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# Ventriculosubgaleal shunting for spontaneous intraventricular haemorrhage: is it a good alternative to external ventricular drainage?

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## Abstract

**Background:** Spontaneous intraventricular haemorrhage (IVH) is a life-threatening condition associated with high morbidity and mortality and is conventionally managed using external ventricular drain (EVD). However, EVD is commonly associated with a high rate of complications, which necessitates another alternative management with a comparable or better outcome. This study aims to compare the efficacy and safety of ventriculosubgaleal shunt (VSGS) compared to EVD for the management of adult patients with spontaneous IVH.

**Results:** A total of 48 patients were enrolled in this study. Twenty patients underwent EVD and 28 had VSGS. Post-operative complications were non-significantly more prevalent in the EVD than in the VSGS group (75 vs. 64.3%,  $p=0.430$ ), including non-CR (20 vs. 32.1%), infection (20 vs. 7.1%), blocked ventricular catheter (15 vs. 3.6%), and dislodged catheter (10 vs. 7.1%). Convulsions and CSF leaks occurred more frequently in the VSGS group (7.1 vs 5%,  $p=1.000$ ). Postoperative GCS and Graeb's score were comparable between the groups ( $p>0.05$ ). The EVD group had a non-significantly higher rate of hydrocephalus after ventricular catheter removal (80 vs. 53.6%,  $p=0.059$ ) and a higher mean GOS 3 months postoperatively (mean score: 4 vs. 3).

**Conclusions:** VSGS is as effective and safe compared to EVD, with a lower rate of infection, blocked/dislodged catheters, as well as a reduced incidence of hydrocephalus. On the other hand, EVD showed better GOS at 3 months. However, these differences did not reach statistical significance.

**Keywords:** External ventricular drainage, Hydrocephalus, Intraventricular haemorrhage, Intracranial haemorrhage, Ventriculosubgaleal shunt

## Background

Spontaneous intraventricular haemorrhage (IVH) is a condition in which brain arteries, veins, and capillaries rupture into the cerebral ventricular system in the absence of trauma. The most frequent cause of

spontaneous IVH is ruptured aneurysms (33%), followed by spontaneous intracranial haemorrhage (ICH, 25%), and ruptured arteriovenous malformations (10%). The condition is idiopathic in approximately 24% of cases [1, 2].

The amount of IVH ranges from a mild layering of the blood in the posterior horn of the lateral ventricle to a complete casting of all the ventricles. The occurrence of IVH in cases with ICH/SAH is associated with poor prognosis and the severity of haemorrhage was an

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independent predictor of mortality and poor functional outcome [3] which was associated with high mortality rate [4].

Many patients suffering from ICH with intraventricular extension experience an elevation of intracranial pressure (ICP) which usually exceeds 20 mmHg caused by the acute obstruction of the normal outflow of cerebrospinal fluid (CSF) and/or the mass effect exerted by haemorrhage [5].

The external ventricular drain (EVD) is typically used in the management of ICH with intraventricular extension to provide temporary drainage of CSF/intraventricular blood, administer required medications, and monitor ICP [6]. However, insertion of an EVD is linked with complications including infection (resulting in ventriculitis and meningitis), haemorrhage, disconnection, misplacement, dislodgement, or blockage of the catheter [7]. In addition, the efficacy of EVD in draining IVH is marred by the slow rate of blood removal [8]. That is why, research continues to seek effective and safe alternatives to EVD for the management of spontaneous IVH.

The ventriculosubgaleal shunt (VSGS) has long been used in the management of infants and children with hydrocephalus, as well as subdural and subarachnoid haemorrhages to temporarily relieve the elevated ICP [9]. The CSF is drained into the subgaleal space that lies beneath the galea aponeurotica, extending from the superior nuchal line to the forehead [10]. However, the role of VSGS in the management of IVH in adults has not been commonly addressed. Hence, the present study aimed to compare the efficacy and safety of VSGS to EVD in the management of adult patients with IVH.

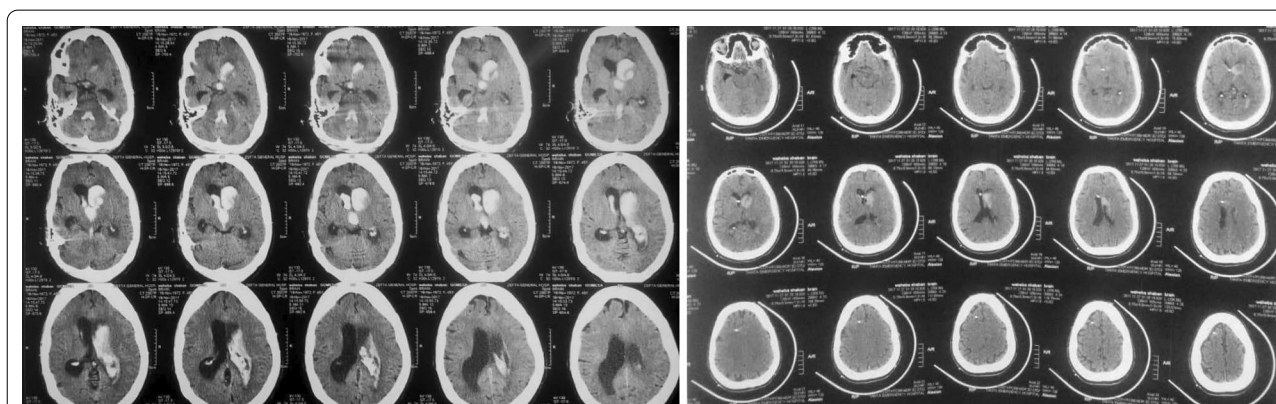
## Methods

This retrospective cohort study was conducted at the Neurosurgery department, Ain Shams University, Tanta University Hospitals, and Elsalam General Hospital, Port Said Governorate, from March 2018 to June 2021. The study enrolled 48 patients with spontaneous intraventricular haemorrhage admitted to the neurosurgery department. The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Tanta University. Written informed consents were obtained from all participants before enrolment. Patients' confidentiality was maintained by keeping the records anonymous after assigning a code number to each patient known only by the investigators.

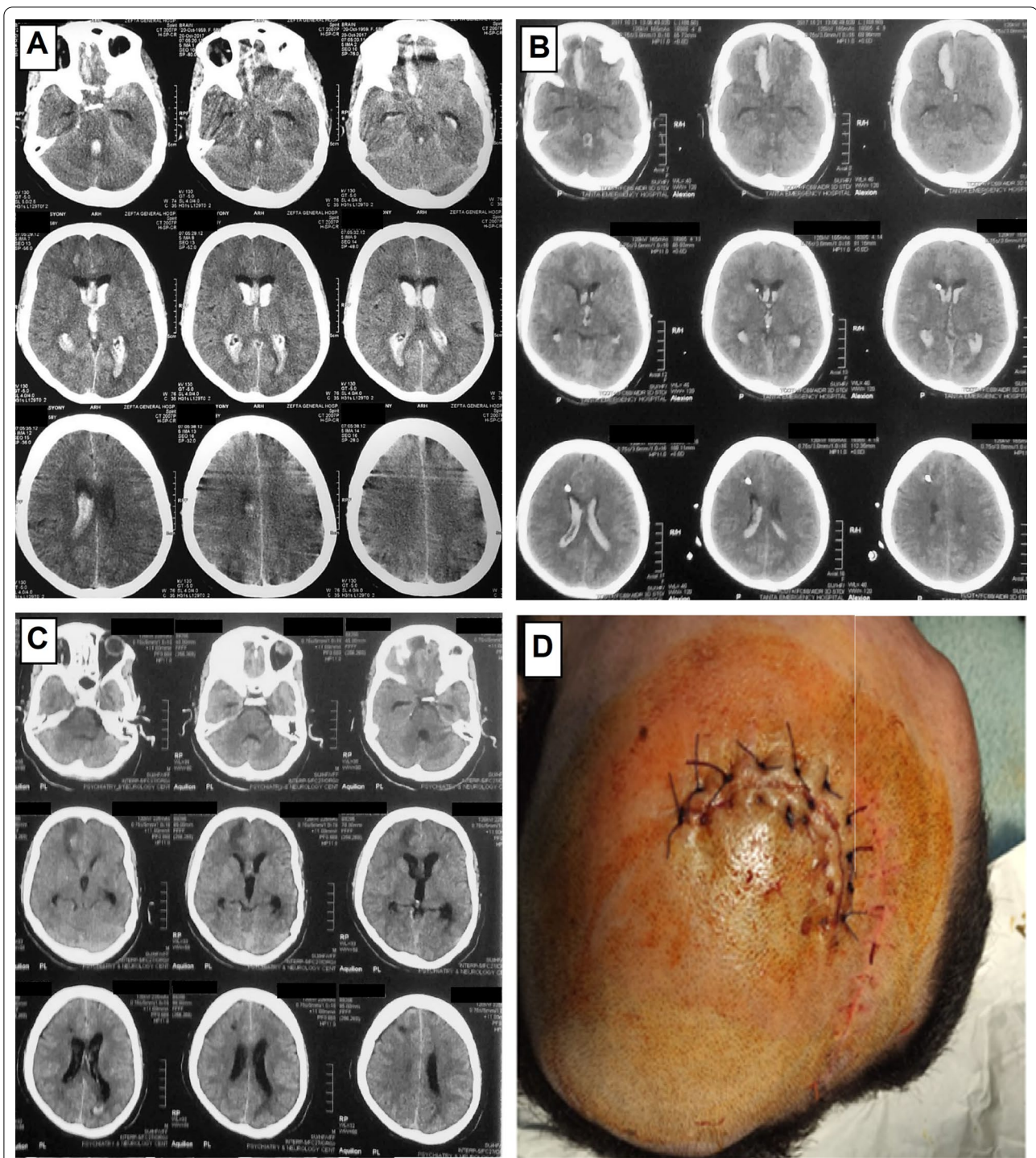
Patients eligible for enrolment had a diagnosis of spontaneous intraventricular haemorrhage on admission CT scan with Graeb's score  $> 3$ , GCS score  $> 3$ , and associated ICH  $< 30 \text{ cm}^3$ . Patients were excluded if they had Graeb's score  $< 3$ , GCS score = 3, ICH  $> 30 \text{ cm}^3$ , brain stem dysfunction, post-traumatic IVH, or death within 3 months.

All eligible enrolled patients underwent EVD or VSGS placement with clinical and radiological follow-up for 3 months. Selection of the procedure was based on surgeon preference and the availability of an EVD closed drainage system. All patients had a history taken (age, gender, and past medical history), a clinical examination (general and neurological examination), and neuroimaging using computed tomography (CT) scan (Figs. 1, 2).

Table 1 illustrates Graeb's grading system used to classify the severity of ICH based on the findings of the first CT scan done at the emergency department. The score was graded as mild (1–4), moderate (5–8), and severe (9–12) [1]. The CT scan was repeated to assess



**Fig. 1** A 56-year-old female presented with intraventricular haemorrhage managed by right-sided external ventricular drain (EVD). Left: axial CT scan before insertion of EVD drain shows blood is filling the left ventricle and dilating both lateral ventricle, third and fourth ventricles with left basal caudate intra-cerebral haematoma. According to Graeb's grading system intraventricular haemorrhage graded as severe with score 9. Right: axial CT scan 7 days after EVD drain insertion shows the end of the drain is seen inserted into the frontal horn of the right lateral ventricle with near-complete drainage of intraventricular blood (successful drainage) and decrease in size of left caudate intra-cerebral haematoma



**Fig. 2** A 51-year-old male presented with intraventricular haemorrhage managed by right-sided ventriculosubgaleal shunt (VSGS). **A** Axial CT scan before insertion of shunt shows blood is filling and dilating both lateral ventricle, third and fourth ventricles with right sub-frontal intra-cerebral haematoma. According to Graeb's grading system, intraventricular haemorrhage is graded as severe with score 12. **B** and **C** Axial CT scan 24 h and 7 days, respectively, after VSGS insertion showing the end of the shunt inserted into the frontal horn of the right lateral ventricle with progressive decrease in the intraventricular blood (successful drainage) and decrease ventricular dilatation. **D** Postoperative image of patient's head showing boggy of the scalp with CSF post-insertion of VSG shunt using C-shaped incision at Kocher's point

**Table 1** Shows Graeb's classification score for IVH (1)

Lateral ventricles	
Score	1 = trace of blood or mild bleeding. 2 = less than half of the ventricle filled with blood. 3 = more than half of the ventricle filled with blood. 4 = ventricle filled with blood and expanded. (Each lateral ventricle is scored separately)
Third and fourth ventricle	
Score	1 = blood present, ventricle size normal. 2 = ventricle filled with blood and expanded.
Total score (maximum = 12)	

hydrocephalic changes after the resolution of blood to determine the need for permanent shunting.

Urgent medications were administered for control of the anticipated increase in intracranial pressure including intravenous mannitol bolus (1 g/kg), furosemide (20 mg), steroids (dexamethasone 4 mg) for all patients preoperatively. Under complete aseptic conditions, EVD or VSGS were placed under general or local anaesthesia according to the patient's clinical condition.

In the **EVD group**, preoperative antibiotics were administered to all patients. In the operating theatre, the ventricular catheter was inserted at Kocher's point. The operative side was chosen according to the site of ventricular enlargement and the amount of IVH. Subcutaneous tunnelling of the catheter was performed for at least 5 cm from the incision site and then externalized. Tunnelling aimed to decrease the rate of infection. The catheter was fixed to the scalp. The catheter was securely attached to a CSF closed drainage system that was placed at 15 cmH<sub>2</sub>O from zero-point (level of the tragus).

In the **VSGS group**, the patients were placed in the supine position, after skin incision, the scalp was bluntly dissected to create a subgaleal pocket. Similar to the EVD group, the ventricular catheter was introduced into the frontal horn. The catheter was then connected to a tube via a right-angled connector, and its distal end was placed in the subgaleal pocket. The VSGS was sutured with the right-angled connector to the periosteum to avoid migration into the ventricle or the subgaleal pocket.

Patients were admitted into the intensive care unit. Prophylactic antibiotics were prescribed with the care of the device. The output of CSF was monitored and recorded in patients with EVD. Removal of EVD or VSGS was determined according to the patient's neurological status.

A routine follow-up CT scan of the brain was done 24 h after surgery, on 7th postoperative day, 1 month later, and whenever indicated to assess the site of the ventricular catheter and the resolution of IVH and hydrocephalic changes. Patients were clinically followed up for

3 months postoperatively using the Glasgow Coma Scale (GCS) and Glasgow Outcome Score (GOS). The GCS was graded as mild (score  $\geq 13$ ), moderate (score: 9–12), and severe ( $\leq 8$ ) [11]. The GOS is a well-known five-point scale that is graded as follows: 1—dead, 2—persistent vegetative state, 3—severe disability, 4—moderate disability, independent, and 5—good recovery [12].

The primary outcomes included the rates of communicating hydrocephalus and complication rate, whereas the secondary outcomes included postoperative Graeb's score, GCS, and GOS.

The Statistical Package for Social Sciences (IBM SPSS Statistics) for Windows, version 26 (IBM Corp., Armonk, N.Y., USA) was used for conducting the analysis. Numerical variables were summarized as mean. Categorical variables were summarized as frequencies. Pearson's Chi-square test for independence, Fisher's exact test, or Fisher–Freeman–Halton exact test were used to examine the association between two categorical variables. A  $p$ -value  $< 0.05$  was considered of statistical significance.

## Results

Sixty-six patients were eligible for enrolment in this study. However, 18 of them died within the first 3 months and thus were excluded. Forty-eight patients were enrolled in this cohort study; 20 patients underwent insertion of an EVD, whereas 28 patients underwent VSGS. Table 2 summarizes patients' preoperative characteristics and the surgical site. Male patients were slightly more prevalent than female patients in both groups (male:female ratio of 3:2 and 4:3 in EVD and VSGS groups, respectively), without significant differences between the groups ( $p = 0.843$ ). The mean age was 48 and 50 years in the EVD and VSGS groups, respectively. Preoperative GCS was severe in nearly half the patients in the two groups, with no significant associations with the treatment group ( $p = 0.737$ ). The fourth ventricle was the most frequent site of blood collection (90% in EVD and 82.1% in VSGS,  $p = 0.683$ ), followed by the third ventricle (80% in EVD and 78.6% in VSGS,  $p = 1.000$ ). The right

**Table 2** Patients' characteristics and surgical side (total  $n = 48$ )

	EVD ( $n = 20$ )	VSGS ( $n = 28$ )	<i>p</i> -value
Gender			
Male	12 (60.0%)	16 (57.1%)	0.843
Female	8 (40.0%)	12 (42.9%)	
M:F ratio	3:2	4:3	
Mean age (years)	48	50	
Preoperative GCS			
Mild	4 (20.0%)	5 (17.9%)	0.737
Moderate	5 (25.0%)	10 (35.7%)	
Severe	11 (55.0%)	13 (46.4%)	
Blood site			
Right lateral ventricle	15 (75.0%)	18 (64.3%)	0.430
Left lateral ventricle	14 (70.0%)	20 (71.4%)	0.915
Third ventricle	16 (80.0%)	22 (78.6%)	1.000
Fourth ventricle	18 (90.0%)	23 (82.1%)	0.683
Surgery side			
Right	12 (60.0%)	15 (53.6%)	0.658
Left	8 (40.0%)	13 (46.4%)	

EVD: external ventricular drain; VSGS: ventriculosubgaleal shunt; GCS: Glasgow Coma Scale

side was the field of surgery in 60% of EVD patients and 53.6% of VSGS patients ( $p = 0.658$ ).

Postoperative complications (Table 3) were slightly more frequent in the EVD group compared to the VSGS group (75 vs. 64.3%,  $p = 0.430$ ). The most common complications included non-CR (20% in EVD and 32.1% of patients in VSGS) and infection (20% in EVD and 7.1% of patients in VSGS). The incidence of blocked catheters in the EVD group was higher than that of the VSGS group (15 vs. 3.6%). Likewise, a higher percentage of patients had dislodged catheters in the EVD group than in the VSGS group (10 vs. 7.1%, respectively).

Convulsions and CSF leaks occurred more frequently in the VSGS group compared to EVD (7.1 vs 5%, respectively). However, these differences did not reach statistical significance ( $p > 0.05$ ). The GCS showed improvement compared to admission GCS on the first postoperative day, the 7th postoperative day, and at discharge from the hospital, without significant differences between the two groups ( $p > 0.05$ ). Similarly, Graeb's score was comparable between the two groups both on the 1st and 7th postoperative days ( $p = 0.749$  and  $0.929$ , respectively).

The rate of developing hydrocephalus after removal of the catheter was non-significantly higher in the EVD group compared to the VSGS group (80 vs. 53.6%,  $p = 0.059$ ). In addition, the mean Glasgow Outcome Score at 3 months postoperatively was slightly better in the EVD group than that of the VSGS group (mean score: 4 vs. 3).

## Discussion

Intraventricular haemorrhage has long been recognized as a serious emergency condition with poor outcomes and a high mortality rate [3]. The present study aimed to compare the efficacy and safety of VSGS and EVD for the management of adult patients with spontaneous IVH. The two groups were comparable in terms of baseline characteristics, including age, gender, preoperative GCS, and site of IVH. To the best of the authors' knowledge, the use of VSGS in adult patients has been investigated in one retrospective cohort study only [13], which included adult patients with acute hydrocephalus caused by various aetiologies. The present study is the first to compare these two treatment modalities in adult patients suffering from spontaneous IVH.

The pre-intervention characteristics of the patients in terms of age, gender, haemorrhage site, and level of consciousness were comparable in the two groups. All patients in this study had impaired consciousness on admission, with varying degrees. Nearly half the patients had a severe degree of decreased consciousness as assessed by GCS. The neurologic injury that occurs in cases of IVH may result from several mechanisms. The obstruction of CSF outflow by blood clots causes obstructive hydrocephalus with elevated ICP. Damage of the neurological structures in the vicinity of haemorrhage may occur due to compression by haematoma. In addition, the blood breakdown products induce an inflammatory reaction with the infiltration of inflammatory cells, the release of inflammatory mediators, and oedema causing further compression and injury to neural tissue. Since the thalamus is affected in these cases, it will result in a decreased consciousness level [14].

In the current study, the rate of overall postoperative complications was non-significantly higher in the EVD group than in the VSGS group (75 vs. 64.3%,  $p = 0.430$ ). The recorded complications could be categorized as cranial (or device-related) and non-cranial. Although the non-cranial complications were more frequent in the VSGS group compared to the EVD group (32.1 vs. 20%), the difference was not statistically significant ( $p = 0.512$ ). Meanwhile, cranial complications were non-significantly more prevalent in the EVD group (55% vs. 32.1%).

Nee and colleagues [13] assessed the use of EVD and VSGS in a retrospective cohort study on 50 patients with acute hydrocephalus (caused by IVH in 26 patients, while the remaining cases were due to infection and trauma). In agreement with the present study's results, they found that the EVD group was significantly associated with a higher rate of overall complications than the VSGS group (90.5% and 69%, respectively,  $p = 0.008$ ). The VSGS group had a higher

**Table 3** Operative complications and patients' outcomes (total  $n = 48$ )

	EVD ( $n = 20$ )	VSGS ( $n = 28$ )	<i>p</i> -value
Patients with complications $n$ (%)	15 (75.0%)	18 (64.3%)	0.430
Non-CR	4 (20.0%)	9 (32.1%)	0.512
Infection	4 (20.0%)	2 (7.1%)	0.218
Blocked	3 (15.0%)	1 (3.6%)	0.294
Dislodged	2 (10.0%)	2 (7.1%)	1.000
Convulsions	1 (5.0%)	2 (7.1%)	1.000
Leak	1 (5.0%)	2 (7.1%)	1.000
1 POD GCS			
Mild	8 (40.0%)	9 (32.1%)	0.825
Moderate	7 (35.0%)	12 (42.9%)	
Severe	5 (25.0%)	7 (25.0%)	
7 POD GCS			
Mild	8 (40.0%)	10 (35.7%)	0.944
Moderate	7 (35.0%)	11 (39.3%)	
Severe	5 (25.0%)	7 (25.0%)	
Discharge GCS			
Mild	7 (35.0%)	10 (35.7%)	0.769
Moderate	7 (35.0%)	12 (42.9%)	
Severe	6 (30.0%)	6 (21.4%)	
1 POD Graeb's score			
Mild	8 (40.0%)	8 (28.6%)	0.749
Moderate	8 (40.0%)	13 (46.4%)	
Severe	4 (20.0%)	7 (25.0%)	
7 POD Graeb's score			
Mild	10 (50.0%)	12 (42.9%)	0.929
Moderate	6 (30.0%)	10 (35.7%)	
Severe	4 (20.0%)	6 (21.4%)	
Hydrocephalus after removal	16 (80.0%)	15 (53.6%)	0.059
Mean Glasgow Outcome Score at 3 months	4	3	

EVD: external ventricular drain; VSGS: ventriculosubgaleal shunt; GCS: Glasgow Coma Scale; POD: postoperative day

rate of extracranial complications (41.4% vs. 19.1%), whereas the EVD group had a higher rate of intracranial complications (71.4% vs. 27.6%).

Among the cranial complications in the present study, infection (meningitis or ventriculitis) was the most common and occurred more frequently in EVD than in the VSGS group (20 vs. 7.1%, respectively,  $p = 0.218$ ). In partial agreement with this finding, Nee and colleagues [13] observed a significantly higher percentage of infection in the EVD group compared to the VSGS group (38.1 vs. 3.4%). The higher rate of infection associated with EVD compared to VSGS is probably due to the connection of the intraventricular environment through the EVD to the exterior, predisposing to contamination and spread of microorganisms to the ventricles, while the probability of infection decreases with the use of VSGS due to the closed system of CSF drainage without a need for manipulation of drains.

The incidence of infection with EVD in the literature varies from 0% up to 22% [5, 15, 16] and is considered as a serious sequel to EVD due to the prolonged hospital stay and related cost as well as increased morbidity and mortality rates. The likelihood of EVD-related infection increases with previous craniotomy, the presence of a depressed cranial fracture or CSF leakage from the insertion site, lack of sufficient tunnelling of the catheter, and duration of the duct above 5 days [17, 18]. The risk of infection could be reduced by following sterile insertion techniques, tunnelling of the catheter > 5 cm, proper wound care, and the use of closed system devices [19].

Other common complications in our sample included blocking and dislodgement of catheters. The EVD group had a higher rate of blockage (15 vs. 3.6%,  $p = 0.294$ ) and dislodged catheters (10 vs. 7.1%, respectively,  $p = 1.000$ ). Similarly, Nee and colleagues [13] reported blocking and dislodgement in 14.3% of cases of EVD, while these

complications were not noted in the VSGS cases. Blocking of the EVD catheter occurs usually due to the large volume of extravasated blood in IVH and results in poor control of ICP. Blocked catheter removal and insertion of another catheter predisposes the patients to an increased risk of haemorrhage and infection [20].

On the other hand, the VSGS group in our study showed a slightly higher percentage of seizures and leakage compared to the EVD group (7.1 vs 5%, respectively,  $p=1.000$ ). In line with this result, Nee and colleagues [13] found that seizures and leaking from subgaleal surgical sites occurred in 10.3% and 6.9%, respectively, while no cases were recorded in the EVD cohort. In the literature, the rate of CSF leakage in patients with VSGS varied widely from as low as 5% [21, 22] to 29% [23]. This complication arises from a high ICP or inadequate wound closure. CSF leakage from surgical sites of VSGS could be avoided by carefully following the proper surgical closure techniques [23]. Whenever CSF leakage is observed, the ICP should be monitored, and the patency and functionality of the catheter should be assessed. The examination of device functionality is easier in the case of EVD, whereas evaluation of VSGS usually requires the performance of brain CT [13]. This may be a reason for the preference of EVD over VSGS in most centres for the management of IVH in adult patients.

Analysis of postoperative GCS in this study on 1st and 7th postoperative days as well as on discharge showed a slight improvement compared to admission GCS in both groups. The percentage of severe cases decreased from 55% on admission to 25% on the seventh postoperative day in the EVD group and from 46.4% preoperatively to 25% on the seventh postoperative day in the VSGS group. However, the EVD group showed an increase in the percentage of patients with severe GCS on discharge despite the previous improvement on the 1st and 7th postoperative days, while the VSGS group showed a further reduction in the percentage of severe cases on discharge. This may suggest better removal of blood and control of ICP in the VSGS group compared to the EVD group. However, Graeb's score in the current study improved slightly in both groups on the 7th postoperative day compared to the 1st postoperative day, with no significant differences between the two groups, indicating that the drainage of blood was nearly similar in the two groups.

A percentage of patients with IVH ranging from 13 to 23.6% develop communicating hydrocephalus on the removal of the EVD or VSGS and will require permanent CSF diversion, particularly when the haemorrhage collects in the third and/or fourth ventricles [24, 25]. This results from the effect of released inflammatory mediators in the CSF that induce an inflammatory reaction and fibrosis in the CSF granulations, causing non-obstructive

hydrocephalus [14]. In the current study, the incidence of communicating hydrocephalus after removal of the catheter was much higher in the EVD group than in the VSGS group (80 vs 53.6%), but the  $p$ -value was near the borderline of significance ( $p=0.059$ ). However, this effect size may bear a considerable clinical significance that reflects on the patients' re-admissions, length of hospital stay, as well as the required procedures to manage hydrocephalus and its associated complications. The conduction of this trial on a larger sample size may demonstrate some statistically significant differences that could not be detected in our relatively small sample size.

Contrary to our findings, Nee and colleagues [13] reported a higher percentage of ventriculoperitoneal shunt requirements in the VSGS group compared to EVD (82.8% vs. 61.9%,  $p=0.097$ ), but without reaching statistical significance. This may be explained by the inclusion of various causes of acute hydrocephalus in their study in addition to IVH, while the present study was restricted to the management of spontaneous IVH.

Functional outcome was assessed in this study using GOS at 3 months postoperatively. The EVD showed a slightly better outcome as observed by the mean GOS of 4 (indicating moderate disability), compared to a mean score of 3 (indicating severe disability) in the VSGS group. Nevertheless, no statistically significant differences were observed in the two groups. The functional outcome after IVH may depend on several factors besides the initial emergency measures of EVD or VSGS. These factors include the presence of comorbidities and the occurrence of complications such as intracranial infection.

The present study bears several points of strength, being the first clinical study to compare VSGS against EVD in patients with spontaneous IVH with the exclusion of other conditions that cause acute hydrocephalus, it also showed fewer complications with VSGS than EVD. It is also worthy to mention that VSGS were more cost-effective than EVD, in terms of price and availability. In addition, it is easier to care for in the ICU, with no special positional precautions and no worries concerning patient's mobility or head elevation, especially in patients suffering from disturbed sensorium or irritability. However, the study showed some limitations, including the relatively small sample size and the lack of randomization.

## Conclusion

The current study revealed that VSGS is as effective and safe compared to EVD, with a lower rate of infection, blocked/dislodged catheters, as well as a reduced incidence of hydrocephalus. On the other hand, EVD showed better GOS at 3 months. However, these differences did

not reach statistical significance. More studies with a larger sample size is required to confirm these findings.

#### Abbreviations

IvH: Intraventricular haemorrhage; EVD: External ventricular drain; VSGS: Ventriculosubgaleal shunt; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; CR: Cranial; Non-CR: Non-cranial; CSF: Cerebrospinal fluid; ICH: Intracerebral haemorrhage; SAH: Subarachnoid haemorrhage; ICP: Intracranial pressure.

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#### Author contributions

AAE, AYS and MAE were responsible for the study conception and design. AAE, CAZ and AE were responsible for the acquisition of data. All authors contributed to the analysis and interpretation of data. AAE and MAE were responsible for the drafting of the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

Please contact the authors for data requests.

#### Declarations

##### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards. The study was approved by Research Ethics Committee, Tanta University, Reference number: 31973/12/17. All participants provided informed written consent to participate in the study.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare that they have no competing interests.

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