged/worse outcome was based on the NPH Scale.

RESULTS

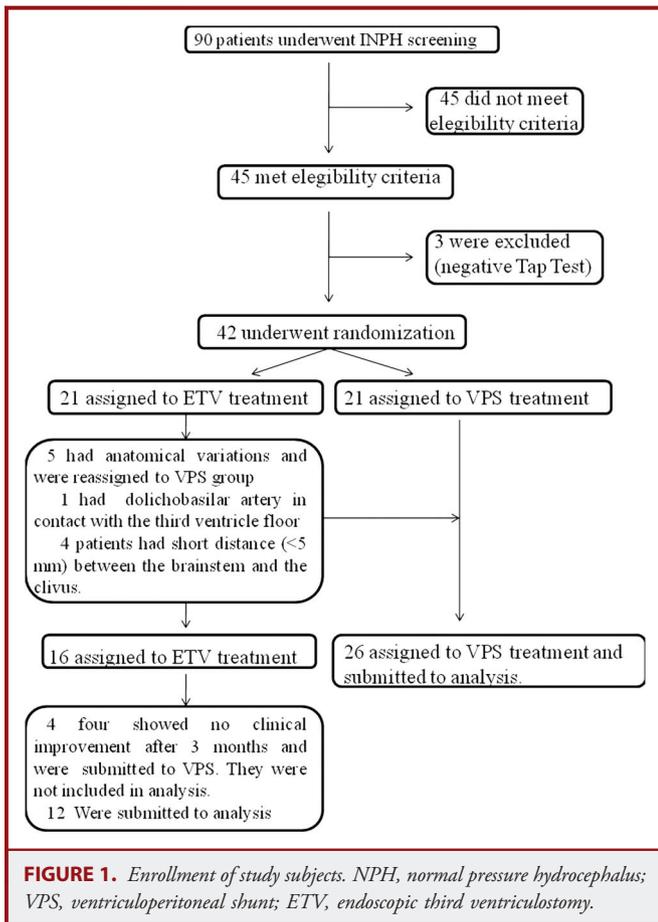
Participant Flow

Of the 90 patients who were diagnosed with NPH and treated during this period, 48 were excluded, because they did not meet the inclusion criteria for this study. Forty-two patients were enrolled. The full participant flow is shown in Figure 1.

Baseline Data

Of these patients, 24 were men and 18 were women. In the VPS group, ages ranged from 60 to 75 years (mean, 70 years). In the ETV group, the mean age was 71 years, ranging from 62 to 73 years. There was no statistically significant difference between the ages and the sex distribution of the VPS and ETV groups ($P > .05$).

Twenty-one patients had the complete NPH clinical triad, 10 patients had gait apraxia and cognitive impairment, 4 patients had



gait apraxia and urinary incontinence, and 7 patients only had gait apraxia. All of the patients had communicating hydrocephalus according to CT and MRI, and the EI ranged from 30% to 50.6% (mean, 38.9%).

At TT, the initial pressure ranged from 20 to 12 cm H₂O (mean, 15), and the final pressure after the withdrawal of 40 mL ranged from 12 to 2 cm H₂O (mean, 6). The results of chemocytological analysis were normal in all samples and showed no reaction for syphilis, tuberculosis, cryptococcosis, or neurocysticercosis.

Table 1 shows the values of the scores on the 6 scales before and after the TT and the postoperative follow-up period (3-12 months).

Group 1: ETV

Outcomes

Of the 21 patients randomly assigned to the ETV group, 5 had anatomical features that made the endoscopic procedure dangerous. One patient had a dolicho basilar artery that was in contact with the third ventricle floor, and 4 patients had a short distance (<5 mm) between the brainstem and the clivus. These 5 patients were relocated to group 2 to avoid basilar artery injury.

Of the 16 patients who constituted group 1, 9 were men and 7 were women. The mean age was 70 years, ranging from 60 to 75 years. The initial pressure ranged from 18 to 10 cm H₂O (mean, 15) before the TT, and the final pressure after the withdrawal of 40 mL ranged from 12 to 3 cm H₂O (mean, 6).

Of the patients undergoing the ETV, 4 showed no clinical improvement after 3 months. These patients underwent an MRI, which showed that they had a patent orifice in the third ventricle floor. The patients then underwent the VPS, but only 2 (50%) showed improvement after 1 year of follow-up. The other 12 patients (12/16, 75%) improved at 3 months post-ETV, but this improvement was only partially maintained after 12 months.

In the 12 patients who had some degree of clinical improvement, oscillatory up and down movements were observed on the third ventricle floor in the intraoperative period immediately after ETV (“flag signal”). The 4 patients who did not improve showed no “flag signal.” A typical subject from the ETV group is shown in Figure 2.

Harms

There were no intraoperative or postoperative complications, such as bleeding, fornix injury, infection, hematoma, or CSF leaks.

No patient in the ETV group showed a significant reduction in ventricular size on the brain CT. The EI ranged from 31% to 50.6% (mean, 39.7%) preoperatively and 31% to 49.1% (mean, 39.1%) 6 months after ETV.

Group 2: VPS

Outcomes

Of the 21 patients randomly assigned to the VPS group and the 5 patients relocated from group 1, 15 were men and 11 were women. The mean age was 71 years, ranging from 62 to 73 years. Seventeen low-pressure valves and 9 medium-pressure valves were initially implanted (PS Medical, Medtronic).

During the TT, the initial pressure ranged from 20 to 12 cm H₂O (mean, 16), and the final pressure after the withdrawal of 40 mL ranged from 10 to 2 cm H₂O (mean, 6). A typical subject from the VPS group is shown in Figure 3.

Harms

In the VPS group, 5 of the patients (5/26, 19%) who underwent implantation of a low-pressure valve had overdrainage with a significant reduction in ventricular size and a chronic subdural hematoma. These patients underwent another operation during which hematoma drainage was performed and the valve was replaced with a medium-pressure valve (PS Medical, Medtronic).

After the 3- and 12-month follow-up periods, 20 patients (20/26, 77%) showed improvement. No patient showed signs of infection.

In the remaining patients, ventricular reduction on the skull CT at 6 months was slight but evident. In these patients, the EI ranged from 30% to 48.1% (mean, 38.1%) preoperatively, and 26.6% to 41.4% (mean, 36.6%) 6 months after VPS.

TABLE 1. Score at Assessments During TT and in the Postoperative Follow-up, Shown by Group, Scale, and Moment^{a,b}

Group	Best Before TT	Best After TT	After 3 Months	After 12 Months
Group 1-ETV (n = 16)				
MMSE	21 (29-8)	21 (30-12)	22 (28-3)	22 (28-9)
BERG	28 (51-1)	35 (56-1)	31 (49-0)	29 (49-0)
FIM	79 (115-22)	85 (116-32)	78 (108-21)	82 (110-22)
DGI	9 (17-1)	13 (24-1)	13 (23-0)	8 (20-0)
NPH Scale	7 (11-2)	6 (10-2)	6 (12-2)	6 (12-3)
TUG	47 (158-10)	34 (110-9)	33 (105-12)	46 (95-12)
Group 2-VPS (n = 26)				
MMSE	21 (29-9)	22 (30-11)	20 (27-12)	20 (30-10)
BERG	27 (51-3)	39 (55-3)	39 (56-5)	37 (56-5)
FIM	76 (111-19)	85 (118-44)	91 (126-49)	92 (124-49)
DGI	10 (20-1)	15 (24-5)	15 (24-0)	14 (24-0)
NPH Scale	6 (11-1)	5 (11-1)	5 (12-0)	4 (12-0)
TUG	42 (156-10)	25 (60-7)	29 (76-7)	32 (110-7)

^aTT, tap test; ETV, endoscopic third ventriculostomy; VPS, ventriculoperitoneal shunt; MMSE, mini-mental state examination; BERG, Berg balance scale; FIM, functional independence measure; DGI, dynamic gait index; NPH Scale, NPH Japanese scale; TUG, timed up and go.

^bValues shown are the average (max–min).

Comparison Between the Groups

The ETV group had slightly better scores on some of the scales (MMSE, BERG, NPH Scale, and TUG) after 3 months, but this improvement was only partially maintained after 12 months. Some of the scales had lower scores (BERG, DGI), whereas the TUG returned to the pre-TT values (Table 1).

The VPS group showed better scores on the motor scales after 3 and 12 months (BERG, FIM, DGI, NPH Scale, and TUG). In addition to maintaining the improvement achieved at 3 months, the patients in these groups had increased scores on 2 additional scales (FIM and NPH Scale). For the rest of the scales, the variations were not significant and were considered stable. The TUG test score was considered better than the pre-TT value (Table 1).

The only surgical complication observed in the follow-up that was present in the VPS group was a subdural hematoma, which happened in 5 of 26 patients. These patients, however, underwent a successful valve replacement operation and had a favorable 12-month outcome (Table 2).

The results were analyzed by the Student *t* test, showing that there was a statistically significant difference between the percentages of patients who improved in both groups after the 12-month follow-up (Table 3). These results suggest that VPS treatment results in a more favorable outcome. In contrast, the results from the ETV group did not show any differences between the initial pre-TT tests and the 12-month follow-up (Table 1).

DISCUSSION

Limitations

Initially, the TT was the only preoperative test used for the treatment of patients because of its applicability, validity and

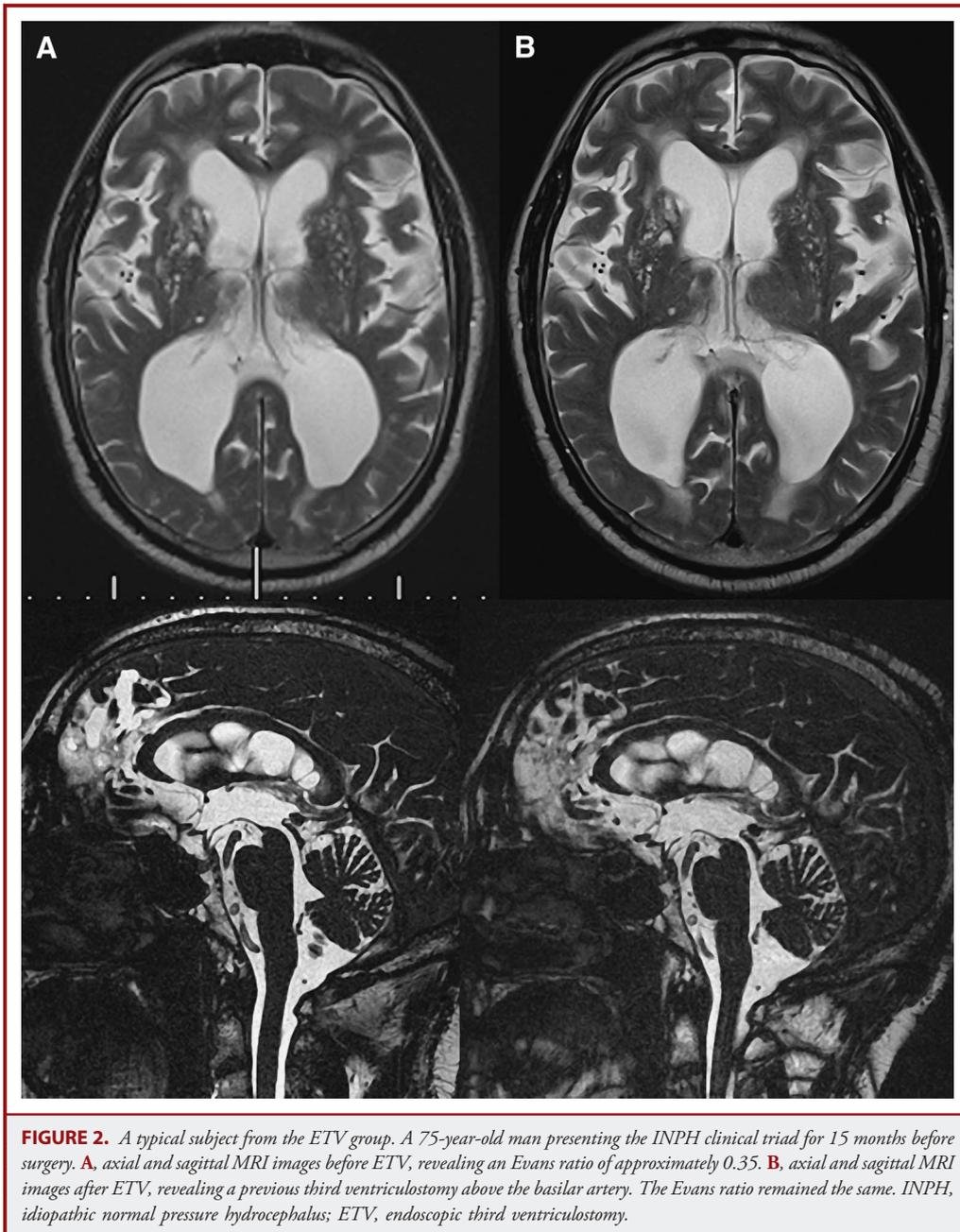
availability, as well as patient comfort, because hospitalization was not required during the protocol. Additionally, we believe that this procedure did not lead to significant issues for the randomization process of the clinical trial.

However, the TT has a limited sensitivity (26%–61%) in comparison with the infusion test (57%–100%) and results in a prolonged external lumbar drainage in excess of 300 mL (50%–100%), which may cause missing of potential patients. In terms of the positive predictive value, the TT is similar to the infusion test (75%–92%), and both tests are below the external lumbar drainage (80%–100%).^{14,16}

In addition, the MMSE has significant limitations, and cognitive questionnaires that are more complete, such as the Montreal Cognitive Assessment and the Cambridge Cognitive Examination, are available.^{27,28} However, the MMSE test is a general tool used worldwide to assess dementia syndromes and is widely used in the literature.

Interpretation of the results should be made cautiously. Because gait apraxia was the only clinical outcome with a significant difference between treatment groups, there may be a potential diagnosis bias because of the limited values of the MMSE. The use of a more elaborate scale (as mentioned above)^{27,28} or a more thorough neuropsychological assessment may resolve the issue of bias.

An important limitation of this trial is that the current management of INPH is the implantation of a programmable VPS. Therefore, the use of nonprogrammable valves may decrease, but not invalidate, the quality of the data presented by the study. We did not use the programmable valve prosthesis in our patients because it is not available for use in the Brazilian public health system. In addition, almost 20% of the patients in the VPS group experienced complications, which included subdural hematomas in the implanted low-pressure valves, that required reoperation.



Although these complications could have been avoided with programmable valves, the final outcome of the results likely would have remained unchanged.

A larger sample follow-up might provide more strength to the conclusions exposed. However, this study highlights the controversy concerning INPH treatment and may generate discussion about future treatment options.

The discrepancies between the results for patients less than 65 years of age compared with those over 65 years of age are

intriguing. It would be useful to compare the CT or MRI images of these 2 groups of patients to determine whether the hydrocephalus pattern is different, because these results would contribute to the understanding of the physiopathological differences between age groups as well as between different treatment options. This knowledge is important in determining which patients would benefit most from INPH treatment. Because this topic is beyond the scope of this article, we hope to address these questions in future scientific communications.

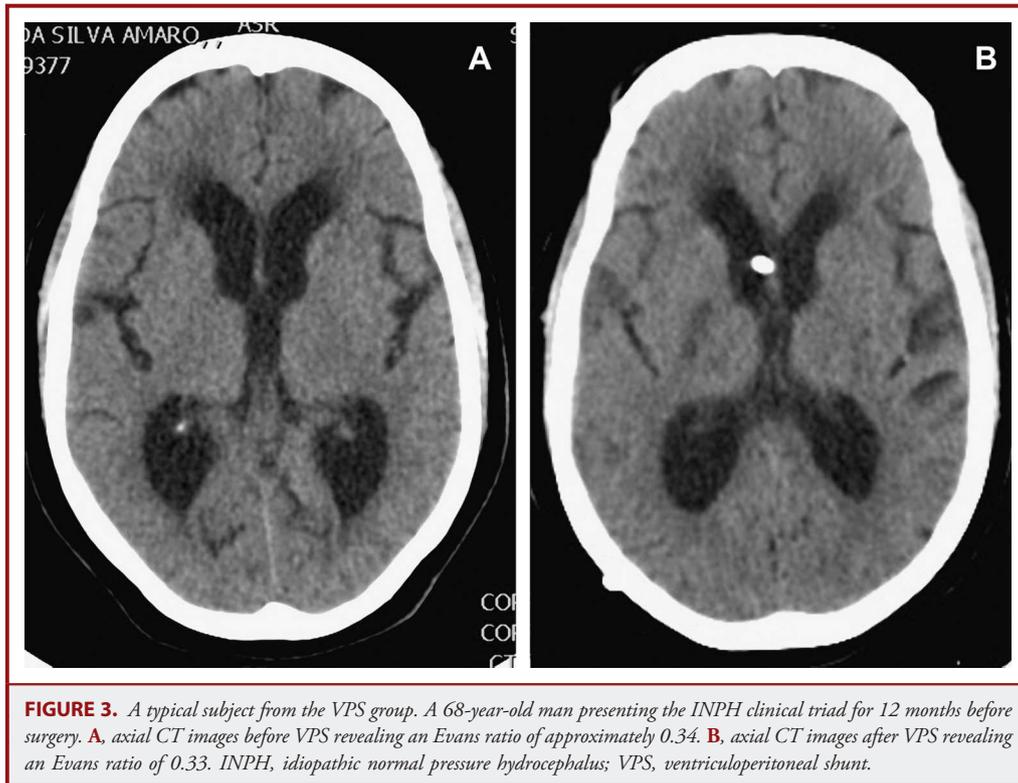


FIGURE 3. A typical subject from the VPS group. A 68-year-old man presenting the INPH clinical triad for 12 months before surgery. **A**, axial CT images before VPS revealing an Evans ratio of approximately 0.34. **B**, axial CT images after VPS revealing an Evans ratio of 0.33. INPH, idiopathic normal pressure hydrocephalus; VPS, ventriculoperitoneal shunt.

Several confounding factors must be considered. Several medical diseases present with the same symptoms as the classical triad of NPH, and we are unable to entirely control for all of those diseases. For example, a large number of patients with dementia-like syndromes have been categorized as having Alzheimer disease,^{9,18,20} and symptoms that are not typical to Alzheimer disease may be present in such patients.

Vascular dementia and other types of dementia are more frequent in older patients, which is also the case with NPH. Clinical comorbidities, such as hypertension and hypercholesterolemia, are also common features of different conditions and might interfere with the diagnosis of patients. Gait and urinary disturbances are also associated with a myriad of other diseases,

such as Parkinson disease and urologic/gynecologic/psychiatric urinary incontinence. Rigid patient selection criteria, as described in Methods, were adopted to address these issues. Therefore, we do not believe that any confounding factors interfered with our analysis. For example, rather than identifying patients as having NPH gait symptoms, we referred to these patients as being unable to walk because of orthopedic diseases.

Generalizability

The identification of patients with INPH and the implementation of effective treatment for INPH are current challenges for physicians and neurosurgeons. INPH is a disorder classified as a type of dementia that affects elderly persons and can be reversed if promptly diagnosed and treated.

With improvements in quality of life and the subsequent increase in life expectancy, it is expected that a greater number of elderly individuals will have this disease. In 2008, the incidence and prevalence of INPH were calculated in a stable community of 220 000 inhabitants in Norway, with values of 5.5/100 000 and 22/1 000 000, respectively.²⁹

The current recommended treatment is the implantation of VPS with a programmable valve. However, this type of treatment presents both the inconvenience of a prosthesis implant and medium- to long-term risk of complications requiring reoperation, such as infection, mechanical malfunction, and overdrainage. The UK registry shows a VPS reoperation rate of 22% in 5 years for the

TABLE 2. Comparison of Complications Between Both Groups^{a,b}

Complication	ETV Group	VPS Group
Significant bleeding	0	0
Fornix injury	0	0
Subdural hematoma	0	5/26 (19%)
Infection, wound dehiscence, and CSF leaks	0	0

^aETV, endoscopic third ventriculostomy; VPS, ventriculoperitoneal shunt.

^bThe only complication observed in the follow-up was present in the VPS group and was a subdural hematoma. Its frequency was high (19%), although with a successful reoperation, valve replacement, and favorable 12-month outcome.

TABLE 3. A Statistically Significant Difference Between the Percentage of Patients Who Improved in Both Groups (ETV or VPS) 1 Year After Surgery ($P < .05$)^{a,b}

Improvement (12 mo After Surgery)	ETV, n (%)	VPS, n (%)	Total, n (%)	VPS After ETV Failure, n (%)
Yes	8 (50)	20 (76.9)	28 (66.7)	2 (50)
No	8 (50)	6 (23.1)	14 (33.3)	2 (50)
Total	16 (100)	26 (100)	42 (100)	4 (100)

^aETV, endoscopic third ventriculostomy; VPS, ventriculoperitoneal shunt.

^bThe patients that were submitted to VPS after ETV failure are shown in the last column.

treatment of hydrocephalus in adults.³⁰ The siphoning effect, which is responsible for overdrainage, can be partially controlled with an antisiphoning device associated with the valve system, a flow-regulated valve, or a change in the programmable valve-opening pressure so that overdrainage indications can be detected (subdural fluid collections).³¹

Thus, if INPH patients could be treated by ETV with the same long-term effects as the VPS, the risk of long-term complications would be reduced. The reduction of long-term complications would be an advantage for elderly patients, who often have comorbidities.

The Italian multicenter retrospective study published in 2008 caused great debate in the neurosurgical community. This study showed a success rate of 69.1% for ETV treatment in 110 patients with INPH after a follow-up period of at least 2 years. Much of the criticism of this work originated for the following reasons: there was a lack of a clear distinction between the cases of idiopathic NPH and possible cases of secondary NPH, and the predictive functional test used was the monitoring of intracranial pressure, rather than the tests that are more widely used in the literature, such as the TT, the lumbar infusion test, and external lumbar drainage monitoring for 72 hours.^{6,14}

Interpretation

To address unresolved issues in the literature, we improved the methodology commonly used and only included the patients with INPH that had a positive response to the TT and a preserved walking capacity. The design of this study was prospective, and the surgical treatment was randomized in the operating room immediately after the induction of anesthesia. The initial objective was to compare the functional neurological outcomes of patients with INPH within 1 year after either the VPS with a fixed pressure valve or ETV. In this study, we did not use the programmable valve prosthesis, because it was not available for use in the Brazilian public health system.

The TT was shown to be a universal predictive test. However, there were different results in the ETV and VPS groups. We observed that the percentage of patients who improved in the first year of follow-up was different in both groups, with values similar to those found in the literature for the VPS, which range from 70% to 90%.⁷⁻¹³ However, patients treated with the VPS showed

a much more significant neurological functional gait improvement after 12 months than patients treated with ETV.

Five patients treated with the VPS (5/26, 19%) showed overdrainage with a significant reduction in ventricular size and chronic subdural hematoma. These patients underwent reoperation with hematoma drainage and valve replacement. We believe that these complications could have been avoided by using a programmable valve.

The patients who did not initially improve with ETV had the VPS implanted, and 50% of them improved after the second surgery, as previously mentioned in the literature. These patients had no pulse on the third ventricle floor (“flag signal”) immediately after ETV. This finding was also described by Gangemi et al⁶ and represents the most important piece of information that is predictive of the therapeutic success of ETV. The results after the second procedure (VPS) were not used for the statistical calculations because we strongly believe that a patient with a previous ETV who is then submitted to a VPS has a very different clinical profile compared with a patient with no previous ETV.

We hypothesize that ETV promotes functional improvement in patients with INPH. We believe that during systole, when there is peak intracranial pressure, the surgically opened third ventricle floor will function as an escape mechanism for this mechanical energy, and, therefore, the frontal lobes, basal ganglia, and thalami will receive a lower intensity of the pressure pulse. This will lead to an improvement in blood perfusion in these regions, enabling the functional recovery of neurons affected by the progression of disease (INPH).^{4,32}

Considering the preliminary results of the first year of follow-ups and the absence of the “flag signal” in all of the patients who underwent an ETV but did not improve, we suggest that if the “flag signal” during ETV treatment is not observed intraoperatively, the patient should immediately undergo VPS through the same burr to avoid a future surgical anesthetic procedure.

To assess the long-term effects of ETV and VPS (5 years), patients in this study remain under surveillance and monitoring. The other patients who have recently been included in the study but who have not yet completed the follow-up period for observation will increase the size of our cohort for future considerations.

Considering what has been observed thus far, we cannot suggest ETV as the best option for initial treatment of INPH, because the

VPS had better functional neurological outcomes after 1 year. However, ETV can be considered a treatment option for INPH. ETV caused no significant improvement, but the scores on the scales were maintained. Having an untreated control group would indicate whether there was any impact on the natural evolution of INPH.

CONCLUSION

ETV and the VPS with fixed pressure represent different tools to manage INPH, and VPS shows the best gait outcome 12 months after surgery.

Future multicenter studies with larger sample sizes are expected to confirm our findings and address any issues about INPH surgical treatment.

Disclosures

The full trial protocol is discussed in the text. Further protocol data are available from the authors.

Trial Registration: CAPPEQ 0348/09. This study was carried out at the Hospital das Clínicas, University of São Paulo, São Paulo, Brazil. There was ethical adherence, and the study was registered with the protocol CAPPEQ 0348/09. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The authors should be complimented for having provided the neurosurgical community with the preliminary results of this perspective randomized clinical trial aiming to clarify which is the best surgical option between endoscopic third ventriculostomy (ETV) and ventriculo-peritoneal shunt (VPS) for the treatment of idiopathic normal pressure hydrocephalus (INPH). We really need well-designed randomized prospective studies to shed light on a disease where Level 1 evidences that favor surgical treatment are still lacking¹ and patient selection is still extremely variable and debated.

This is not surprising, since even today the actual physiopathological basis of the disease are not yet completely understood and certain diagnosis is further complicated by the variability in the clinical presentation and course.

We fully agree with the authors that chose and applied strict inclusion criteria in order to obtain the most homogeneous population possible. As a consequence of this, out of 90 patients screened, only 42 were included. This supports the general feeling that multicenter trials involving big caseload centers need to be designed.

This study again confirms that ETV is able to obtain a kind of therapeutic result in some of INPH patients, thus stressing how complicate is the issue of cerebrospinal fluid (CSF) circulation and reabsorption, how simplistic is the classification of communicating and non-communicating hydrocephalus, and, once again, our lack of a complete understanding of the physiopathology of this disease. In addition, what further complicates the issue of correct surgical indication in iNPH is patient selection and recognition of similar clinical entities such as long-standing overt ventriculomegaly of adulthood-LOVA² in which the hydrocephalus is invariably due to aqueductal stenosis and for which ETV appears as the best form of treatment, when needed (i.e. decompensated patients).

The main limitations of this study are represented by the kind of tests used for patients selection, the tap test (TT), the small sample and the use of nonprogrammable valves, although there is consensus that TT alone has low sensitivity³ and the implantation of programmable VPS seems to be beneficial in the management of INPH.⁴

Finally, the best functional outcome at 1 year follow-up obtained by VPS reinforces its role in the treatment of true INPH and limits the indication of ETV to a subgroup of patients that still requires to be clearly identified.

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