

ORIGINAL ARTICLE

A Randomized Trial of Shunting for Idiopathic Normal-Pressure Hydrocephalus

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ABSTRACT

BACKGROUND

Idiopathic normal-pressure hydrocephalus is a neurologic disorder characterized by impaired gait, balance, cognition, and bladder control in older adults. The disorder is treated with shunt surgery, but the effectiveness of shunting is unclear.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial involving participants selected for shunt surgery on the basis of gait-velocity improvement with cerebrospinal fluid (CSF) drainage. Participants were randomly assigned to an open-shunt valve setting (opening pressure, 110 mm of water) or a placebo valve setting (opening pressure, >400 mm of water) of a noninvasively adjustable shunt. The primary outcome was the change in gait velocity 3 months after surgery. Secondary outcomes were the change at 3 months in the Tinetti scale total score (range, 0 to 28; lower scores indicate worse gait and balance), Montreal Cognitive Assessment (MoCA) score (range, 0 to 30; lower scores indicate worse cognition), and Overactive Bladder Questionnaire score (range, 0 to 100; higher scores indicate worse urinary incontinence).

RESULTS

A total of 99 participants underwent randomization and received the assigned intervention. At 3 months, gait velocity had increased in the open-shunt group (mean [$\pm$ SD] change, 0.23 $\pm$ 0.23 m per second; assessed in 49 participants) and was unchanged in the placebo group (mean change, 0.03 $\pm$ 0.23 m per second; assessed in 49 participants), resulting in a treatment difference of 0.21 m per second (95% confidence interval, 0.12 to 0.31; $P<0.001$). A significantly greater improvement in the open-shunt group than the placebo group was seen for the Tinetti scale score (mean change, 2.9 points vs. 0.5 points; $P=0.003$) but not the MoCA score (1.3 points vs. 0.3 points) or the Overactive Bladder Questionnaire score (–3.3 points vs. –1.5 points). The results regarding adverse events were mixed, with more participants in the placebo group reporting falls (46% vs. 24%), an equal percentage having cerebral bleeding (2% in both groups), and more participants in the open-shunt group having subdural bleeding (12% vs. 2%) and positional headaches (59% vs. 28%).

CONCLUSIONS

Among participants with idiopathic normal-pressure hydrocephalus who had a response to temporary CSF drainage, shunting resulted in significant improvements at 3 months in gait velocity and a measure of gait and balance but not in measures of cognition or incontinence. (Funded by the National Institute of Neurological Disorders and Stroke and the Trial Innovation Network; PENS ClinicalTrials.gov number, NCT05081128.)

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IDIOPATHIC NORMAL-PRESSURE HYDROCEPHALUS, a disorder first described in 1965, is characterized by neurologic gait and balance impairment, urinary urgency and incontinence, cognitive impairment, and cerebral ventriculomegaly in persons older than 60 years of age.¹ The prevalence of the disorder is estimated to be as high as 1.5% (1500 per 100,000 persons) among those 65 to 70 years of age and increases with age, reaching as high as 7.7% among persons 86 years of age or older.²⁻⁴ Neurologic impairment becomes more severe and death is more likely the longer idiopathic normal-pressure hydrocephalus remains untreated.⁵⁻⁷ Although no medical treatment exists, the symptoms of idiopathic normal-pressure hydrocephalus have long been reported to be reversible with surgical implantation of a cerebrospinal fluid (CSF) shunt, most commonly ventriculoperitoneal or lumboperitoneal shunts.^{8,9} Since 2005, international and Japanese guidelines for the treatment of idiopathic normal-pressure hydrocephalus have standardized patient selection for shunt surgery,^{10,11} which has resulted in studies in which improvement was observed in 70 to 80% of the patients selected on the basis of response to temporary CSF drainage or CSF infusion testing.^{8,9,12-14}

Nonetheless, the clinical effectiveness of shunt surgery in idiopathic normal-pressure hydrocephalus has been subject to skepticism to the point of a call for a moratorium on the procedure because of variability of study results, questionable durability of benefit, the risks of surgery, and the potential for a strong placebo effect.^{15,16} The results of three small-sample, randomized, placebo-controlled trials suggested that shunt surgery was effective, but a 2024 Cochrane review noted, “there is a need for similar studies to increase the certainty of the findings presented.”¹⁷⁻²⁰ Therefore, we designed and conducted the Placebo-Controlled Efficacy in iNPH [Idiopathic Normal-Pressure Hydrocephalus] Shunting (PENS) trial.

METHODS

TRIAL DESIGN

We conducted an international, multicenter, prospective, double-blind, randomized, placebo-controlled trial. The trial intervention was the initial valve setting (open-shunt or placebo) of a commercially available, noninvasively adjustable shunt valve (Codman Certas Plus Programmable Valve with

SiphonGuard, Integra LifeSciences). Because the shunt valves were considered part of standard care, the cost of the valves was covered by the patients' insurance; the shunt-valve manufacturer had no role in the design or conduct of the trial.

The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). The Johns Hopkins University Clinical Coordinating and Administrative Center gathered the data, and the University of Utah Data Coordinating Center analyzed the data. Trial sites were selected on the basis of their experience in managing idiopathic normal-pressure hydrocephalus. Approval was obtained from a central institutional review board at Johns Hopkins Medicine for all U.S. sites and from local institutional review boards for the Canadian and Swedish sites. Additional details are provided in the Supplementary Appendix (available at NEJM.org).

PARTICIPANTS

In accordance with the international idiopathic normal-pressure hydrocephalus guidelines, patients selected for ventriculoperitoneal shunt surgery on the basis of their gait-velocity response to temporary CSF drainage were eligible. At baseline, patients who could not walk 10 m or who required assistance from a person to walk were excluded, as were those with a gait velocity of 1.0 m per second or higher unless velocity improved at least 30% with CSF drainage.

Patients were allowed to participate if they had coexisting diseases that did not interfere with participation in trial assessments. Patients with secondary hydrocephalus, previous cranial neurosurgical procedures, or who received long-term anticoagulation were excluded.

RANDOMIZATION AND BLINDING

Immediately before surgery, participants were randomly assigned in a 1:1 ratio to an open-shunt valve setting or a placebo valve setting. The placebo group was assigned valve setting 8 (opening pressure, >400 mm of water).²¹ The open-shunt group was assigned valve setting 4 (opening pressure, 110 mm of water); however, valve settings 5 and 6 (145 or 180 mm of water, respectively) were allowed at the surgeon's discretion for participant safety.²¹ Trial-group assignments were concealed from trial participants and personnel, except for the investigators responsible for shunt



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adjustments, and were disclosed only for reasons related to participant safety.

After completion of 3-month outcome evaluations, shunts in both groups were adjusted to an open valve setting while the initial valve setting remained concealed. The participants were informed that the shunt would remain open.

OUTCOME MEASURES AND METHODS

Because eligibility was based on response to CSF drainage, an interval of at least 4 weeks was required to allow symptoms to return before baseline trial assessments were performed. The primary outcome was assessed 3 months after surgery. Data on the outcomes for all the participants at 12 months after adjustment to the open-shunt valve setting are being collected, including the results of detailed neuropsychological testing and CSF and imaging biomarkers, which are not included in this article.

The primary outcome was the change from baseline to 3 months in maximum gait velocity (in meters per second), which was measured over three assessments in which participants walked 10 m. Participants were instructed to walk as fast as they felt safe, without running, to a goal 2 m beyond the finish line. Time was recorded from a standing start (toes at the starting line) until one foot crossed the finish line. Participants were permitted assistive devices but not assistance from another person.

Secondary outcomes were the change at 3 months in the Performance-Oriented Mobility Assessment (Tinetti scale) total score (scores range from 0 to 28, with lower scores indicating worse gait and balance)²²; Montreal Cognitive Assessment (MoCA), version 8.1, score (scores range from 0 to 30, with lower scores indicating worse cognition)²³; and the Overactive Bladder Questionnaire, Short Form, score (scores range from 0 to 100, with higher scores indicating worse urinary incontinence).²⁴ Tertiary outcomes were the change at 3 months in scores on the Symbol Digit Modalities Test (the mean score in the normal-health population ranges from 33.31±9.02 to 69.91±12.64, with lower scores indicating decreased attention and processing speed)²⁵; the Flanker Inhibitory Control and Attention Test (scores range from 0 to 100, with lower scores indicating worse inhibitory control and attention) and the Dimensional Change Card Sort Test

(scores range from 0 to 100, with lower scores indicating worse cognitive flexibility), both from the NIH (National Institutes of Health) Toolbox²⁶; the Beck Depression Inventory–II (scores range from 0 to 63, with higher scores indicating worse depression)²⁷; the Lawton Activities of Daily Living and Instrumental Activities of Daily Living questionnaire (scores range from 0 to 32, with higher scores indicating worse function)²⁸; the modified Rankin scale (scores range from 0 to 6, with higher scores indicating worse disability)^{29,30}; and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) visual analogue scale for quality of life (scores range from 0 to 100, with lower scores indicating worse health).³¹ Magnetic resonance imaging (MRI) evaluation to calculate lateral ventricular volume and the Evans ratio was performed on deidentified T1 images with the use of segmentation from spatially localized atlas network tiles and a deep-learning “brain extraction” tool.^{32,33}

ASSESSOR TRAINING AND QUALITY CONTROL

Research coordinators were trained to administer the gait and neuropsychological assessments. All gait assessments were video recorded for blinded review, quality control, and feedback. Recordings were not used for data acquisition. Research coordinators were approved by a trial neuropsychologist and required to have MoCA certification. For quality control, discrepancies in administration and scoring were reviewed by either of two neuropsychologists, and training was provided when needed.

SAFETY MONITORING

Prespecified safety outcomes included total reported falls, clinically significant falls, surgical complications, and complications related to CSF overdrainage, including subdural hygromas and hematomas. Prespecified thresholds for stopping the trial were regularly reviewed with the data and safety monitoring board. Shunt valve settings were checked at each visit and after MRI scans and, if needed, were adjusted to the appropriate setting while the initial shunt valve setting remained concealed.

STATISTICAL ANALYSIS

We calculated that a sample size of 100 participants would provide more than 90% power to detect a mean (±SD) between-group difference in

gait-velocity improvement of 0.20 ± 0.29 m per second, which accounted for interim analyses and attrition.¹⁹ Two conservative interim efficacy analyses of 3-month outcomes were prespecified on enrollment of approximately one third and two thirds of the target population.³⁴

The reported analyses implemented multiple imputation, which assumes that differences between missing and available 3-month outcome data can be accounted for by available participant baseline and follow-up information. Outcomes at 3 months were analyzed with the use of linear regression, with trial group as the predictor and adjustment for baseline values and prespecified covariates (age for all outcomes and educational attainment for neuropsychological measures). Separate variances were modeled according to trial group. Robustness assessments included replication of trial results with the use of the mean of the three gait assessments, exclusion of participants with off-protocol valve adjustments (the per-protocol population), use of the regimen implemented as of the 3-month evaluation as a predictor (the as-treated population), and modeling with the use of imputed missing outcome data (Tables S8 through S11 in the Supplement Appendix).

Significance testing was two-sided, with an alpha level of 0.05 for the primary outcome. The overall type I error for secondary outcomes was controlled with a Bonferroni–Holm procedure.³⁵ Analyses of tertiary outcomes were not controlled for multiplicity; results are shown as point estimates with 95% confidence intervals without formal hypothesis testing. A post hoc logistic-regression analysis of dichotomized 3-month modified Rankin scale scores (grouped as 0 to 2 points and 3 to 6 points) was also performed, with control for trial group as the predictor and adjustment for modified Rankin scale score at baseline. The percentage of participants with complications was compared between trial groups with the use of two-sided Fisher’s exact testing with mid-P-value correction.³⁶

RESULTS

PARTICIPANT RECRUITMENT AND CHARACTERISTICS

A total of 301 of 1424 patients undergoing CSF drainage between April 25, 2022, and January 29, 2025, were eligible for inclusion in the trial. Of

237 patients approached for the trial, 125 (53%) provided consent and 99 underwent randomization (49 were assigned to the open-shunt group and 50 to the placebo group). In the placebo group, 3 participants withdrew from the trial and 1 died before the primary outcome was assessed (Fig. S1 and Tables S1 through S5).

A total of 52% of the participants were men and 48% were women, with a mean age of 75.0 ± 5.7 years; 63% had a bachelor’s degree or higher. Age, sex, educational attainment, and coexisting diseases were similar in the two trial groups (Tables 1 and 2 and Table S6).

After the first planned interim analysis on February 5, 2024, the data and safety monitoring board determined that the trial could continue. After the second interim analysis (involving 74 of the 99 randomly assigned participants with 3-month outcomes) on January 29, 2025, showed a significant treatment effect favoring the open-shunt valve setting (observed $P < 0.001$; the monitoring boundary for stopping enrollment in the trial was $P < 0.024$), the data and safety monitoring board stopped enrollment while allowing the trial to continue to completion at 12 months of the open-shunt valve setting. After the central institutional review board was consulted, the shunts for 2 participants in the placebo group who had not reached the 3-month outcome assessment were changed to an open setting; these 2 participants were included in the placebo group for the trial analyses, and their 3-month outcomes were imputed.

OUTCOMES AT 3 MONTHS

Primary Outcome

Gait velocity increased in the open-shunt group (mean change, 0.23 ± 0.23 m per second) and was unchanged in the placebo group (mean change, 0.03 ± 0.23 m per second), resulting in a treatment difference of 0.21 m per second (95% confidence interval [CI], 0.12 to 0.31; $P < 0.001$) (Table 3). The distribution of the change in gait velocity, with imputed missing data excluded, is shown in Figure 1. A total of 37 of 46 participants with available data (80%) in the open-shunt group and 10 of 42 participants with available data (24%) in the placebo group had a change in gait velocity of at least 0.1 m per second, which exceeded the threshold of substantial meaningful change of 0.10 m per second in older adults.³⁷

Table 1. Demographic Characteristics of the Participants Who Underwent Randomization.*

Characteristic	Open Shunt (N=49)	Placebo (N=50)	Overall (N=99)
Age at randomization — yr	75.1±5.7	74.9±5.8	75.0±5.7
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	0	0
Asian	2 (4)	3 (6)	5 (5)
Black	2 (4)	1 (2)	3 (3)
Native Hawaiian or other Pacific Islander	0	0	0
White	45 (92)	45 (90)	90 (91)
Multiracial	0	0	0
Unknown or not reported	0	1 (2)	1 (1)
Hispanic or Latino ethnic group — no. (%)‡			
Yes	2 (4)	0	2 (2)
No	47 (96)	50 (100)	97 (98)
Unknown or not reported	0	0	0
Female sex — no. (%)	23 (47)	25 (50)	48 (48)
Educational attainment — no. (%)			
High school or less	12 (24)	12 (24)	24 (24)
Vocational school or associate's degree	5 (10)	8 (16)	13 (13)
Bachelor's degree	13 (27)	16 (32)	29 (29)
Graduate degree	19 (39)	14 (28)	33 (33)
Country — no. (%)			
United States	41 (84)	41 (82)	82 (83)
Canada	5 (10)	8 (16)	13 (13)
Sweden	3 (6)	1 (2)	4 (4)
Baseline gait velocity — m/sec	0.87±0.25	0.82±0.27	0.84±0.26
Baseline Tinetti scale score‡	20.3±5.1	18.8±6.1	19.6±5.6
Baseline MoCA score§	21.4±4.0	20.7±4.2	21.0±4.1
Baseline Overactive Bladder Questionnaire, Short Form, score¶	16.9±8.3	17.3±7.6	17.1±7.9

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

† Ethnic group and race were reported by the participants.

‡ The Tinetti scale (Performance-Oriented Mobility Assessment) total score ranges from 0 to 28, with lower scores indicating worse gait and balance.

§ The Montreal Cognitive Assessment (MoCA), version 8.1, total score ranges from 0 to 30, with lower scores indicating worse cognition.

¶ The Overactive Bladder Questionnaire, Short Form, score ranges from 0 to 100, with higher scores indicating worse urinary incontinence. Two patients in the open-shunt group and two in the placebo group had missing data.

Secondary Outcomes

The improvement in the Tinetti scale score was significantly greater in the open-shunt group than the placebo group (mean change, 2.9 points vs. 0.5 points; $P=0.003$). However, the open-shunt group did not have a significantly greater improvement than the placebo group in the MoCA score (mean

change, 1.3 points vs. 0.3 points) or the Overactive Bladder Questionnaire, Short Form, score (−3.3 points vs. −1.5 points) (Table 3).

Tertiary and Imaging Outcomes

Results for tertiary outcomes are shown in Table 3. The EQ-5D-5L visual analogue scale score

Table 2. Coexisting Diseases in the Randomized Population.*

Coexisting Disease	Open Shunt (N = 49)	Placebo (N = 50)	Overall (N = 99)
	number (percent)		
Any coexisting disease	33 (67)	46 (92)	79 (80)
Myocardial infarction	4 (8)	4 (8)	8 (8)
Congestive heart failure	0	1 (2)	1 (1)
Peripheral vascular disease	0	1 (2)	1 (1)
Cerebrovascular disease	4 (8)	3 (6)	7 (7)
Dementia	2 (4)	6 (12)	8 (8)
Chronic pulmonary disease	2 (4)	2 (4)	4 (4)
Connective-tissue disease	0	1 (2)	1 (1)
Liver disease	0	0	0
Diabetes	15 (31)	17 (34)	32 (32)
Renal disease	1 (2)	3 (6)	4 (4)
Acquired immunodeficiency syndrome	0	0	0
Peripheral neuropathy	7 (14)	6 (12)	13 (13)
Obesity	14 (29)	16 (32)	30 (30)
Parkinsonian syndrome	0	0	0
Schizophrenia or any major psychiatric diagnosis	0	0	0
Conditions impairing gait†	0	0	0

* Participants may have more than one coexisting disease.

† Conditions include hemiparesis, spasticity, cerebellar ataxia, or musculoskeletal and joint disease.

appeared to increase in the open-shunt group (mean change, 10.9 points) and decrease in the placebo group (mean change, −3.6 points), resulting in a difference of 12.4 points (95% CI, 4.4 to 20.4). The percentage of participants with a modified Rankin scale score of 0 to 2 points appeared to increase from 56% at baseline to 78% at 3 months in the open-shunt group and decrease from 45% to 43% in the placebo group (Fig. S2). The open-shunt group appeared to have a greater decrease in lateral ventricular volume than the placebo group (mean change, −27.4 ml vs. −4.4), resulting in a difference of −21.0 ml (95% CI, −33.9 to −8.1) (Table 3).

SAFETY MONITORING AND SERIOUS ADVERSE EVENTS

Safety monitoring outcomes and serious adverse events are shown in Table 4 and Table S7. More participants reported falls in the placebo group (23 of 50 participants; 46%) than in the open-shunt group (12 of 49 participants; 24%) ($P=0.03$).

The number of participants with clinically significant falls was low and did not differ substantially between groups (2 in the open-shunt group and 3 in the placebo group).

A total of 13 participants in the open-shunt group and 9 in the placebo group had serious adverse events. One death occurred in the placebo group after 1 participant (2%) had a parenchymal hemorrhage during surgery and subsequent complications that were unrelated to the assigned trial regimen. An additional parenchymal hemorrhage occurred in 1 participant (2%) in the open-shunt group. More participants had a subdural hematoma or hemorrhage in the open-shunt group (6 participants; 12%) than the placebo group (1 participant; 2%) ($P=0.04$). In the open-shunt group, 3 participants with a subdural hematoma or hemorrhage underwent surgical drainage, middle meningeal artery embolization, or both. Of these participants, 1 had a subdural hematoma that resolved by 3 months, 1 underwent shunt revision surgery, and 1 underwent shunt

Table 3. Trial Outcomes.*

Outcome	Baseline Value		Change at 3 Months		P Value†
	Open Shunt (N=49)	Placebo (N=49)	Open Shunt (N=49)	Placebo (N=49)	
Primary outcome					
Gait velocity — m/sec	0.87±0.25	0.82±0.27	0.23±0.23	0.03±0.23	<0.001
Secondary outcomes					
Tinetti scale score‡	20.3±5.1	18.8±6.1	2.9±3.8	0.5±5.3	0.003
MoCA score‡	21.4±4.0	20.8±4.1	1.3±2.1	0.3±2.9	NS
Overactive Bladder Questionnaire, Short Form, score‡	16.6±8.2	17.1±7.6	-3.3±6.4	-1.5±6.3	NS
Tertiary outcomes					
Symbol Digit Modalities Test score§	26.6±8.7	25.4±8.8	2.6±7.6	-0.7±5.8	3.5 (0.7 to 6.4)
Score on the Flanker Inhibitory Control and Attention Test from the NIH Toolbox¶	80.6±10.9	79.9±12.6	5.2±10.4	-0.9±10.6	6.3 (2.5 to 10.1)
Score on the Dimensional Change Card Sort Test from the NIH Toolbox¶	89.4±11.3	86.5±12.6	2.6±10.8	0.5±9.5	3.7 (0.3 to 7.0)
Beck Depression Inventory—II score**	11.5±7.4	11.9±7.8	-1.4±8.8	0.0±7.7	-1.4 (-4.8 to 2.0)
Modified Rankin scale score††	2.3±0.9	2.5±0.9	-0.5±1.2	0.0±0.9	-0.7 (-1.1 to -0.2)
Lawton ADL and IADL total score‡‡	6.8±5.2	6.9±5.6	-2.5±3.7	-1.2±3.9	-1.3 (-2.5 to -0.1)
Score on the EQ-5D-5L visual analogue scale for quality of life§§	65.4±17.3	69.4±20.1	10.9±17.8	-3.6±24.8	12.4 (4.4 to 20.4)
Imaging outcomes					
Evans ratio	0.36±0.03	0.36±0.03	-0.02±0.05	0.00±0.03	-0.02 (-0.04 to 0.00)
Lateral ventricular volume — ml	138.1±37.6	131.6±29.9	-27.4±35.5	-4.4±19.4	-21.0 (-33.9 to -8.1)

* The population includes participants who underwent randomization and were eligible for the outcome analysis, with outcome data imputed when necessary. One participant in the placebo group who underwent randomization was deceased at the 3-month time point and is not included in this table. NS denotes not significant.

† The results are based on a linear regression model, which was adjusted for assessment value at baseline and age at randomization (categorical: 60 to 69 years, 70 to 79 years, and 80 years or older). Cognitive assessments were adjusted for assessment value at baseline, age at randomization (continuous), and years of education (continuous). Significance assessments are not reported for tertiary outcomes; for these outcomes, the reported 95% confidence intervals must be interpreted cautiously because with respect to multiple comparisons, the chance of at least one interval not containing the true treatment effect may be markedly higher than 5%, increasing the chance of false positive conclusions.

‡ For the three secondary efficacy outcomes, a Bonferroni-Holm step-down test procedure was implemented. The change in the Tinetti scale score remained significant after adjustment for multiplicity.

§ The mean Symbol Digit Modalities Test score in the normal-health population ranges from 33.31±9.02 to 69.91±12.64, with lower scores indicating decreased attention and processing speed.

¶ Scores on the Flanker Inhibitory Control and Attention Test from the NIH (National Institutes of Health) Toolbox range from 0 to 100, with lower scores indicating worse inhibitory control and attention.

|| Scores on the Dimensional Change Card Sort Test from the NIH Toolbox range from 0 to 100, with lower scores indicating worse cognitive flexibility.

** Beck Depression Inventory—II scores range from 0 to 63, with higher scores indicating worse depression.

†† Modified Rankin scale scores range from 0 to 6, with higher scores indicating worse disability.

‡‡ Lawton Activities of Daily Living and Instrumental Activities of Daily Living scores range from 0 to 32, with higher scores indicating worse function.

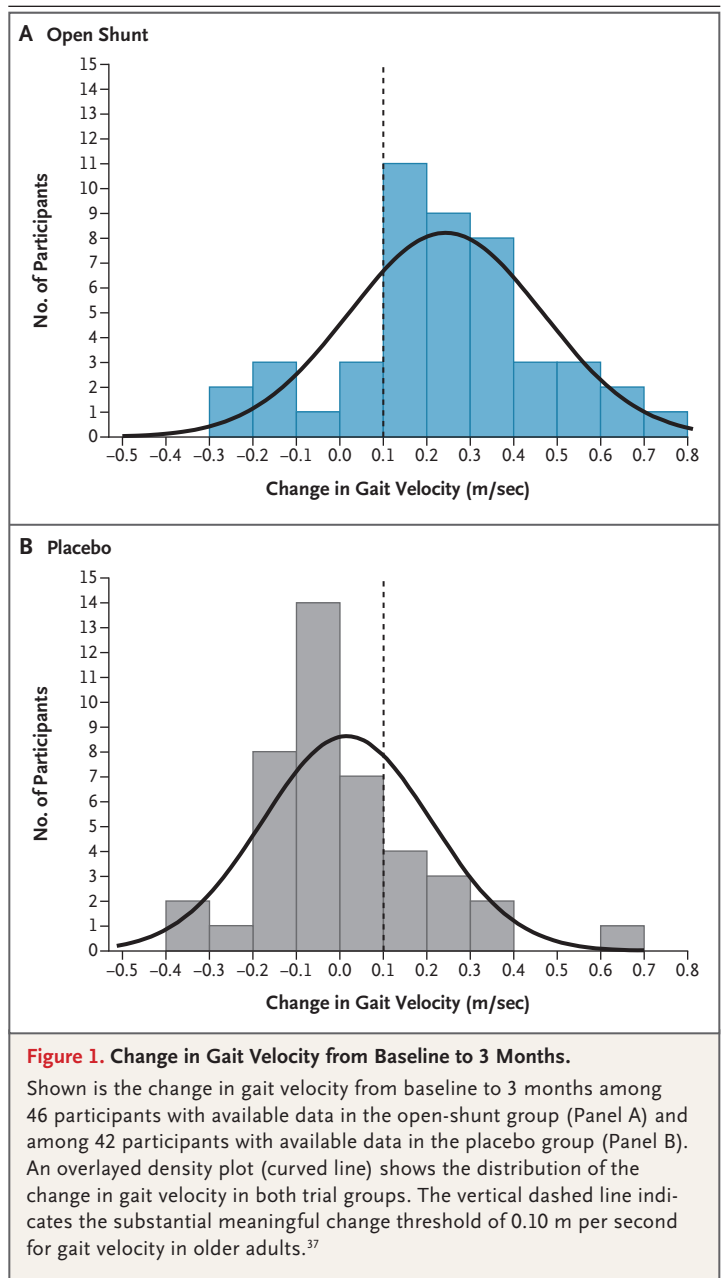
§§ Scores on the EuroQol 5-Dimension 5-Level (EQ-5D-5L) visual analogue scale for quality of life range from 0 to 100, with lower scores indicating worse health.

removal owing to wound dehiscence. Four participants had small subdural hematomas that were either addressed with adjustment of the shunt valve setting (in 3 participants, of whom 2 had hematomas that resolved by 3 months) or not treated (in 1 participant whose hematoma was not resolved by 3 months). A subdural hygroma or effusion occurred in 3 participants in the open-shunt group and none of those in the placebo group ($P=0.06$); all 3 participants were treated with adjustment of the shunt valve setting adjustment.

More participants reported positional headaches suggesting low CSF pressure in the open-shunt group (29 of 49 participants; 59%) than the placebo group (14 of 50 participants; 28%) ($P=0.002$). Changes in the initial shunt valve setting before assessment of the primary outcome (i.e., off-protocol changes) occurred in more participants in the open-shunt group (13 participants; 27%) than the placebo group (5 participants; 10%) ($P=0.03$). The setting was increased owing to symptoms of low-pressure headache in all 13 participants with off-protocol changes in the open-shunt group. In the placebo group, the setting was decreased (i.e., changed to an open valve setting) owing to symptoms of underdrainage in 3 participants and as a result of the decision of the data and safety monitoring board in 2 participants.

DISCUSSION

This trial provides evidence that ventriculoperitoneal shunt surgery is an effective treatment for improving gait velocity in patients with idiopathic normal-pressure hydrocephalus selected for surgery on the basis of response to temporary CSF drainage in accordance with the international idiopathic normal-pressure hydrocephalus guidelines. Within 3 months after surgery, the participants with an open-shunt valve setting had a clinically meaningful improvement in gait velocity, the primary outcome. The open-shunt group also had small improvements in gait and balance as measured on the Tinetti scale but no significant change in screening measures of cognition or bladder symptoms. However, tertiary outcome measures of cognition, functional independence, and quality of life appeared to improve. The open-shunt valve setting appeared to reduce lateral ventricular volume, which is consistent with a func-



tioning shunt. In contrast, in the placebo group, gait velocity was unchanged and nearly all secondary and tertiary outcome measures appeared to be unchanged or to have worsened, including lateral ventricular volume.

A total of 80% of the participants in the open-shunt group had a change in gait velocity that surpassed the substantial meaningful change threshold of 0.10 m per second in older adults.³⁷ To achieve this degree of improvement, the number needed to treat with shunt surgery is 1.79

Table 4. Safety Monitoring Outcomes and Serious Adverse Events in the Randomized Population.

Outcome or Event	Open Shunt (N = 49)	Placebo (N = 50)	P Value*
Safety monitoring outcome†			
Fall — no. (%)	12 (24)	23 (46)	0.03
Clinically significant fall — no. (%)‡	2 (4)	3 (6)	0.84
Subdural hematoma or hemorrhage — no. (%)	6 (12)	1 (2)	0.04
Resulting in surgery — no.	3	0	
Subdural hygroma or effusion — no. (%)	3 (6)	0	0.06
Positional headaches — no. (%)	29 (59)	14 (28)	0.002
Stroke — no. (%)	1 (2)	1 (2)	0.75
Death — no. (%)	0	1 (2)	0.75
Shunt-surgery complications†			
Wound infection — no. (%)	1 (2)	0	0.25
Additional surgery and interventions — no. (%)†			
Shunt revision or removal surgery	2 (4)	0	0.12
Burr-hole drainage of subdural hematoma	2 (4)	0	0.12
Initial off-protocol change in shunt valve setting — no. (%)†	13 (27)	5 (10)	0.03
Serious adverse events — no. (%)§			
Cerebral hemorrhage	1 (2)	1 (2)	0.75
Subdural hematoma or hemorrhage	4 (8)	0	0.03
Subdural hygroma or effusion	3 (6)	0	0.06
Ischemic stroke	0	1 (2)	0.75
Conversion to high-pressure hydrocephalus	1 (2)	0	0.25
Headache	0	1 (2)	0.75

* Fisher's exact test with a mid-P-value correction was used to compare the trial groups.

† These outcomes include those that are categorized as either serious adverse events or adverse events.

‡ A clinically significant fall is defined as a fall warranting a clinic or emergency department visit for injury.

§ Some participants had multiple serious adverse events. A full list of serious adverse events is presented in Table S7.

persons. Furthermore, the mean change in gait velocity in the open-shunt group (0.23 m per second) was more than twice the substantial meaningful change in older adults and exceeds the large minimum clinically important difference of 0.22 m per second in parkinsonism.³⁸

Gait velocity and change in gait velocity are recognized markers of health and functional capacity in older adults. A low gait velocity is associated with a substantially higher risk of falling. Healthy older adults with a gait velocity of less than 0.7 m per second have a risk of falling that is more than 5 times as high as the risk among those with a gait velocity of more than 1.1 m per second.³⁹ The combined finding of a greater improvement in gait velocity and a lower percent-

age of participants with falls in the open-shunt group than the placebo group suggests that shunt surgery may have a broad beneficial clinical effect on the health of older patients with idiopathic normal-pressure hydrocephalus.

The results of this trial are consistent with the results of many studies and clinical series.^{8,9,12-14,40} The improvement in gait velocity with the open-shunt valve setting at 3 months in our trial is similar to that at 4 months (0.25 m per second) in a prospective registry series involving 193 patients and that at 4 months (0.28 m per second) in a pilot, blinded, placebo-controlled study.^{12,19}

Although complications of idiopathic normal-pressure hydrocephalus treatment occurred in the first 3 months in this trial, the rates were simi-

lar to those in previous clinical trials of idiopathic normal-pressure hydrocephalus and lower than those found in national surveys.^{8,41,42} The most serious adverse events in our trial were two parenchymal hemorrhages at the time of surgery, one of which ultimately resulted in death, and three subdural hematomas that resulted in treatment. However, three subdural hematomas and three hygromas were treated with noninvasive adjustment of the shunt valve setting. Similarly, low-pressure headaches were treated by adjustment of the shunt valve setting.

The major strengths of the trial include its blinded design, statistical power, rigorous training of clinical assessors, and quality-control procedures. The generalizability of the findings is supported by the selection of patients for shunt surgery across multiple centers in accordance with the widely used international guidelines.

Our trial has several limitations. Because the primary outcome was the change in gait velocity, participants who could not walk 10 m or whose velocity was too fast were not eligible, and the trial results may not be applicable to such persons. Participants taking long-term anticoagulation medication were excluded to avoid bleeding complications, although previous studies have shown that careful management can mitigate these risks.^{43,44}

Another potential limitation is the 3-month time point for the primary outcome, which is standard for research on idiopathic normal-pressure hydrocephalus. This trial has not yet addressed the long-term outcomes. However, the outcome measures and complications reported here are being collected for all the participants through 12 months and will be supplemented by a comprehensive neuropsychological battery in approximately two thirds of the participants and imaging and CSF biomarkers in all the participants. These extra assessments may yield more insight into the extent, pace, and timing of outcomes as well as the neuronal or glial biologic mechanisms responsible for symptom development and recovery in idiopathic normal-pressure hydrocephalus.

Although the use of a specific shunt valve might raise concern about generalizability, the function of all differential pressure valve mechanisms is essentially the same, and previous studies that used different shunt valves have shown similar improvements.^{8,12,14} There is no indication that the

valve used in this trial has advantages or disadvantages as compared with other valves with similar characteristics and adjustability.

The PENS trial provides evidence that shunt surgery is effective for improving gait velocity at 3 months in patients with idiopathic normal-pressure hydrocephalus selected for shunt surgery in accordance with the international guidelines. The results of this trial support the potential benefits of evaluating patients who have symptoms, neurologic findings, and brain imaging consistent with idiopathic normal-pressure hydrocephalus and treating them with shunt surgery when indicated.

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