One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt

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OBJECTIVE Idiopathic normal pressure hydrocephalus (iNPH) is treated with cerebrospinal fluid shunting, and implantation of a ventriculoperitoneal shunt (VPS) is the current standard treatment. The objective of this study was to compare the efficacy and safety of VPSs and lumboperitoneal shunts (LPSs) for patients with iNPH.

METHODS The authors conducted a prospective multicenter study of LPS use for patients with iNPH. Eighty-three patients with iNPH (age 60 to 85 years) who presented with ventriculomegaly and high-convexity and medial subarachnoid space tightness on MR images were recruited from 20 neurological or neurosurgical centers in Japan between March 1, 2010, and October 19, 2011. The primary outcome was the modified Rankin Scale (mRS) score 1 year after surgery, and the secondary outcome included scores on the iNPH grading scale (iNPHGS). A previously conducted VPS cohort study with the same inclusion criteria and primary and secondary end points was used as a historical control.

RESULTS The proportion of patients who achieved a favorable outcome (i.e., improvement of at least 1 point in their mRS score) was 63% (95% CI 51%–73%) and was comparable to values reported with VPS implantation (69%, 95% CI 59%–78%). Using the iNPHGS, the 1-year improvement rate was 75% (95% CI 64%–84%) and was comparable to the rate found in the VPS study (77%, 95% CI 68%–84%). The proportion of patients experiencing serious adverse events (SAEs) and non-SAEs did not differ significantly between the groups at 1 year after surgery (SAEs: 19 [22%] of 87 LPS patients vs 15 [15%] of 100 VPS patients, $p = 0.226$; non-SAEs: 24 [27.6%] LPS patients vs 20 [20%] VPS patients, $p = 0.223$). However, shunt revisions were more common in LPS-treated patients than in VPS-treated patients (6 [7%] vs 1 [1%]).

CONCLUSIONS The efficacy and safety rates for LPSs with programmable valves are comparable to those for VPSs for the treatment of patients with iNPH. Despite the relatively high shunt failure rate, an LPS can be the treatment of choice because of its minimal invasiveness and avoidance of brain injury.

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KEY WORDS cerebrospinal fluid; functional status; magnetic resonance imaging; subarachnoid space; ventriculomegaly; hydrocephalus

IDIOPATHIC normal pressure hydrocephalus (iNPH), which is a disease of uncertain etiology that characteristically afflicts the elderly, is treated with cerebrospinal fluid (CSF) shunting. iNPH is characterized by cognitive decline, gait and balance impairments, and urinary incontinence.² Recent reports showing prevalence rates of 0.51%–2.9% in community-dwelling elderly people have

suggested that iNPH is more common than previously thought.^{3,10–12,29}

Ventriculoperitoneal shunt (VPS) implantation is the current standard treatment for patients with iNPH.⁵ A previous multicenter, prospective cohort study (i.e., Study of Idiopathic Normal Pressure Hydrocephalus on Neurological Improvement [SINPHONI]), in which 100 patients

ABBREVIATIONS ADL = activity of daily living; BMI = body mass index; CSF = cerebrospinal fluid; DESH = disproportionately enlarged subarachnoid space hydrocephalus; FAS = full analysis set; iNPH = idiopathic normal pressure hydrocephalus; iNPHGS = iNPH grading scale; LOCF = last observation carried forward; LPS = lumboperitoneal shunt; MMSE = Mini-Mental State Examination; mRS = modified Rankin Scale; PPS = per protocol set; SAE = serious adverse event; SAS = safety analysis set; SINPHONI = Study of Idiopathic Normal Pressure Hydrocephalus on Neurological Improvement; TUG = Timed Up and Go; VPS = ventriculoperitoneal shunt.

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were enrolled between November 2004 and November 2006, showed that specific MRI features in patients with iNPH, i.e., tight high-convexity and medial subarachnoid spaces and ventriculomegaly, which is defined as disproportionately enlarged subarachnoid space hydrocephalus (DESH), were associated with high responsiveness to VP shunting.⁸ However, to date, there have been no randomized controlled trials or systematic or prospective studies of lumboperitoneal shunt (LPS) implantation for the treatment of iNPH. Thus, the international iNPH guidelines suggest that LPSs can only be considered for patients with a preexisting seizure or other relative contraindication to VPS implantation.⁵ In addition, LPSs have not generally been favored by neurosurgeons because of high failure rates and the possibility of symptomatic overdrainage.^{6,16,31,33} However, the risk of symptomatic intraparenchymal hematoma from ventricular catheter placement, which is approximately 1% in patients with iNPH, is never present with LPS use, as LPSs avoid damage to the brain induced by punctures.⁷ There has been an increase in the use of LPSs rather than VPSs for the treatment of iNPH, particularly in Japan.^{15,26} However, in western countries, VPSs are used to treat iNPH in most cases because currently there is no established evidence to support using LPSs for this purpose. The long-term outcome of patients with iNPH who receive an LPS with a programmable valve remains to be determined. Therefore, we conducted a prospective multicenter trial to assess LPS implantation in patients with iNPH (SINPHONI-2), which integrated a 3-month randomized controlled trial (i.e., RCT phase) comparing LPS implantation to conservative therapy and a 12-month extension study (i.e., extension phase) in which all subjects received an LPS and were examined over the 12 months following implantation. The short-term and long-term beneficial effects of LPS use were obvious and have been reported previously.¹⁸ In this paper, we present in further detail the long-term outcome of patients who received an LPS during the SINPHONI-2 trial and a comparative analysis of the results from the SINPHONI and SINPHONI-2 trials, which used common inclusion criteria and primary and secondary end points. The goal of this pooled analysis was to compare the efficacy and safety of VPS and LPS implantation in patients with iNPH specified as DESH.

Methods

Study Design

The SINPHONI-2 (registered with the University Hospital Medical Information Network Clinical Trials registry: UMIN000002730) protocol has been described in detail elsewhere.¹⁸ In brief, it was a prospective multicenter trial of LPS placement in patients with iNPH that integrated a 3-month randomized controlled phase, in which parallel groups received an LPS or conservative therapy, and a long-term phase, in which all participants received an LPS and were assessed for a 12-month period after surgery. The primary measure of efficacy for the 3-month randomized controlled phase was favorable outcome, which was defined as an improvement of 1 point or more on the modified Rankin Scale (mRS)³² at 3 months after

randomization, and the long-term end point was the same favorable outcome at 12 months after surgery. In contrast, the SINPHONI study was a prospective cohort study that was designed to test the safety and efficacy of VPS implantation in patients with iNPH. The study protocol was identical to that of SINPHONI-2 except that patients with severe vertebral degenerative diseases or spinal canal stenosis were excluded, and shunt surgery was postponed for 3 months in patients who were allocated to the control arm. SINPHONI-2 was conducted in compliance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki (2002) of the World Medical Association. The study protocol was approved by the institutional review board at each site, and all patients (or their representative when applicable) provided written informed consent for participation. Twenty centers in Japan were involved in this study (*Appendix*). An independent committee monitored all clinical and imaging data, data related to safety issues, and protocol compliance via a web-based case report system.

Patients

Candidates for the SINPHONI-2 study were patients with suspected iNPH. The following inclusion criteria were adopted: 1) patient age between 60 and 85 years; 2) triad of symptoms, which were measurable on the iNPH grading scale (iNPHGS);²¹ 3) both ventriculomegaly with an Evans' index > 0.3 and high-convexity and medial subarachnoid space tightness on coronal MR images;¹⁹ 4) absence of disorders known to produce ventriculomegaly; and 5) normal CSF content and pressure and a negative Queckenstedt's test.³⁰ All patients who exhibited severe vertebral degenerative diseases or spinal canal stenosis on plain radiograph or MR images were excluded.

Procedure

Eligible patients were screened and selected by either neurologists or neurosurgeons and preregistered on the web system. Patients who met all the above criteria were enrolled. Then, participants were randomly assigned to either the immediate-shunt group (i.e., immediate group) or the postponed-shunt group (i.e., postponed group). Patients in the immediate group underwent LPS implantation within 1 month after randomization. They were evaluated before and 3, 6, and 12 months after surgery. Patients in the postponed group were instructed only to perform physical exercises (i.e., conservative therapy) for 3 months after randomization and were evaluated before and after the conservative therapy. After this therapy, they also underwent LPS implantation and were evaluated 3, 6, and 12 months after surgery.

LPS implantation was conducted under general anesthesia using a Codman-Hakim programmable valve with a Siphon-Guard (Codman and Shurtleff, Johnson and Johnson Inc.). Initial pressure for the shunt system was set before surgery according to the height and weight of the patient.²⁵ Valve pressure was readjusted in 1- to 3-cm H₂O intervals afterward, as required. Shunt function was assessed at each institution whenever needed. In addition, shunt function was checked when there was no improvement in clinical symptoms or when tight high-convexity

and medial subarachnoid spaces, enlarged sylvian fissures, or acute callosal angles were observed.

Outcome Measures

The primary outcome measure was mRS. Secondary outcome measures included iNPHGS score,²¹ the 3-minute Timed Up and Go (TUG) test,²⁷ and the Mini-Mental State Examination (MMSE). These evaluations and tests were performed by specialists other than the attending neurosurgeons, including neurologists, psychiatrists, clinical psychologists, and physical therapists. The primary end point was an improvement of 1 or more points in the patient's mRS score at 1 year after surgery (i.e., favorable outcome). A positive response to LPS implantation (i.e., shunt response) was defined as an improvement of more than 1 point in the mRS score at any evaluation point within 1 year. According to the protocol, if there was no significant difference in the improvement in activities of daily living (ADL) between the immediate and postponed groups at 12 months after shunt surgery, the 2 groups were combined. The utility of the LPS was compared with that of the VPS using the SINPHONI study data as a historical control.

Safety assessments included the recording of all adverse events throughout the study, regardless of whether they were related to treatment. A serious adverse event (SAE) was defined as 1 of the following: 1) death; 2) an event that could result in death; 3) an event for which treatment required hospitalization, admittance to a clinic, or an extension of the hospitalization period; and 4) an event that could result in morbidity.

Statistical Analysis

The full analysis set (FAS) was defined as all patients who underwent intervention and who had at least 1 valid postbaseline assessment of mRS score, whereas the per protocol set (PPS) was defined as all patients in the FAS excluding those with major protocol deviations. We used the PPS for all efficacy analyses, which made the data set compatible with that of the SINPHONI study. When mRS or iNPHGS scores were missing at any follow-up, scores were inputted using the "last observation carried forward" (LOCF) if the underlying assumption was justified. Adverse events were analyzed based on the safety analysis set (SAS), in which all patients who received an LPS were included. If there was no significant difference in the primary outcome measure between the groups at 12 months after surgery, the 2 groups were combined as a single LPS group, which was compared with the historical VPS controls in the SINPHONI study. Nonparametric statistical methods were used in all analyses. The Mann-Whitney U-test was used for comparisons between groups. Fisher's exact test was used to compare the 2 proportions. We compared the differences in the changes between the groups using analysis of covariance. The outcome variables at 6 months after randomization or the outcome variables at 12 months after surgery were entered in the model as a dependent variable. The baseline value of the outcome variable was included as a covariate, and the study group was included as a categorical variable. We calculated the 95%

confidence intervals for proportions using the Clopper-Pearson binomial confidence method. The significance level was set at 2-sided $p = 0.05$. Statistical data were analyzed using SPSS version 22.

Results

Trial Profile

The first patient was recruited on March 1, 2010, and the follow-up for the last patient was completed on December 5, 2012. The flowchart for this study is shown in Fig. 1. Preregistration was completed for 102 patients. Of these patients, 49 were randomly assigned to the immediate group, and 44 to the postponed group. Three patients in the immediate group (1 diagnosed with pneumonia, 1 with burns, and 1 who withdrew consent) were excluded from analysis before LPS implantation, whereas 2 patients in the postponed group who withdrew consent were excluded before starting physical exercises. Thus, 88 patients were included in the FAS, of whom 46 were assigned to the immediate group and 42 to the postponed group. In the postponed group, 1 patient did not undergo shunt surgery because of an accumulation of ascites fluid of unknown etiology, whereas another patient was not evaluated after shunt surgery because of hospital transfer. Thus, the FAS of the postponed group after LPS implantation consisted of 40 patients. The central MRI review committee excluded 2 patients from the postponed group because they did not meet MRI criteria. Seven patients (5 in the immediate group and 2 in the postponed group) failed to undergo the 1-year final follow-up; of these patients, 6 patients remained in the PPS, with their scores inputted as LOCF. Thus, the PPS comprised 83 patients, of whom 45 belonged to the immediate group and 38 to the postponed group.

Characteristics of Patients at Baseline

The demographic characteristics of PPS patients are summarized in Table 1. Patients in SINPHONI-2 (the present study) were 2 years older than those in the SINPHONI study. There were no differences in functional status and symptoms between patients in the SINPHONI-2 and SINPHONI studies at baseline.

Clinical Outcomes

The mean overall initial valve pressure was 13.5 ± 3.9 cm H₂O. This pressure was maintained throughout the follow-up period in 34 patients (40%) and was readjusted in the other patients. Significant differences in mRS and iNPHGS gait scores were observed between the immediate and postponed groups during the 6-month period after randomization (Table 2). Although there was an improvement in mRS and iNPHGS gait scores over the 6-month period after randomization, scores were still higher in the postponed group than in the immediate group (Fig. 2). Furthermore, the proportion of patients with improvement in their mRS score was significantly higher in the immediate group (65%, 95% CI 51%–79%) than in the postponed group (29%, 95% CI 14%–45%; $p = 0.027$) at 6 months after randomization. Improvement in the postponed group was somewhat less than that in the immediate group at 6 months after randomization.

FIG. 1. Flowchart of the trial profile showing the number of patients from initial screening to final analysis. PSP = progressive supranuclear palsy.

There were no significant changes in mRS, iNPHGS, TUG, or MMSE scores between the immediate and postponed groups at 1 year after surgery (Table 3). A favorable outcome was achieved in 63% of patients (immediate group 67%, postponed group 58%; Table 4). The number of patients without functional impairment (mRS score < 1) increased from 1 (1%) at preoperative assessment to 26 (31%) by 1 year after surgery, whereas the number of independent patients (mRS score ≤ 2) increased from 31 (37%) at preoperative assessment to 53 (63%) at 1 year after surgery (Fig. 3). When clinical improvement is defined as a decrease of 1 or more points in the total iNPHGS score, benefits occurred in 75% of patients (immediate group 80%, postponed group 68%) by 1 year after surgery. The proportion of shunt responders was 71% (immediate group 78%, postponed group 63%). Given that there was a significant difference in mRS scores between the 2 groups at 6 months after randomization, the recovery of the postponed group was delayed by the same interval of 6 months, although the scores in the postponed group almost caught up to those of the immediate group by 12 months after LPS implantation (Fig. 2).

Adverse Events Associated With LPS Implantation

The SAS included 87 patients from the SINPHONI-2 study. One patient in the postponed group was excluded from the analysis of adverse events at 1 year after LPS implantation because she did not receive an LPS. SAEs were observed in 19 patients, among whom death occurred in 2 patients (lung cancer and suicide). The outcome at 1 year after surgery was favorable in 9 of the patients and unfavorable in 10 patients (including the 2 deaths). Ten SAEs were directly related to surgery or the LPS: 3 subdural hematomas requiring surgery, 5 shunt tube migrations, 1 shunt tube rupture, and 1 case of meningitis. In addition, 29 nonserious, shunt-related adverse events were recorded in 24 patients: asymptomatic subdural fluid collection or hematoma was observed in brain imaging in 7 patients, and postural headache occurred in 21 patients; all of these adverse events were successfully controlled by the adjustment of valve pressure (Table 5).

Comparison Between SINPHONI-2 and SINPHONI

The proportion of favorable outcomes as measured

TABLE 1. Patient characteristics at baseline: PPS analysis

Parameter	SINPHONI-2 (LPS)			SINPHONI (VPS)	p Value
	Immediate Surgery	Postponed Surgery	All		
No. of patients	45	38	83	100	
Demographic details, no. (%) unless otherwise noted					
Mean age in yrs $\pm$ SD	76.5 $\pm$ 4.4	76.3 $\pm$ 5.0	76.4 $\pm$ 4.7	74.5 $\pm$ 5.1	0.011
F/M sex	27/18 (60/40)	11/27 (29/71)	38/45 (46/54)	42/58 (42/58)	0.655
History of hypertension	27 (60)	20 (53)	47 (57)	60 (60)	0.655
History of diabetes	10 (22)	10 (26)	20 (24)	20 (20)	0.591
History of lipid disorder	15 (33)	13 (34)	28 (34)	31 (31)	0.752
Preop clinical findings, mean $\pm$ SD					
mRS	2.8 $\pm$ 0.8	2.9 $\pm$ 0.8	2.9 $\pm$ 0.8	3.0 $\pm$ 1.0	0.218
Total iNPHGS	6.5 $\pm$ 2.0	6.6 $\pm$ 2.1	6.6 $\pm$ 2.4	6.5 $\pm$ 2.0	0.941
Gait score	2.3 $\pm$ 0.7	2.4 $\pm$ 0.7	2.4 $\pm$ 0.7	2.4 $\pm$ 0.7	0.878
Cognitive score	2.3 $\pm$ 0.9	2.3 $\pm$ 0.8	2.3 $\pm$ 0.9	2.3 $\pm$ 1.0	0.939
Urinary score	1.9 $\pm$ 1.0	1.9 $\pm$ 1.1	1.9 $\pm$ 1.0	1.9 $\pm$ 1.3	0.813
TUG	34.8 $\pm$ 39.8	28.9 $\pm$ 31.8	32.1 $\pm$ 36.5	22.5 $\pm$ 15.6	0.534
MMSE	20.3 $\pm$ 6.1	18.9 $\pm$ 6.7	19.6 $\pm$ 6.4	21.0 $\pm$ 6.3	0.093
Combinations of symptoms, no. (%)					
Triad	25 (56)	20 (53)	45 (54)	51 (51)	0.990
Gait and cognitive	8 (18)	9 (24)	17 (20)	23 (23)	
Gait and urinary	2 (4)	1 (3)	3 (4)	5 (5)	
Cognitive and urinary	2 (4)	1 (3)	3 (4)	3 (3)	
Gait only	4 (9)	6 (16)	10 (12)	12 (12)	
Cognitive only	3 (7)	1 (3)	4 (5)	3 (3)	
Urinary only	0 (0)	1 (3)	1 (1)	1 (1)	
CSF pressure in cm H ₂ O*	12.5 $\pm$ 2.9	12.7 $\pm$ 3.2	12.6 $\pm$ 3.0	11.9 $\pm$ 3.4	0.303

* The CSF pressure data correspond with opening pressure taken as the opening pressure at lumbar puncture.

by mRS and iNPHGS scores between the SINPHONI-2 and the SINPHONI study was comparable (Table 4). The changes in mRS scores at 12 months after surgery were not different from those in SINPHONI (Table 6). The proportion of patients with SAEs and non-SAEs did not differ significantly between SINPHONI-2 and SINPHONI at 1 year after surgery (SAEs: 19 [22%] of 87 patients in the LPS group vs 15 [15%] of 100 patients in the VPS group, $p = 0.226$; non-SAEs: 24 [27.6%] in the LPS group vs 20

[20%] in the VPS group, $p = 0.223$). Shunt failures requiring revision (6 [7%] patients in the LPS group vs 1 [1%] in the VPS group) and postural headache after surgery were more common with the use of LPS (Table 5). All postural headaches improved within 3 months of LPS surgery.

Discussion

The present study examined the usefulness of an MRI-

TABLE 2. Changes in clinical variables within the treatment groups at 6 months after randomization: PPS analysis

Variable	Immediate Group		Postponed Group		Difference (95% CI)	p Value*
	No.	Mean (SD)	No.	Mean (SD)		
mRS	45	-0.8 (0.9)	38	-0.3 (0.5)	0.5 (0.2-0.8)	0.005
Total iNPHGS	45	-2.1 (1.8)	38	-1.4 (1.9)	0.8 (0-1.5)	0.056
Gait iNPHGS	45	-0.8 (0.8)	38	-0.4 (0.8)	0.4 (0-0.7)	0.029
Cognitive iNPHGS	45	-0.5 (0.9)	38	-0.3 (0.6)	0.2 (-0.1 to 0.6)	0.182
Urinary iNPHGS	45	-0.7 (1.1)	38	-0.7 (1.0)	0.2 (-0.2 to 0.6)	0.400
TUG in sec	45	-13.8 (35.4)	37	-7.8 (16.4)	8.0 (-8.2 to 9.7)	0.868
MMSE	45	1.4 (3.7)	38	1.6 (3.6)	-0.1 (-1.7 to 1.5)	0.932

* Analysis of covariance: comparison between immediate and postponed groups, adjusted by baseline value.

FIG. 2. Change in the mRS score between randomization and 1 year after LPS implantation. Error bars indicate the standard deviation. * $p < 0.05$, ** $p < 0.0001$. Figure is available in color online only.

based diagnostic scheme and the 1-year beneficial effect of LPS implantation in patients with iNPH. The most relevant finding of the present study was that 63% of patients with iNPH, who were diagnosed and referred for shunts based on clinical and MRI findings, experienced improved outcomes at 12 months after LPS implantation, as measured by mRS scores. The corresponding improvement rate was 75% when measured using iNPHGS scores. After VPS surgery, 69% of patients showed improvement at 1 year as measured by mRS scores, a proportion identical to the results from 2 previously reported European and Japanese (SINPHONI) multicenter studies.^{8,20} Compared with these 2 previous studies, there was no significant difference in ADL improvement between VPS and LPS. In addition, the SINPHONI trial reported an improvement of

77% at 1 year after VPS implantation, as measured by the same iNPHGS used here. The present study showed that by 1 year after LPS implantation, clinical improvement of iNPH was nearly on par with that achieved using a VPS (Table 4). Actual changes in the mRS and iNPHGS scores in the SINPHONI-2 trial were comparable to those in the SINPHONI trial (Table 6).

The initial progression of iNPH symptoms is extremely gradual; therefore, the present study was planned on the assumption that a 3-month change in the procedure would have no impact on the efficacy of the surgery. However, contrary to what was expected and although clinical symptoms did not worsen in the 3-month period following diagnosis, by 1 year after surgery the postponed group showed improvement in ADLs and in symptoms that, while not significantly different from those in the immediate group, had decreased. It thus became clear that discovery of iNPH is difficult because of the extremely gradual progression of symptoms and because therapeutic efficacy decreases with delays in treatment. Recently, Andrén and colleagues reported that the natural course of iNPH is a progression of symptoms over time, with worsening gait, balance, and cognitive symptoms.⁴ Moreover, this deterioration is only partially reversible. Therefore, the authors recommended performing surgery soon after diagnosis to maximize the benefits of shunt treatment.

We observed SAEs in 19 patients and shunt failures requiring revision in 6 patients. Although the SINPHONI study reported SAEs in 15 patients, only 1 patient required revision because of ventricular shunt tube obstruction. Shunt failures directly related to LPS included 4 patients with a prolapse of the peritoneal catheter from the abdominal cavity and 1 patient with a lumbar catheter migration from the spinal canal. Conversely, the SINPHONI study using VPS found no cases of prolapse of the peritoneal catheter from the abdominal cavity⁸ (Table 5). In a study in which Bloch and McDermott used LPSs for the treatment of iNPH, there was 1 reported case of peritoneal catheter migration out of 33 patients, which indicates that the peritoneal catheter is more prone to prolapse after LPS implantation than after VPS insertion.⁶ This complication must be taken into consideration and is thought to be related to the lateral position of the patient during the operation as well as the abdominal subcutaneous adipose tissue content of the patient. Such shunt catheter migration can be avoided by using a recently developed surgical

TABLE 3. Changes in clinical variables within the treatment groups 1 year after surgery: PPS analysis

Variable	Immediate Group		Postponed Group		Difference (95% CI)	p Value*
	No.	Mean (SD)	No.	Mean (SD)		
mRS	45	-0.8 (1.1)	38	-0.6 (0.7)	0.2 (-0.2 to 0.6)	0.337
Total iNPHGS	45	-1.9 (2.6)	38	-1.6 (1.7)	0.3 (-0.6 to 1.3)	0.483
Gait iNPHGS	45	-0.8 (1.0)	38	-0.6 (0.9)	0.2 (-0.2 to 0.6)	0.348
Cognitive iNPHGS	45	-0.6 (1.0)	38	-0.4 (0.7)	0.2 (-0.2 to 0.6)	0.340
Urinary iNPHGS	45	-0.7 (1.1)	38	-0.6 (0.9)	0.1 (-0.3 to 0.5)	0.716
TUG in sec	37	-13.5 (41.3)	35	-9.0 (20.0)	-3.1 (-10.8 to 4.5)	0.416
MMSE	40	2.6 (5.8)	36	1.2 (2.8)	-1.8 (-3.8 to 0.2)	0.071

* Analysis of covariance: comparison between immediate and postponed groups, adjusted by baseline value.

TABLE 4. Patient improvement of 1 point or more on mRS and iNPHGS 1 year after surgery: PPS analysis

Parameter	SINPHONI-2								p Value†
	Immediate Group		Postponed Group		All		SINPHONI*		
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI	
No. of patients	45		38		83		100		
mRS (favorable outcome‡)	30 (67)	51–80	22 (58)	41–74	52 (63)	51–73	69 (69)	59–78	0.496
mRS (shunt responder§)	35 (78)	63–89	24 (63)	46–78	59 (71)	60–81	80 (80)	71–87	0.155
iNPHGS (favorable outcome)	36 (80)	65–90	26 (68)	51–83	62 (75)	64–84	77 (77)	68–84	0.312
iNPHGS (shunt responder)	40 (89)	76–96	31 (82)	66–92	71 (86)	76–92	89 (89)	81–94	0.368

* SINPHONI data (historical control) extracted from Hashimoto et al.⁸

† All p values were obtained using Fisher's exact test in comparing the immediate group versus the postponed group.

‡ Favorable outcome refers to outcomes 1 year after shunt placement.

§ Shunt responder refers to patients who responded at any evaluation point.

technique,¹⁷ but further efforts to prevent shunt failure are required. Orthostatic headaches (a complication of excessive shunting of spinal fluid) were observed during the perioperative period in 21 patients, and subdural effusion or hematomas were observed in 10 patients. Of these 10 patients, remedial bur hole surgery was performed in 3. In the early postoperative period, reported problems unique to LPSs included spinal fluid leakage from the location of the access site into the epidural space. When postoperative orthostatic headaches are observed, the shunt pressure setting must be set to high pressure, and the patient must rest in a recumbent position until the headache subsides.^{14,23}

In a systematic review by Hebb and Cusimano, the overall complication rate was 38%, with 22% of patients requiring additional surgery.⁹ Even with the use of programmable valves, modern iNPH series have reported nontraumatic subdural hematoma rates as high as 10%, with up to 7% requiring surgical evacuation.^{20,24,34} We used programmable valves with an antisiphon device in the present study,

which may have resulted in 3 cases (3%) of subdural hematoma that required surgery, resulting in lower revision rates. Compared with rates in previous studies, the complication rate in the present study is acceptable.

We are aware of the criticism of LPSs in European and North American countries with regard to the higher revision rate than that with VPSs. Given this criticism, an

TABLE 5. Adverse events

Parameter	SINPHONI-2	SINPHONI*
Total no. of patients	87	100
SAEs		
No. of patients	19 (22%)	15 (15)
Total no. of events	21	17
Subdural hematoma requiring surgery	3 (3.4%)	1 (1%)
Shunt tube migration requiring revision	5 (5.7%)	
Shunt tube rupture requiring revision	1 (1.1%)	
Shunt tube obstruction		1 (1%)
Bowel perforation		1 (1%)
Meningitis	1 (1.1%)	
Pneumonia		3 (3%)
Malignancy		2 (2%)
Head injury		1 (1%)
Cerebral infarction	6 (6.9%)	3 (3%)
Myocardial infarction		1 (1%)
Femoral fracture	2 (2.3%)	2 (2%)
Lumbar vertebral compression fracture	1 (1.1%)	
Death	2 (2.3%)	2 (2%)
Non-SAE		
No. of patients	24 (27.6%)	20 (20%)
Total no. of events	29	21 (21%)
Postural headache	21 (24.1%)	8 (8%)
Asymptomatic subdural effusion	5 (5.7%)	8 (8%)
Subdural hematoma conservative	2 (2.3%)	5 (5%)
Bronchial asthma	1 (1.1%)	

* SINPHONI data (i.e., historical control) extracted from Hashimoto et al.⁸

FIG. 3. Bar graph depicting the functional status of patients based on mRS scores prior to shunt implantation (Pre-OP) and at 1 year after LPS placement.

TABLE 6. Changes in clinical variables within the 2 studies 1 year after surgery (PPS analysis)

Variable	SINPHONI-2		SINPHONI*	
	No.	Difference (95% CI)	No.	Difference (95% CI)
mRS				
All	83	-0.7 (-0.9 to -0.5)		
Immediate	45	-0.8 (-1.1 to -0.5)	100	-1.0 (-1.2 to -0.8)
Postponed	38	-0.6 (-0.8 to -0.3)		
iNPHGS				
Total score	83	-1.7 (-2.2 to -1.2)	100	-2.6 (-3.1 to -2.1)
Gait score	83	-0.7 (-0.9 to -0.5)	100	-1.0 (-1.2 to -0.8)
Cognitive score	83	-0.4 (-0.7 to -0.3)	100	-0.8 (-1.2 to -0.8)
Urinary score	83	-0.7 (-0.9 to -0.4)	100	-0.9 (-1.0 to -0.7)
TUG in sec	72	-11.3 (-18.8 to -3.8)	80	-7.7 (-11.0 to -4.3)
MMSE	76	1.9 (0.9 to 3.0)	98	2.2 (1.2 to 3.2)

* SINPHONI data (i.e., historical control) extracted from Hashimoto et al.⁸

LPS is not commonly used for the treatment of iNPH, but rather has been primarily adopted for treating idiopathic intracranial hypertension, a disease that tends to occur in younger patients.^{1,31,33} Despite the unfavorable view of LPSs in European and North American countries, we adopted the use of LPSs in the present study. The following reasons provide the rationale behind this decision. First, one of the advantages of an LPS is that surgical procedures can be performed exclusively extracranially, minimizing intracranial complications. Second, the prevalence of obesity in the Japanese population (body mass index [BMI] in this study 23.8 ± 3) is dramatically lower than that in European and North American studies (BMI 26–28).^{13,22,28} This may have played an important role in preventing malfunction of the LPS by keeping the abdominal catheter in place.

The present study has several notable limitations that require discussion. The most critical issue is that the study lacked a direct comparison with VPSs. Therefore, data from the SINPHONI study were used as a historical control. A second crucial issue is the nonblinded design of the study: neurosurgeons and neurologists in charge of patient care and evaluation were aware of the treatment, which represents a possible source of performance and detection bias. Third, the inclusion criteria were based on the diagnostic criteria of the Japanese iNPH guidelines, which are somewhat different from the criteria of the international iNPH guidelines. These issues should be taken into consideration before the findings are generalized. Moreover, our follow-up period was limited to 1 year. To clearly define the benefit of LPSs, this period should be extended in future trials. In addition, we did not evaluate the effect of LPSs on the health-related quality of life of patients, which needs to be addressed in further studies.

Conclusions

The efficacy and safety of LPSs with programmable valves are comparable to those of VPSs for the treatment of patients with iNPH. Because LPSs are still not widely used for the treatment of iNPH, LPSs must be technically

improved to prevent shunt failure. Despite its relatively high shunt failure rate, an LPS is the treatment of choice because of its minimal invasiveness and avoidance of brain injury in elderly patients.

Appendix

Location of Work

SINPHONI-2 was a project of the Japanese Society of Normal-Pressure Hydrocephalus and involved 20 centers in Japan.

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Conception and design: all authors. Acquisition of data: Miyajima, Kazui, Ishikawa. Analysis and interpretation of data: all authors. Drafting the article: Miyajima. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Miyajima. Statistical analysis: Miyajima, Mori. Administrative/technical/material support: Kazui. Study supervision: Mori, Ishikawa.

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