World Neurosurgery: X 22 (2024) 100293

Contents lists available at ScienceDirect

World Neurosurgery: X

journal homepage: www.journals.elsevier.com/world-neurosurgery-x

17 years of experience with shunt systems in normal pressure hydrocephalus - From differential pressure to gravitational valves

Julian Zipfel [a,b], Cristina Kohlmann-Dell'Acqua [a,b], Susan Noell [a], Leonidas Trakolis [a,*]

[a] Department of Neurosurgery, University Hospital Tuebingen, Germany
[b] Centre for Clinical Studies, Neuropsychiatric Study Centre, University Hospital Tuebingen, Germany

ARTICLE INFO

Keywords:
Normal pressure hydrocephalus
Shunt
Overdrainage

ABSTRACT

Objective: Complication rate of shunting for normal pressure hydrocephalus (NPH) has significantly improved over the last decades. Especially the use of overdrainage protection has reduced the incidence of subdural hematoma and collections. However, gravitational valves were associated with other complications of shunt dysfunction. We present our 17 years of experience with patients with normal pressure hydrocephalus who changed from a differential pressure valve to a gravitational valve system.

Methods: We retrospectively identified all patients with the diagnosis of normal pressure hydrocephalus, in whom primary shunt implantation was performed between 2004 and 2020. Shunt implantation was performed as per our internal standard. Review of imaging, charts and patient reports was performed.

Results: In total, 409 patients were included in the analysis. Mean age was 73.0 ± 7.1years. Between 2004 and 2010, predominantly Hakim valves (n = 100, 24.4%) were implanted, whilst from 2009 until 2020, proGAV valves (n = 296, 72.4%) were used. Mean follow-up was 8.9 ± 4.5 years. Initial subjective improvement of symptoms was reported in 69.9%, whilst this number decreased at the last follow-up to 29.8%. No significant differences were observed between the valves in the frequency of surgery for subdural hematoma. Shunt assistant implantation was performed in 17% of patients with Hakim valve, in 9.5% of patients with proGAV, a shunt assistant was added. Shunt obstruction was significantly higher in proGAV valves ($p < 0.001$).

Conclusions: Our findings confirm the observation of frequent overdrainage in shunts without anti-siphon/gravitational component. Gravitational valves on the other hand may be associated with more obstruction.

1. Introduction

Hydrocephalus is one of the most common pathologies treated by neurosurgeons at all ages not only as an own entity but also as in context of other diseases.[1] In older patients, normal-pressure hydrocephalus (NPH) is the most frequent pathology requiring shunting.[2] Idiopathic NPH, not associated with other primary reasons for hydrocephalus such as hemorrhage or infection may be associated with restricted arterial pulsations, thus reducing glymphatic flow. Consecutively, reduced intracranial compliance occurs and an obstruction of paravascular and interstitial spaces may be responsible for retrograde transventricular route of cerebrospinal fluid (CSF) flow.[3] Patients report of significantly impaired subjective quality of life.[4] Ventriculo-peritoneal (VP)-shunting is the standard treatment for patients with NPH with good long-term results.[5] Proper evaluation of the success of the treatment may be difficult to achieve. Especially in patients with NPH, long-term outcome assessment is under-represented in existing literature. Cognitive and neuropsychological outcome is sometimes, partly due to other diagnoses, difficult to evaluate. Reliable measures in this cohort may be gait disturbance, concentration deficits and urine incontinence.[6,7] Especially the first year after shunt implantation may predict the further course of quality of life for patients.[8]

The prevalence of NPH is reported to be around 1.5% in the general population.[9] A vascular etiology for NPH has been proposed. Vascular risk factors associated with NPH include hyperlipidemia, diabetes, obesity and psychosocial factors.[10] Shunting improves quality of life.[11] Whilst short term follow-up shows good clinical improvement (83%), this parameter decreases to 38% long term.[12] There is little evidence to show the superiority of a specific type of valve over another.[13,14] Anti-siphon/gravity devices are associated with less subdural CSF collections and hematomas[9] Quality of life in patients with NPH is associated with pre-operative cognitive status, overweight and age.[15] Lumboperitoneal shunting is also performed with good surgical results

* Corresponding author. Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany.
E-mail address: leonidastra86@hotmail.com (L. Trakolis).

https://doi.org/10.1016/j.wnsx.2024.100293
Received 8 March 2023; Accepted 20 February 2024
Available online 25 February 2024

Abbreviations

CSF	cerebrospinal fluid
NPH	normal pressure hydrocephalus
VP	ventriculoperitoneal

but is not the shunt method of choice in NPH patients.[16] Testing of CSF dynamics may provide a better understanding of shunt function and potentially shunt response through shunt testing in vivo.[17]

Complication rate after shunting with the need of surgical revision is about 18–19% (3% infection, 11% shunt failure, SDH 4%). Other complications may arise from, amongst others, clinical symptoms of under- or overdrainage, pain, abdominal hernia, scarring or local irritation. Randomized control studies have shown that implantation of gravitational valves can avoid overdrainage complications in about a third of patients.[18] Programmable valves tend for lower complication rate.[19,12] Valve dysfunction can be associated with diffuse and obscure clinical manifestation and may appear as malfunction rather than complete obstruction.[20] One study didn't find significant differences in the incidence of hygromas and subdural hematomas between flow-regulated and gravitational valves. In patient with flow-regulated valves, less revisions were necessary.[21] Shunt valves are susceptible to gravity-dependent overdrainage, which is why gravitational valves and antisiphon devices have been developed.[22]

Complication rate of shunting for normal pressure hydrocephalus (NPH) has significantly improved over the last decades. Especially overdrainage protection has reduced the incidence of subdural hematoma and collections.[23] However, gravitational valves may be associated with other complications of shunt dysfunction. We present our 17 years of experience with changing from a differential pressure valve to a gravitational valve system in patients with NPH.

The goal of our study was to assess our longitudinal cohort of patients with NPH and shunt implantation and to evaluate the therapeutic effect as well as complications of the valves used.

2. Materials and methods

We retrospectively identified all patients with the diagnosis of normal pressure hydrocephalus, in whom primary shunt implantation was performed between 2004 and 2020. Shunt implantation was performed as per our internal standard via burr-hole trephination at a 2,5 cm lateral pre-coronal location and distal catheter implantation via a supraumbilical lateral incision.

Inclusion criteria were as follows: radiological and clinical features of NPH, age >18years at the time of admission, positive clinical response to tap test or lumbar drain via gait analysis and neuropsychiatric testing. Exclusion criteria were insufficient data points.

2.1. Baseline characteristics

Baseline characteristics of each patient including age, sex, duration of symptoms, medical history, follow-up time, shunt type, reoperations and revisions were collected. MRI reports were assessed for signs of NPH: ventriculomegaly, increased Evans' index >0.3, acute callosal angle, dilated Sylvian fissures, tight high convexity.

2.2. Outcomes

Primary outcomes were the incidence of complications such as infection, obstruction, SDH and catheter displacement with the need of revision surgery. Shunt obstruction was defined by intraoperative testing with a glass manometer. Secondary outcomes were the number of valve setting changes, subjective improvement after shunting and the incidence of headaches. The latter outcomes were evaluated via a standard questionnaire, patients receive at every outpatient visit the hydrocephalus clinic.

Statistics were analyzed using SPSS Statistics 25 (IBM, NY, U.S.A.). Continuous data were presented as mean (±SD), whereas categorical data were shown as percentages. Continuous variables were tested for equality of variances by Levene's test. Normal distributed parametric variables with equal variances were compared using the unpaired or paired *t*-test, otherwise Mann–Whitney *U* test was performed. Nominal variables were tested with Fisher's exact test. p values < 00.05 were regarded as significant. For multiple comparisons, Bonferroni correction was utilized via ANOVA. The work has been approved by the local ethics committee; a waiver was granted for patient consent due to the retrospective analysis. Institutional board approval was granted (630/2021BO2).

3. Results

In total, 409 patients were included in the analysis. Patients were predominantly male (male: 57.2%, $n = 234$; female: 42.8%, $n = 175$). Mean age was 73.0 ± 7.1 years (range 43–92).

Spinal tap was performed in 246 patients prior to surgery (60.1%), lumbar drain in 135 (33.0%) and no CSF drainage in 28 (6.8%). Table 1 provides the basic patient parameters,

Postoperative improvement was significant in 286 patients (69.9%), moderate in 113 (27.6%) and in 10 patients (2.4%), no clinical change was observed. At last follow-up, only 122 patients reported of persisting improvement (29.8%).

4. Valves

Implanted valves were Codman® Hakim® (Integra Lifesciences) in 100 cases (24.4%), GAV® in 11 (2.7%), proGAV® in 296 (72.4%) and miniNav® in 2 (0.5%) (Christoph Miethke GmbH & Co. KG). Hakim valves, primarily without anti-siphon-device, were utilized between 2004 and 2010, proGAV with gravitational component from 2009 until 2020. Choice of shunt system was guided by internal standard at our institution and availability of shunt systems which changed 2009–2010. Surgical technique was not adapted other than vertical positioning of the gravitational valve. Mean follow-up was 8.9 ± 4.5 years (range 0.7–17.3 years). Mean age for Hakim was 73.1 ± 6.2 years and for proGAV 73.0 ± 7.3 years.

Initial differential pressure valve settings ranged from 0 to 18 cmH2O. In 55.0%, 10cmH2O ($n = 225$), in 25.4% 12cmH2O ($n = 104$) and in 6.8% 8 cmH2O ($n = 28$) was used. Gravitational pressure setting was chosen at 25 cmH2O in 96.4% ($n = 297/308$)

Frequency of valve setting changes ranged from 0 to 19 in our cohort (0 $n = 85$, 20.8%, 1 $n = 55$, 13.4%, 2 $n = 51$, 12.5%, 3 $n = 59$, 14.4%). Complete Hakim trias was observed in 76.0% of patients ($n = 311$), partial in 23.7% ($n = 97$) and none in 1.

Subjective postoperative outcome differed significantly between

Table 1
basic patients characteristics.

	mean 73.0 ± 7.1 years (range 43–92 years)			
sex	42.8% female ($n = 175$)	57.2% male ($n = 234$)		
preoperative evaluation	60.1% spinal tap ($n = 246$)	33.0% lumbar dran ($n = 135$)	6.8% clinical/imaging ($n = 28$)	
primary implanted valve	72.4% proGAV ($n = 296$)	24.4% Hakim ($n = 100$)	2.7% GAV ($n = 11$)	0.5% miniNAV ($n = 2$)
postoperative improvement of symptoms	69.9% significant ($n = 286$)	27.6% moderate ($n = 113$)	2.4% none ($n = 10$)	
follow-up	mean 8.9 ± 4.5 years (range 0.7–13a)			

Hakim and proGAV. 99% of patients with proGAV reported of improved symptoms (significant $n = 187$, moderate $n = 105$) and 95% of patients with Hakim (significant $n = 89$, moderate $n = 6$) (overall improvement $p = 0.034$, significant improvement proGAV 63,1% vs Hakim 89%, moderate improvement proGAV 35.5% vs Hakim 6%, $p < 0.001$). At last follow-up, 34% of patients with proGAV and 20% of patients with Hakim still reported of a persisting improvement of symptoms ($p = 0.009$). Fig. 1 illustrates the subjective outcome between the main valve types.

No significant difference was seen between the other valves.

5. Complications

Subdural hematomas without the need of surgical intervention were observed in 4 patients with Hakim (4%) and 1 patient with proGAV ($p = 0.006$) In total, subdural hematomas with the need of surgical intervention were observed in 15 patients (3.7%), of these 6 with Hakim (6%) and 9 with proGAV (3%). No significant differences were observed between different valves for the prevalence of SDH with need of surgery. Valve revisions were performed in 64 patients (15.6%), of these 4 with Hakim (4%), 2 with GAV (18.2%), 58 in proGAV (19.6%) and none in miniNAV. Table 2 summarizes the absolute numbers of revisions.

Valve revisions were performed significantly more often in proGAV as compared to Hakim ($p < 0.001$). Secondary implantation of a shunt assistant was performed in 17% of Hakim valves ($n = 17$) and not in the other valves. In all patients with miniNAV, proSA valves were implanted additionally. In 9.5% of patients with proGAV ($n = 28$), a proSA valve was implanted instead of the SA-Unit.

Table 2
comparison of primary follow-up interventions for different valves.

	primary_valve				total
	Hakim	GAV	proGAV	miniNAV	
cSDH	6	0	9	0	15
valve revision	4	2	58	0	64
shunt assistant	17	0	0	2	19
total no. of interventions	27	2	67	2	98
total no. of patients	100	11	296	2	409

Table 1 and Fig. 2 summarize the primary surgical interventions for the different shunt systems.

Further surgeries performed were: conversion to ventriculoatrial shunt 1x (0.2%), endoscopic third-ventriculostomy 1x (0.2%), ventricular catheter obstruction 5 (1.2%), peritoneal catheter obstruction 21 (5.1%), infection 7 (1.7%). Infections were observed in 2 cases with proGAV and in 5 cases with Hakim (5%).

The frequency of further surgeries was as follows: 0 in 268 (65.5%), 1 in 82 (20.3%), 2 in 36 (8.8%), 3 in 9 (2.2%), 4 in 8 (2.0%), 5 in 4 (1.0%). No significant difference in the total number of further surgeries could be observed between the different valves.

The overall number of associated surgeries correlated to the number of valve setting changes ($p < 0.001$), the rate of SDH ($p < 0.001$) and the number of valve revisions ($p < 0.001$). Furthermore, the type of primary

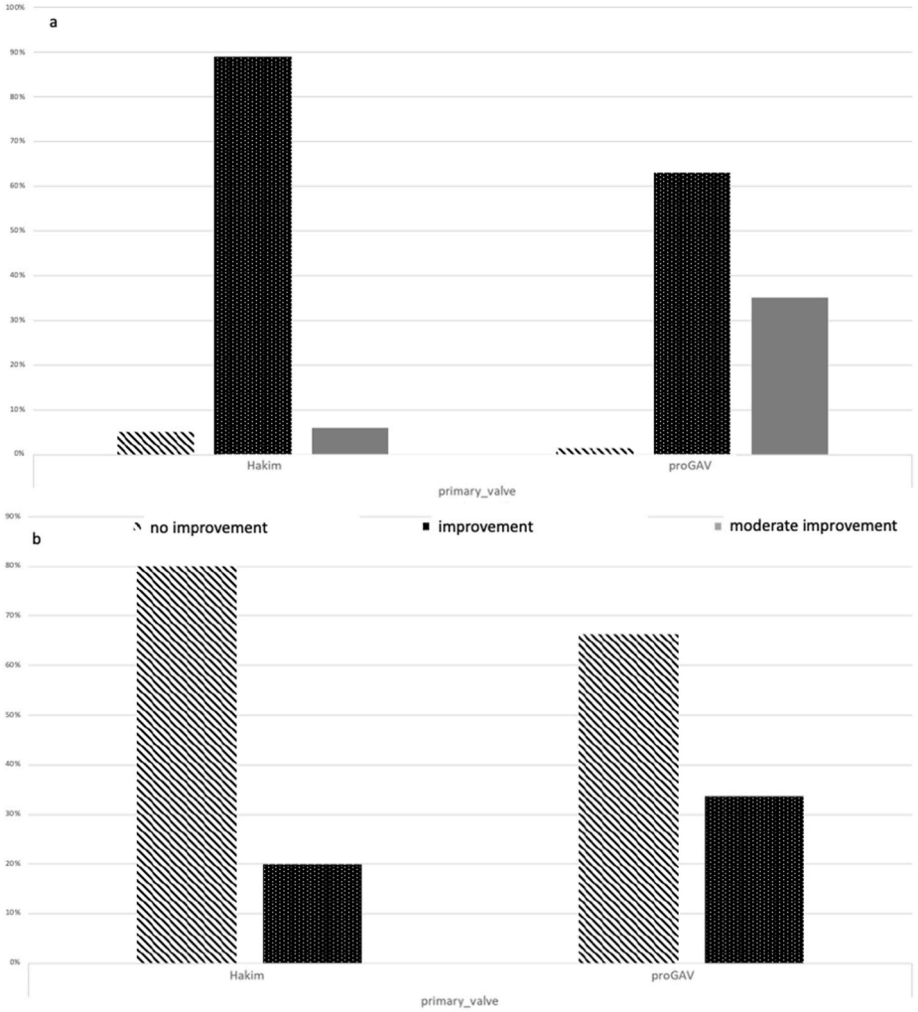

Fig. 1. Comparison of outcome in primary valve types proGAV and Hakim a) postoperatively b) at last follow-up.

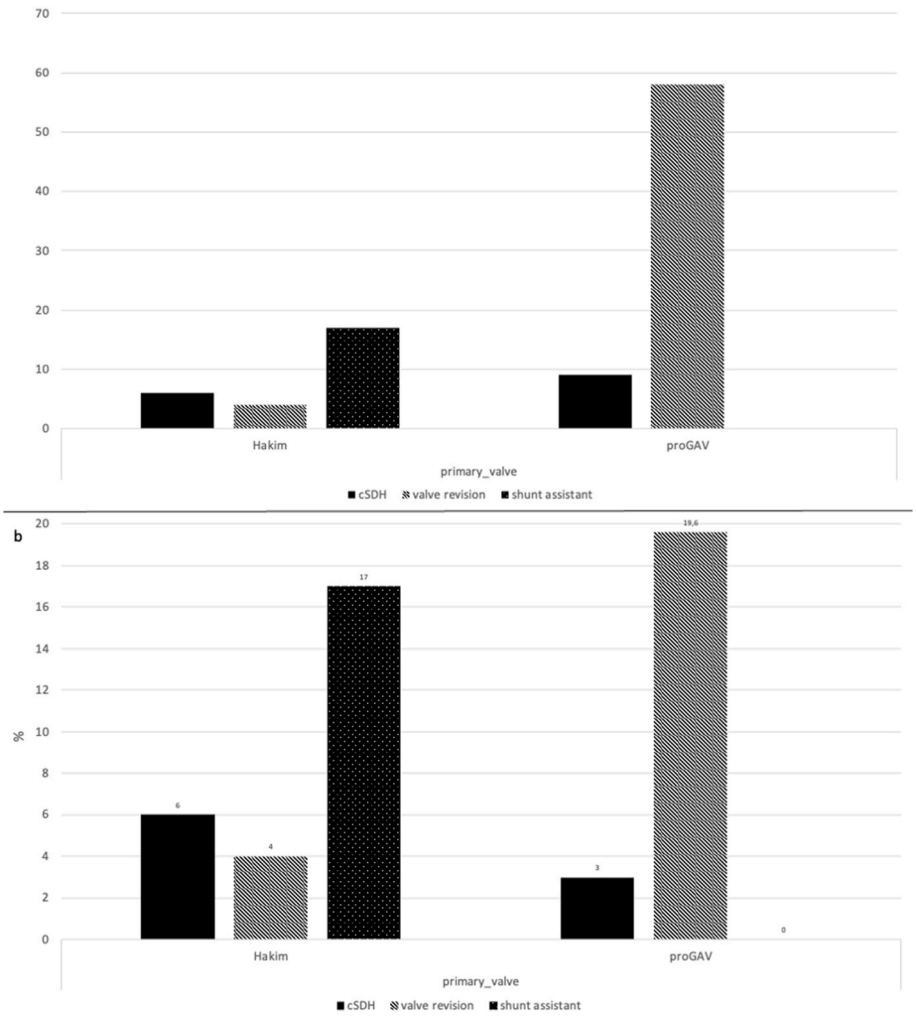

Fig. 2. Comparison of primary revision surgeries between Hakim and proGAV a) absolute number of interventions b) relative percentage of interventions compared to total number of patients.

valves correlated to the number of valve setting changes ($p < 0.001$), the rate of headaches ($p = 0.005$) and the number of valve revisions ($p < 0.001$). The primary differential pressure setting correlated to the rate of headaches ($p = 0.003$), the number of SDH ($p = 0.004$) and the rate of shunt revisions ($p = 0.033$)

6. Valve settings

Initial valve settings in programmable valves were significantly higher in Hakim as compared to proGAV (11.9 ± 0.9 vs 9.8 ± 1.7 cmH2O, $p < 0.001$), the same was true for the last documented valve setting (10.2 ± 3.6 vs 5.5 ± 3.7 cmH2O, $p < 0.001$). When comparing the first to last setting, Δ was significantly higher in proGAV (1.7 ± 3.5 vs 4.2 ± 3.9 cmH2O, $p < 0.001$). The overall number of valve setting changes also was higher in proGAV (2.1 ± 2.3 vs 3.9 ± 3.3 $p < 0.001$). Figs. 3 and 4 summarize the mean initial and last valve settings as well as Δ between Hakim and proGAV.

7. Discussion

In conclusion, no superiority of one valve system over the other was observed. Whilst overdrainage was the most common problem of differential pressure valves without anti-siphon function, later valve systems with gravitational function were prone to a higher rate of dysfunction. The cohort of patients with NPH are a challenging population due to age and further comorbidities. Symptomatology is often not clear as not all aspects of the Hakim trias may present. Most patients present with concentration deficit and urine incontinence, symptoms that are mostly associated with dementia or Alzheimer disease.[24,25] As a result, such comorbidities have to be identified before the decision for shunt surgery is met. During the recent years the diagnostic and therapy of NPH patients has become more sophisticated. MRI Imaging and lumbar CSF drainage are standard of care. Treatment, however, is not standardized and as such, utilization of different valve systems is performed. Furthermore, surgical approaches are also not standardized, and no superiority of occipital vs frontal ventricular catheter insertion points has been shown.[26] For this study, only frontal approaches were included, as posterior insertion is rarely done in our institution.

In a recent meta-analysis of 33 studies, complication rate of VP shunting ranged 13–38%, 26–38% of cases shunted with a fixed-pressure valve and 9–16% of cases shunted with an adjustable valve required a revision surgery as the only significant difference between both groups.[27]

In our cohort we found a high rate of overdrainage with Hakim valves, prompting in many cases for secondary implantation of a shunt assistant. Overdrainage is not a new issue and correlates with the era of valves without gravitational unit.[28,29] The rate of subdural hematomas with the need of surgical evacuation did not however differ between the valves. On the other hand, proGAV valves were associated with significantly less overdrainage problems but the apparent valve malfunction rate was higher. Similar results were seen in pediatric population prompting the authors consider that this problem lies in the younger age

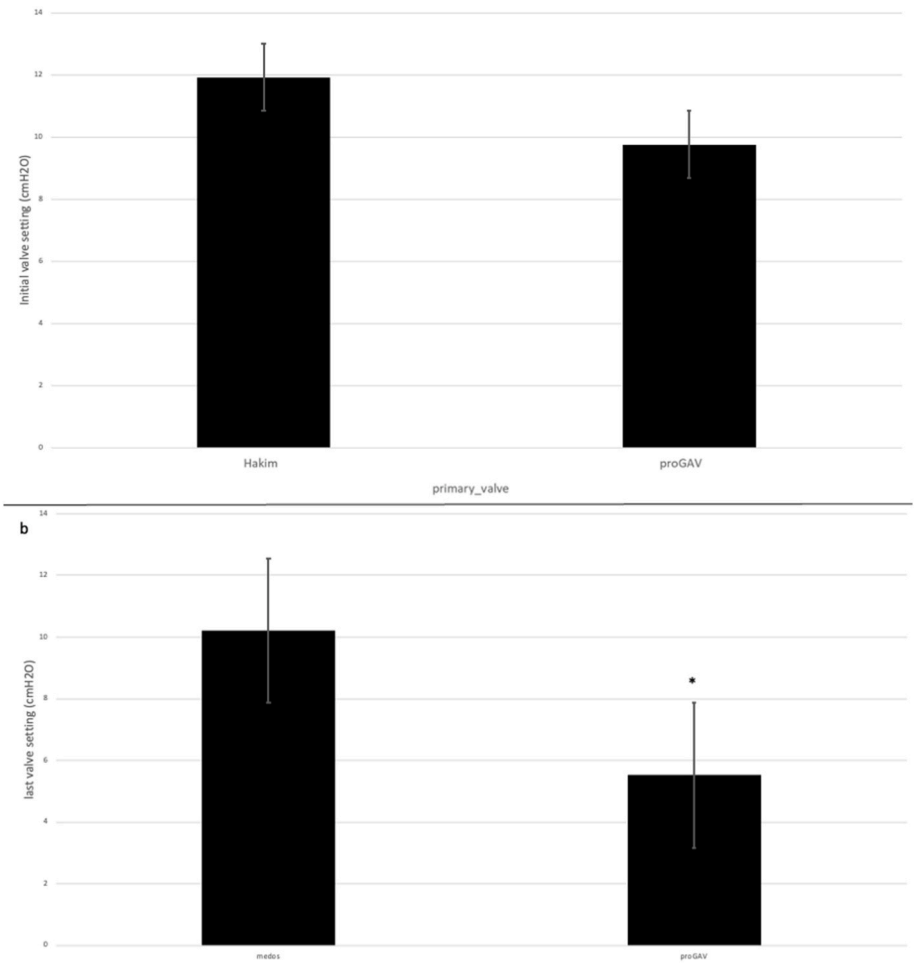

Fig. 3. Comparison of a) initial and b) valve setting at las follow-up between Hakim and proGAV; * signifies $p < 0.001$.

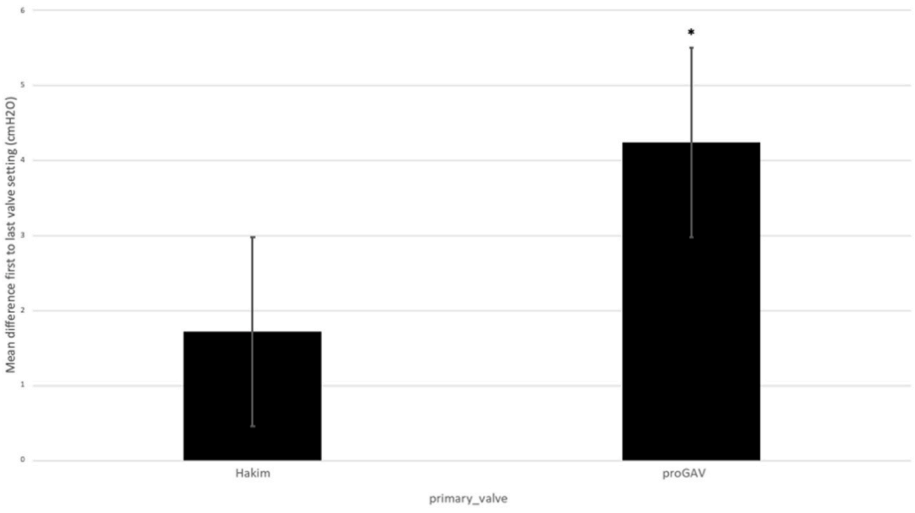

Fig. 4. Comparison of Δ valve setting between initial and last follow up between Hakim and proGAV; * signifies $p < 0.001$.

of the patients.[30]

The first shunts were less complicated but also less sophisticated.[31] They were not adjustable and had no antisiphon device which was introduced later on. Patients often suffered from overdrainage and sometimes developed hygromas or subdural blood collections. To face this problem, newer shunt systems an antisiphon device were developed.[32,33] However these devices may show a tendency for more frequent valve dysfunction.[34]

Nowadays, many valves available in western countries are adjustable and come with gravitational units. Some of them will be delivered with non-adjustable shunt assistants while for more complex cases adjustable shunt assistants are available as well. This may lead to more flexibility in adjustment but also to a more complex procedure to find the right configuration for each patient.

Our data shows that, although the need for a secondary shunt assistant implantation was greatly decreased, the rate of shunt revisions and replacements increased with gravitational valves. The patients suffered significantly less often from overdrainage but more often valve malfunction was diagnosed. This could be due to a lower flow rate through the valve and pooling of protein in the fine mechanism of the valves. The retrospective character of this study doesn't allow for an in-depth investigation and prospective controlled analysis would be necessary to evaluate.

On the other hand, identifying shunt malfunction in NPH can be a major problem as imaging studies may not suffice. Emerging techniques such as infusion studies have become more important in our practice and may be a very important confounder in the number of identified valve dysfunctions.[17] This has to be considered for our retrospective historical analysis, as valve dysfunctions with mild NPH-symptoms may have been missed and thus were not available for analysis. Furthermore, only two different valve systems were compared with a vast number of other systems available on the market.

Unsurprisingly, valve settings were significantly lower in proGAV as compared to Hakim valves both at the time of implantation as well as the last follow up. Also, the difference of first to last setting was higher. Thus, these valves allow for lower settings of the differential pressure component in horizontal position with a lower risk of overdrainage. This leads to significantly lower possible valve setting (and thus also a higher net CSF flow?). The hypothesis which is yet to prove is, that gravitational valves may allow for better symptom control, as the progression character of NPH often leads to the necessity of reducing shunt resistance.

We found indices for this hypothesis in the observation, that the initial effect of shunting may even be less pronounced in proGAV as compared to Hakim (overall improvement 99 vs 95% but significantly higher incidence of significant improvement!), whilst long-term follow-up showed significantly better subjective outcome in the former group.

In total, complication rates of all shunt systems were similar when comparing overdrainage problems with valve dysfunction. Initially 69%, then around 30% of clinical improvement after shunt insertion may seem like a low number, but as NPH is a slowly progressing disease, adaptation of valve setting to lower levels is often needed. In many cases, symptoms may deteriorate even with minimal shunt settings.[35,36]

The limitations of our study arise from the retrospective character of the analysis. Different valve techniques are compared in a historical cohort. Whilst our patients cohort still shows no significant selection bias, the diagnosis of NPH is – to this day – challenging.

In the cohort of patients with NPH – due to the progressing nature of the disease – a subsequent lowering of valve settings is observed. This prompts for an even higher rate of overdrainage problems in this population. Whilst the overall rate of follow-up surgeries was comparable, the nature of a valve replacement versus an – often times urgently operated – subdural hematoma evacuation is inherently different. Valve dysfunction manifests in the recurrence of NPH symptoms such as gait disturbance, incontinence, and cognitive impairment. Whilst significantly impairing quality of life, these symptoms are not as threatening as subdural hematomas or collections, potentially life-threatening problems. Therefore, we plead for the use of overdrainage protected valves in patients with NPH. This may not lead to a lower rate of complications or revision surgery, but shunt dysfunction is clearly the lesser problem as compared to overdrainage. Furthermore, overdrainage protected valves may be adjusted to lower differential pressure settings as compared to non-protected valves due to this issue, leading to a potentially longer period of symptom control. This has to be further evaluated.

Our experience showed that not every patient after valve surgery has an improved quality of life. This could be due to insufficient drainage or misinterpretation of the symptoms and wrong diagnosis or further comorbidities. Further insight in this problem will be hopefully given in the near future. A prospective analysis of quality of life measures in patients with hydrocephalus is being conducted in our institution.

8. Conclusion

Patients with NPH are a demanding population concerning diagnosis and treatment, especially when considering long-term follow-up. In our institution, the development of valve technologies has led to a shift from overdrainage-associated problems to issues with shunt malfunction in gravitational valves. Quality of life as one of the most important outcome measures in these patients has to be further evaluated prospectively.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Julian Zipfel: Investigation, Writing – original draft, Formal analysis, Writing – review & editing, Conceptualization. **Cristina Kohlmann-Dell'Acqua:** Formal analysis, Data curation, Investigation. **Susan Noell:** Methodology, Project administration, Supervision, Conceptualization. **Leonidas Trakolis:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Iseki C, Takahashi Y, Adachi M, et al. Prevalence and development of idiopathic normal pressure hydrocephalus: a 16-year longitudinal study in Japan. *Acta Neurol Scand. Nov*. 2022;146(5):680–689. https://doi.org/10.1111/ane.13710.
2. Sundstrom N, Lundin F, Arvidsson L, Tullberg M, Wikkelso C. The demography of idiopathic normal pressure hydrocephalus: data on 3000 consecutive, surgically treated patients and a systematic review of the literature. *J Neurosurg. Apr*. 2022;8:1–11. https://doi.org/10.3171/2022.2.JNS212063.
3. Skalicky P, Mladek A, Vlasak A, De Lacy P, Benes V, Bradac O. Normal pressure hydrocephalus-an overview of pathophysiological mechanisms and diagnostic procedures. *Neurosurg Rev. Dec*. 2020;43(6):1451–1464. https://doi.org/10.1007/s10143-019-01201-5.
4. Junkkari A, Sintonen H, Nerg O, et al. Health-related quality of life in patients with idiopathic normal pressure hydrocephalus. *Eur J Neurol. Oct*. 2015;22(10):1391–1399. https://doi.org/10.1111/ene.12755.
5. Popal AM, Zhu Z, Guo X, et al. Outcomes of ventriculoperitoneal shunt in patients with idiopathic normal-pressure hydrocephalus 2 Years after surgery. *Front Surg*. 2021;8, 641561. https://doi.org/10.3389/fsurg.2021.641561.
6. Savolainen S, Hurskainen H, Paljarvi L, Alafuzoff I, Vapalahti M. Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. *Acta Neurochir (Wien). Jun*. 2002;144(6):515–523. https://doi.org/10.1007/s00701-002-0936-3. ; discussion 523.
7. Toma AK, Tarnaris A, Kitchen ND, Watkins LD. Working towards patient oriented outcome assessment in normal pressure hydrocephalus, what is the most important? *Acta Neurochir (Wien). Jan*. 2011;153(1):177–180. https://doi.org/10.1007/s00701-010-0781-8.
8. Klinge P, Marmarou A, Bergsneider M, Relkin N, Black PM. Outcome of shunting in idiopathic normal-pressure hydrocephalus and the value of outcome assessment in shunted patients. *Neurosurgery*. Sep 2005;57(3 Suppl):S40–S52. https://doi.org/10.1227/01.neu.0000168187.01077.2f. ; discussion ii-v.
9. Nakajima M, Yamada S, Miyajima M, et al. Guidelines for Management of idiopathic normal pressure hydrocephalus (third edition): Endorsed by the Japanese Society of normal pressure hydrocephalus. *Neurol Med -Chir*. Feb 15 2021;61(2):63–97. https://doi.org/10.2176/nmc.st.2020-0292.
10. Israelsson H, Carlberg B, Wikkelso C, et al. Vascular risk factors in INPH: a prospective case-control study (the INPH-CRasH study). *Neurology*. Feb 7 2017;88(6):577–585. https://doi.org/10.1212/WNL.0000000000003583.
11. Israelsson H, Larsson J, Eklund A, Malm J. Risk factors, comorbidities, quality of life, and complications after surgery in idiopathic normal pressure hydrocephalus: review of the INPH-CRasH study. *Neurosurg Focus*. Oct 2020;49(4):E8. https://doi.org/10.3171/2020.7.FOCUS20466.
12. de Oliveira MF, Sorte Jr AAB, Emerenciano DL, Rotta JM, Mendes GAS, Pinto FCG. Long term follow-up of shunted idiopathic normal pressure hydrocephalus patients: a single center experience. *Acta Neurol Belg. Dec*. 2021;121(6):1799–1806. https://doi.org/10.1007/s13760-020-01538-5.
13. Poca MA, Gandara DF, Rosas K, Alcina A, Lopez-Bermeo D, Sahuquillo J. Considerations in the Use of gravitational valves in the Management of

hydrocephalus. Some Lessons Learned with the Dual-Switch valve. J Clin Med. Jan 12 2021;10(2)doi:10.3390/jcm10020246.
14. Sahuquillo J, Rosas K, Calvo H, et al. How to Choose a shunt for patients with normal pressure hydrocephalus: a short Guide to selecting the best shunt Assembly. *J Clin Med. Mar*. 2021;15(6):10. https://doi.org/10.3390/jcm10061210.
15. Junkkari A, Sintonen H, Danner N, et al. 5-Year health-related quality of life outcome in patients with idiopathic normal pressure hydrocephalus. *J Neurol. Sep*. 2021;268(9):3283–3293. https://doi.org/10.1007/s00415-021-10477-x.
16. Kimura T, Yamada S, Sugimura T, et al. Preoperative predictive factors of short-term outcome in idiopathic normal pressure hydrocephalus. *World Neurosurg*. Jul 2021; 151:e399–e406. https://doi.org/10.1016/j.wneu.2021.04.055.
17. Lalou AD, Czosnyka M, Placek MM, Smielewski P, Nabbanja E, Czosnyka Z. CSF dynamics for shunt Prognostication and revision in normal pressure hydrocephalus. *J Clin Med. Apr*. 2021;15(8):10. https://doi.org/10.3390/jcm10081711.
18. Lemcke J, Meier U, Muller C, et al. Safety and efficacy of gravitational shunt valves in patients with idiopathic normal pressure hydrocephalus: a pragmatic, randomised, open label, multicentre trial (SVASONA). *J Neurol Neurosurg Psychiatry. Aug*. 2013;84(8):850–857. https://doi.org/10.1136/jnnp-2012-303936.
19. Desai VR, Sadrameli SS, Jenson AV, et al. Ventriculoperitoneal shunt complications in an adult population: a comparison of various shunt designs to prevent overdrainage. *Surg Neurol Int*. 2020;11:269. https://doi.org/10.25259/SNI_38_2020.
20. Bettag C, von der Brelie C, Freimann FB, Thomale UW, Rohde V, Fiss I. In vitro testing of explanted shunt valves in hydrocephalic patients with suspected valve malfunction. *Neurosurg Rev*. May 24 2021. https://doi.org/10.1007/s10143-021-01564-8.
21. Scheffler P, Oertel MF, Stieglitz LH. Comparison between flow-regulated and gravitational shunt valves in the treatment of normal pressure hydrocephalus: flow-Grav study. *Neurosurgery*. Aug 16 2021;89(3):413–419. https://doi.org/10.1093/neuros/nyab176.
22. Koueik J, Iskandar BJ, Yang Z, et al. Ventriculoperitoneal shunt drainage Increases with gravity and cerebrospinal fluid pressure pulsations: Benchtop Model. *Neurosurgery. Nov 18*. 2021;89(6):1141–1147. https://doi.org/10.1093/neuros/nyab336.
23. Gehlen M, Eklund A, Kurtcuoglu V, Malm J, Schmid Daners M. Comparison of anti-siphon devices-how do they affect CSF dynamics in supine and upright posture? *Acta Neurochir*. Aug 2017;159(8):1389–1397. https://doi.org/10.1007/s00701-017-3249-2.
24. Malm J, Graff-Radford NR, Ishikawa M, et al. Influence of comorbidities in idiopathic normal pressure hydrocephalus - research and clinical care. A report of the ISHCSF task force on comorbidities in INPH. *Fluids Barriers CNS*. Jun 10 2013;10 (1):22. https://doi.org/10.1186/2045-8118-10-22.
25. Golomb J, Wisoff J, Miller DC, et al. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. *J Neurol Neurosurg Psychiatry. Jun*. 2000;68(6):778–781. https://doi.org/10.1136/jnnp.68.6.778.
26. Keykhosravi E, Shahmohammadi MR, Rezaee H, Abouei Mehrizi MA, Tavakkol Afshari HS, Tavallaii A. Strengths and weaknesses of frontal versus occipital ventriculoperitoneal shunt placement: a systematic review. *Neurosurg Rev. Aug*. 2021;44(4):1869–1875. https://doi.org/10.1007/s10143-020-01391-3.
27. Giordan E, Palandri G, Lanzino G, Murad MH, Elder BD. Outcomes and complications of different surgical treatments for idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis. *J Neurosurg. Nov*. 2018;1: 1–13. https://doi.org/10.3171/2018.5.JNS1875.
28. Meier U, Stengel D, Muller C, et al. Predictors of subsequent overdrainage and clinical outcomes after ventriculoperitoneal shunting for idiopathic normal pressure hydrocephalus. *Neurosurgery*. Dec 2013;73(6):1054–1060. https://doi.org/10.1227/NEU.0000000000000155.
29. Khan QU, Wharen RE, Grewal SS, et al. Overdrainage shunt complications in idiopathic normal-pressure hydrocephalus and lumbar puncture opening pressure. *J Neurosurg. Dec*. 2013;119(6):1498–1502. https://doi.org/10.3171/2013.7.JNS13484.
30. Hall BJ, Sg C, Hennigan D, Bagga V, Mallucci C, Pettorini B. Efficacy and safety of the Miethke programmable differential pressure valve (proGAV(R)2.0): a single-centre retrospective analysis. *Childs Nerv Syst. Aug*. 2021;37(8):2605–2612. https://doi.org/10.1007/s00381-021-05162-3.
31. Weisenberg SH, TerMaath SC, Seaver CE, Killeffer JA. Ventricular catheter development: past, present, and future. *J Neurosurg. Dec*. 2016;125(6):1504–1512. https://doi.org/10.3171/2015.12.JNS151181.
32. Aschoff A, Kremer P, Benesch C, Fruh K, Klank A, Kunze S. Overdrainage and shunt technology. A critical comparison of programmable, hydrostatic and variable-resistance valves and flow-reducing devices. *Childs Nerv Syst. Apr*. 1995;11(4): 193–202. https://doi.org/10.1007/BF00277653.
33. Lam CH, Dubuisson D. Treatment of hemispheric collapse and herniation beneath the falx in a case of shunted hydrocephalus. *Surg Neurol. Mar*. 1990;33(3):202–205. https://doi.org/10.1016/0090-3019(90)90185-r.
34. Huang AP, Kuo LT, Lai DM, Yang SH, Kuo MF. Antisiphon device: a review of existing mechanisms and clinical applications to prevent overdrainage in shunted hydrocephalic patients. *Biomed J. Aug*. 2021:16. https://doi.org/10.1016/j.bj.2021.08.001.
35. Oliveira LM, Nitrini R, Roman GC. Normal-pressure hydrocephalus: a critical review. *Dement Neuropsychol*. Apr-Jun 2019;13(2):133–143. https://doi.org/10.1590/1980-57642018dn13-020001.
36. Andren K, Wikkelso C, Tisell M, Hellstrom P. Natural course of idiopathic normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry. Jul*. 2014;85(7):806–810. https://doi.org/10.1136/jnnp-2013-306117.