Idiopathic normal pressure hydrocephalus (iNPH) is a treatable condition, first described by Hakim in 1965. It is characterized clinically by gait disturbance, cognitive impairment, and urinary incontinence and radiologically by ventriculomegaly. The condition is typically diagnosed in the elderly and most often treated by insertion of a ventriculoperitoneal (VP) shunt.

After shunt surgery in iNPH patients, improvement rates between 61% and 90% have been reported, with recent studies revealing a rate above 80%. The complication rates are high, up to 50%, although a rate of 20% is evident in recent studies. The major complications are mechanical obstruction, infection, and subdural hematoma (SDH); the frequency of SDH is between 2% and 16%.

A Dutch NPH study recommended the use of a low-opening pressure shunt. A randomized controlled dual-center trial on shunt complications in idiopathic normal-pressure hydrocephalus treated with gradually reduced or “fixed” pressure valve settings

Clinical article

Terje Sehle, M.D.,1 Dan Farahmand, M.D.,2 Per Kristian Eide, M.D., Ph.D.,1,3 Magnus Tisell, M.D., Ph.D.,2 and Carsten Wikkelso, M.D., Ph.D.2

1Department of Neurosurgery, Oslo University Hospital–Rikshospitalet; 2Faculty of Medicine, University of Oslo, Norway; and 3Hydrocephalus Research Unit, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Sweden

Object. This study was undertaken to investigate whether a gradual reduction of the valve setting (opening pressure) decreases the complication rate in patients with idiopathic normal-pressure hydrocephalus (iNPH) treated with a ventriculoperitoneal (VP) shunt.

Methods. In this prospective double-blinded, randomized, controlled, dual-center study, a VP shunt with an adjustable valve was implanted in 68 patients with iNPH, randomized into two groups. In one group (the 20–4 group) the valve setting was initially set to 20 cm H2O and gradually reduced to 4 cm H2O over the course of the 6-month study period. In the other group (the 12 group), the valve was kept at a medium pressure setting of 12 cm H2O during the whole study period. The time to and type of complications (hematoma, infection, and mechanical problems) as well as overdrainage symptoms were recorded. Symptoms, signs, and outcome were assessed by means of the iNPH scale and the NPH grading scale.

Results. Six patients in the 20–4 group (22%) and 7 patients in the 12 group (23%) experienced a shunt complication; 9 had subdural hematomas, 3 mechanical obstructions, and 1 infection (no significant difference between groups). The frequency of overdrainage symptoms was significantly higher for a valve setting ≤ 12 cm H2O compared with a setting > 12 cm H2O. The 20–4 group had a higher improvement rate (88%) than the 12 group (62%) (p = 0.032). There was no significant relationship between complications and body mass index, the use of an antisiphon device, or the use of anticoagulants.

Conclusions. Gradual lowering of the valve setting to a mean of 7 cm H2O led to the same rate of shunt complications and overdrainage symptoms as a fixed valve setting at a mean of 13 cm H2O but was associated with a significantly better outcome.

Key Words • normal-pressure hydrocephalus • shunt surgery • opening pressure • postoperative complications • subdural hematoma • randomized controlled trial

Abbreviations used in this paper: ASD = antisiphon device; ICP = intracranial pressure; iNPH = idiopathic NPH; NPH = normal-pressure hydrocephalus; PL = performance level; SDH = subdural hematoma; VP = ventriculoperitoneal.
opening pressure for a better clinical effect despite the increased risk of SDH.\(^2\) Similarly, in a randomized controlled study Delwel et al. found more SDHs in a low-pressure group than in a high pressure group\(^3\) but the same outcome in the 2 groups. No controlled study has addressed the question of how to use adjustable valves for optimal prevention of complications and optimal effect.

The objective of this prospective, randomized, and blinded dual-center study was to investigate whether a gradual reduction of the valve setting level (opening pressure) decreases the complication rate in iNPH patients treated with a VP shunt.

**Methods**

**Patients**

Sixty-eight consecutive patients diagnosed with iNPH—46 at Sahlgrenska Hospital in Gothenburg and 22 at Oslo University Hospital in Oslo—were included in the study between July 2007 and July 2011. Their median age was 71 years (range 50–89 years). A summary of the patients’ characteristics is presented in Table 1.

The diagnosis of iNPH was based on clinical symptoms and radiological signs (Evans index > 0.3) of ventriculomegaly, a normal intracranial pressure (ICP), and an open cerebral aqueduct in accordance with the iNPH Guidelines for probable iNPH.\(^21\) The patients included in Oslo also had to present with abnormal ICP dynamics, defined as mean ICP wave amplitude above 4 mm Hg and >5 mm Hg for at least 10% of the recording time.\(^7\)

The patients included in Gothenburg were assessed by means of the iNPH scale,\(^19\) which comprises 4 domains (gait, neuropsychology, balance, and continence) and yields a total score (iNPH scale score) ranging between 0 and 100, where 100 represents normal performance among healthy individuals in an iNPH typical age range of 70–74 years.

Patients included in Oslo were assessed by means of the NPH grading scale,\(^7\) which comprises 3 domains (gait, cognitive function, and continence), each with a score between 1 and 5, resulting in a total score of 3–15, where a higher score represents less severe symptoms.

The patients were reexamined 6 months after surgery using the same protocol as preoperatively. An increase ≥5 points in iNPH scale score or ≥1 in the NPH score was considered significant.

Weight, height, and the use of anticoagulants were recorded. Anticoagulant medication was discontinued at least 1 week prior to shunt surgery.

**Shunt Surgery**

All patients had a shunt with a Codman Hakim programmable valve (Codman & Shurtleff/Johnson & Johnson Co.) inserted. The valve allows adjustment of the opening pressure in 18 different steps between 3 and 20 cm H₂O. The patients who underwent surgery in Gothenburg received a shunt with a SiphonGuard antisiphon device (Codman & Shurtleff/Johnson & Johnson Co.) whereas those who underwent surgery in Oslo were implanted with a shunt without an ASD.

**Randomization Procedure**

The patients were randomized into 2 groups. The group assignment was determined by opening a sealed envelope in the operating room immediately before surgery. Only the surgeon was aware of the group to which the patient was randomized. The patients themselves and the researchers who examined them were blinded to the randomization. The randomization was made in blocks of 4 in both centers. In patients randomized to the 20–4 group, the shunt valve was set to 20 cm H₂O, and in those randomized to the 12 group it was set to 12 cm H₂O.

**Follow-Up**

All patients were followed up in the outpatient clinic at 1, 2, 3, and 4 months postoperatively and in the ward for the final examination 6 months postoperatively.

In the 20–4 group, the initial valve setting of 20 cm H₂O was gradually reduced in monthly intervals to 16, 12, 8, and 4 cm H₂O; this last setting (4 cm H₂O) was maintained until the 6-month evaluation. In the 12 group, the valve setting procedure was the same as in the 20–4 group, but the setting was maintained at 12 cm H₂O during follow-up.

During follow-up, the patients were asked about improvement and symptoms of complications or under- or overdrainage. If the patients had improved, adjustments were made according to the protocol. In cases of no clinical improvement, a CT scan was performed. If the ventricle size had decreased, the shunt was considered to be functioning, but if not, it was checked by a radionuclide method (shuntography)\(^23\) or by ICP monitoring. When the shunt function was established, the valves were adjusted according to the protocol. Complications were classified as SDH, shunt infection, or shunt obstruction. Symptoms of under- or overdrainage (headache, vertigo, nausea) were recorded.

Thirty-four patients were randomized to the 20–4 group and 34 to the 12 group (Fig. 1). Three patients in

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**TABLE 1: Patient characteristics in the 2 groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>20–4 Group (n = 34)</th>
<th>12 Group (n = 34)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age in yrs (mean ± SD)</td>
<td>70.3 ± 8.2</td>
<td>71.1 ± 7.7</td>
<td>0.58</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>20 (58.8%)</td>
<td>23 (67.6%)</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>14 (41.2%)</td>
<td>11 (32.4%)</td>
<td>0.62</td>
</tr>
<tr>
<td>weight in kg (mean ± SD)</td>
<td>76.8 ± 11.0</td>
<td>78.7 ± 18.9</td>
<td>1.00</td>
</tr>
<tr>
<td>height in cm (mean ± SD)</td>
<td>171.2 ± 10.1</td>
<td>172.9 ± 12.0</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI in kg/m² (mean ± SD)</td>
<td>26.2 ± 3.3</td>
<td>26.1 ± 4.1</td>
<td>0.96</td>
</tr>
<tr>
<td>ASD</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>24 (70.6%)</td>
<td>22 (64.7%)</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>10 (29.4%)</td>
<td>12 (35.3%)</td>
<td>0.80</td>
</tr>
<tr>
<td>anticoagulant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>7 (20.6%)</td>
<td>19 (55.9%)</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>27 (79.4%)</td>
<td>15 (44.1%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* BMI = body mass index.
Shunt complications and opening pressure

the 20–4 group withdrew from further participation, referring to the inconvenience coming to the hospital for monthly evaluation—2 before surgery and 1 directly after. One patient in the 12 group was lost to follow-up after the 3-month evaluation due to the inconvenience of traveling to the hospital. Seven patients (4 in group 20–4 and 3 in group 12) were lost to follow-up after symptoms of overdrainage treated by upregulation of the valve setting. One patient was lost to follow-up after having a spontaneous SDH treated by upregulation of the valve setting.

The frequency of overdrainage symptoms could thus be evaluated in 64 patients (31 in the 20–4 group and 33 in the 12 group) and the complication rate evaluated in 57 patients (27 in the 20–4 group and 30 in the 12 group).

In the case of complications or symptoms of overdrainage, the code (for study condition) was opened, and the patient was treated and kept in the study at the optimal valve setting without further valve adjustments until the final evaluation.

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and Regional Committee for Medical and Health Research Ethics in South East Norway, and the Oslo University Hospital authority. All patients provided written informed consent.

Statistical Analysis

Between-group comparisons were performed using the Fisher’s exact test for dichotomous variables and the Mann-Whitney U-test for continuous variables. Within each group the sign test was employed for categorical variables. Time-to-event analyses were performed by means of the Kaplan-Meier method, and between-group comparisons were investigated with the log-rank test. The effect of continuous variables on time-to-event variables was assessed using the Cox proportional hazards model.

All tests were 2-tailed and conducted at the 0.05 significance level. The analyses were performed using SAS v9.2.

Results

Shunt Complications

Six patients in the 20–4 group (22%) and 7 in the 12 group (23%) experienced a shunt complication (Fig. 2) (nonsignificant difference). These included 2 cases of shunt obstruction distal to the valve, both of which were converted to ventriculoatrial shunts; 1 case of shunt obstruction proximal to the valve, leading to a proximal shunt revision; 1 case of shunt infection. However, the majority of the complications involved SDH—4 patients in the 20–4 group and 5 in the 12 group.

There was no significant difference in the rate of SDH between the groups. All cases were symptomatic and diagnosed by means of a head CT. The time to appearance of the SDH is presented in Fig. 3. Surgical treatment of SDH was necessary in 4 patients; 3 in the 12 group and 1 in the 20–4 group. The remaining 5 patients were successfully treated by increasing the valve setting. Two pa-
patients in the 20–4 group had SDH with a low valve setting (4 cm H₂O) while SDHs in the 12 group were observed at an earlier stage (Fig. 3).

In 2 of the SDH cases (1 in each group) there was a known head trauma prior to the event, and both patients were diagnosed and treated during the 1st postoperative month. The rest of the SDH cases were interpreted as spontaneous SDHs.

**Overdrainage**

Eleven patients presented with overdrainage symptoms: 7 (23%) in the 20–4 group and 4 (12%) in the 12 group. As can be seen in Fig. 4, there was no significant difference between the 2 groups over time, but significantly more overdrainage symptoms in the 20–4 group when the valve setting was ≤ 12 cm H₂O (n = 7) compared with > 12 cm H₂O (n = 0) (p = 0.016).

**Clinical Outcome and Final Valve Setting**

Both groups improved significantly 6 months after surgery; 88% of the patients in the 20–4 group and 62% of the patients in the 12 group were found to have improved at the 6-month follow-up evaluation. This difference was statistically significant (p = 0.032).

At the end of the study, 18 of the 26 patients in the 20–4 group had a valve setting of 4 cm H₂O, 7 had a valve setting of 12 cm H₂O, and 1 had a setting of 16 cm H₂O. In the 12 group, 25 patients had a valve setting of 12 cm H₂O, 2 a setting of 20 cm H₂O, and 2 a setting of 10 cm H₂O. Thus, the mean opening pressure at the end of the study was 7 cm H₂O in the 20–4 group and 13 cm H₂O in the 12 group.

There was no significant difference in clinical outcome between patients with or without an ASD and with or without anticoagulant treatment.

**Antisiphon Device and Anticoagulant Medication**

Subdural hematomas were found in 16% of patients with an ASD (Gothenburg) compared with 17% of patients without an ASD (Oslo). Overdrainage symptoms were seen in 9% of the patients with an ASD and in 50% of the patients without an ASD (p = 0.002). Furthermore, the rate of SDH was the same with and without anticoagulants (Table 1).

**Height and Body Mass Index**

There was no significant difference in body mass index, height, or weight between those patients who had SDH and those who did not (p = 0.15, 0.97, and 0.38, respectively).
Shunt complications and opening pressure

**Discussion**

The main finding of this double-blinded, randomized study was that a gradual reduction of the valve setting from 20 to 4 cm H\textsubscript{2}O did not reduce the shunt complication rate in iNPH patients compared with a fixed pressure of 12 cm H\textsubscript{2}O. The results could also be interpreted as indicating that starting with a valve setting of 12 cm H\textsubscript{2}O is equally as safe as gradually reducing it from 20 cm H\textsubscript{2}O. The rate of overdrainage symptoms was also identical in both groups, but such symptoms occurred significantly more frequently at a valve setting of ≤ 12 cm H\textsubscript{2}O.

We found that the group in which the opening pressure was reduced to a low level improved more than the control group with a medium-level opening pressure, which is in accordance with the Dutch normal-pressure hydrocephalus study on low- and medium-pressure fixed-pressure valves.\textsuperscript{2} When analyzed by intention to treat, there was no significant (p = 0.14) difference between our 2 groups (23 of 34 patients improved in the 20–4 group vs 17 of 34 patients in the 12 group). It seems probable that the reason why more patients improved in the 20–4 group than in the 12 group might be the final lower valve setting, however the valve setting level related to the higher improvement rate could not be determined in this study.

Adjustable shunt valves were introduced to ensure more optimal CSP drainage by enabling noninvasive adjustment of the valve setting.\textsuperscript{9} They are widely used despite a lack of randomized clinical trials or consensus regarding their benefit in shunt treatment of iNPH.\textsuperscript{1,20,26} The iNPH guidelines\textsuperscript{1} recommend starting with a high opening pressure and gradually lower it to reduce the frequency of complications, especially SDH.

At first glance, our study does not support this recommendation, as we found no significant difference between the SDH rates in the two groups.

The results differ from those in the 2 Dutch studies.\textsuperscript{2,5} In the study by Boon et al.,\textsuperscript{2} 2 fixed valves with a medium or low opening pressure were investigated. The group with the low opening pressure experienced more complications than the group with the medium opening pressure. Similarly, Delwel et al.\textsuperscript{5} observed a higher rate of SDH in the group that started at a low/medium valve setting (Strata performance level [PL] 1.0) compared with the group that started at a high valve setting (Strata PL 2.5), which was gradually lowered. This is not supported by our study, in which the patients in the 20–4 group that ended up at a low valve setting (4 cm H\textsubscript{2}O) presented with the same rate of SDH as the group with a medium valve setting (12 cm H\textsubscript{2}O). The discrepancy between the results could be interpreted to mean that gradual lowering of the opening pressure might have prevented the development of SDH, which thus might even support the recommendations presented in the iNPH guidelines.\textsuperscript{2} However, one should take into account that the 3 studies were conducted using different methodologies and 3 different valve types, which makes the conclusion speculative, but interesting.

In Boon and colleagues' study,\textsuperscript{2} the clinical effect of shunt treatment was better in the group treated with a low opening pressure than in the group treated with a medium opening pressure, which contradicts the results in the study by Delwel et al.,\textsuperscript{5} where the clinical effect was the same in both groups (low/medium valve setting group and high valve setting group). The purpose of the latter study was to lower the valve setting until the optimal level was reached. No patient in the high valve setting group had his or her setting downregulated to a low valve setting (Strata PL 0.5), and at the end of the study, only 2 patients in the

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**Fig. 4.** Kaplan-Meier curve of days to overdrainage symptoms in the 20–4 and 12 groups. At the time of shunt insertion the valve was preset to 20 cm H\textsubscript{2}O in the 20–4 group and 12 cm H\textsubscript{2}O in the 12 group. The valve setting at each monthly clinical evaluation is presented above the x-axis. There was no significant difference between the groups (log-rank test).
low/medium group achieved a low valve setting. The mean valve setting at the end of the study was 1.1 in the low/medium and 1.9 in the high valve setting group. The study design may have restricted the inclination to lower the valve setting further when a satisfactory clinical effect was achieved at a certain level. Thus further improvement due to a lower valve setting could not be investigated. However, a confounding factor when comparing overdrainage symptoms and clinical outcome in the 3 studies is that there are no common criteria for overdrainage and that different outcome scales were used.

Based on these studies, it is reasonable to stress the importance of lowering the valve setting as much as possible to achieve the optimal effect of shunting and still prevent overdrainage. The results of our study indicate that gradually lowering the valve setting does not increase the complication rate but does increase the incidence of symptoms of overdrainage, which can be easily managed by slightly upregulating the valve setting to the lowest level at which overdrainage symptoms were absent. Of course, it would be best if a preoperative test could predict the optimal valve setting for each individual, but such studies are scarce.

Possible Selection Biases

Differences between the study sites could have influenced the results of our study. The inclusion criteria in Oslo required that the patients had abnormal ICP dynamics preoperatively, defined as mean ICP wave amplitude above 4 mm Hg and > 5 mm Hg for at least 10% of the recording time. The patients at both centers had to fulfill the guidelines criteria for probable iNPH, but in Gothenburg no further CSF dynamic testing was required for inclusion. The CSF dynamic testing in Oslo was an established evaluation procedure that we decided to retain, as changing local policies often results in more problems than benefits. Similarly, we decided to keep the 2 different scoring scales used in Oslo and Gothenburg, as we expected validation problems if we changed the scale at one center. Due to administrative policies at each hospital we also decided to retain the established routines for shunts with an ASD in Gothenburg and shunts without an ASD in Oslo.

As the patients were randomized into 2 groups and there were no significant differences between them in terms of demographic characteristics or with respect to the site-dependent differences described above, we believe that the 2 groups are comparable and the results valid.

The extensive neurological and psychological evaluations in the study required a minimum level of function on the part of the patient. The findings may not be applicable to iNPH patients who did not participate in the study due to severe neurological or cognitive dysfunction as well as inability to travel to the hospital.

The sample size of 60 was deemed appropriate based on the assumption of a complication rate of 30% ± 8% and a power of 90%. The drop-out rate was fairly high due to complications, overdrainage problems, and unwillingness to travel to the hospital for the evaluations.

Antisiphon Device

The SiphonGuard antisiphon device, which was used in our Gothenburg site, was designed to prevent overdrainage. However, prospective studies of the effect of an ASD at different opening pressures are scarce. The objective of this study was not to evaluate the effect of the ASD on shunt complications, overdrainage symptoms, or clinical outcome. Our observation of a significantly lower rate of overdrainage symptoms in patients with an ASD could be due to a preventive effect of the ASD, but a confounding factor was that its use was site dependent and therefore not assessed in a randomized controlled manner. The gravitational valve is a siphon regulatory device that in a recent study was associated with a lower rate of overdrainage symptoms compared with differential pressure valves without an ASD. It would be valuable to investigate the ASD variable in a randomized clinical trial to further evaluate its effect on SDH and overdrainage symptoms.

Conclusions

A gradual lowering of the valve setting to a mean of 7 cm H$_2$O resulted in the same rate of shunt complications and overdrainage symptoms as a fixed valve setting, at a mean of 13 cm H$_2$O, but a significantly better outcome. Symptoms of overdrainage occurred more frequently when the valve setting was ≤ 12 cm H$_2$O, while the SDH rate remained the same, even at the lowest setting.

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Disclosure

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