External ventricular drainage alone versus endoscopic surgery for severe intraventricular hemorrhage: a comparative retrospective analysis on outcome and shunt dependency

LUCA BASALDELLA, M.D.,¹ ELISABETTA MARTON, M.D.,¹ ALESSANDRO FIORINDI, M.D., PH.D.,¹ BRUNO SCARPA, PH.D.,² HADI BADREDDINE, M.D.,¹ AND PIERLUIGI LONGATTI, M.D.¹

¹Department of Neurosurgery, Treviso Regional Hospital, University of Padova, Treviso; and ²Department of Statistical Sciences, University of Padova, Italy

Object. Massive intraventricular hemorrhages (IVHs) require aggressive and rapid management to decrease intracranial hypertension, because the amount of intraventricular blood is a strong negative prognostic predictor on outcome. Neuroendoscopy may offer some advantages over more traditional surgical approaches on outcome and may decrease the number of shunt procedures that need to be performed.

Methods. The authors retrospectively reviewed the clinical and radiological data in 96 patients treated for massive IVH who were admitted between January 1996 and June 2008 to the neurosurgery unit after undergoing emergency CT scanning. Forty-eight patients (Group A) were treated with endoscopic aspiration surgery using a flexible endoscope with a “freehand” technique. A historical group of 48 patients (Group B) treated using external ventricular drain (EVD) placement alone was used as a comparison. The authors compared the radiological results with the clinical outcomes at 1 year according to the modified Rankin Scale and the need for internal CSF shunt treatment in the 2 groups.

Results. Endoscopic aspiration did not significantly affect the outcome at 1 year as determined using the modified Rankin Scale. Patients who underwent endoscopy had an EVD in place for 0.18 days fewer than patients treated with an EVD alone. Patients undergoing external ventricular drainage alone had a 5 times greater chance of requiring a shunting procedure than those treated using neuroendoscopy and external ventricular drainage. Neuroendoscopy plus external drainage reduces shunting rates by 34% when compared with external drainage alone.

Conclusions. The reduction in internal shunt surgery encourages the adoption of neuroendoscopic aspiration of severe IVH as a therapeutic tool to decrease shunt dependency.

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KEY WORDS • intraventricular hemorrhage • neuroendoscopy • ventriculoperitoneal shunt • external ventricular drainage

DURING the past decade, there has been a considerable and increasing interest in the medical and surgical management of massive IVHs.^{4,8,16,20,26,36,37,51} Intraventricular blood brings about multiple noxious effects^{10,13} on the brain causing impairment of CSF circulation,²⁹ intracranial hypertension,¹⁹ and acute¹⁴ or delayed hydrocephalus.¹⁵

Mortality estimates for IVH range from 50% to 80%. The most common cause of IVH is spontaneous ICH,^{6,18}

followed by SAH.⁴⁰ The incidence of IVH in intracerebral hemorrhage is roughly twice that in SAH.¹⁸ Approximately 10% of patients suffering aneurysmal SAH and 40% of those suffering primary ICH experience IVH.^{6,18,40} At present, medical management of ICH and IVH revolves around the control of ICP. Despite medical management, mortality remains high, with only 38% of patients surviving the 1st year.⁶ Even with the best medical management, mortality rates have been reported to be as high as 50%. These studies suggest that measures to control ICP through control of factors such as hydrocephalus have little effect.³³ Massive IVH requires aggressive and rapid management to decrease intracranial hypertension. The amount of intraventricular blood is a strong prognostic factor,^{3,44} and its fast removal should be considered a priority. The immediate control of ICP by external ventricular drainage is a res-

Abbreviations used in this paper: AVM = arteriovenous malformation; EVD = external ventricular drain; GCS = Glasgow Coma Scale; ICH = intracranial hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; LOS = length of stay; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; VP = ventriculoperitoneal.

cue surgical action,²¹ but tetraventricular blood inundation should be managed using bilateral ventricular catheters, which frequently become obstructed by blood clots and need to stay in place for a longer period for blood washout. Naff et al.³¹ clearly demonstrated that the percentage of clot resolution is 10.8% per day and is independent from the initial clot volume, patient age and sex, type of underlying hemorrhage, and use of external ventricular drainage.²⁴

The fibrinolytic system of CSF is limited.²⁴ Blood may remain for weeks after hemorrhage; acute clots obstruct ventricular CSF pathways, and clot degradation products obstruct extraventricular CSF pathways. When present, blood degradation products continue to contribute to patients' poor clinical statuses^{5,6,9–11} and are responsible for chronic shunt-dependent hydrocephalus in more than 30% of them.^{15–17,30} At present, reduction in the ventricular clot size seems to be the only method for reducing mortality rates after the ICH has stabilized. Many studies have demonstrated the independent effect of IVH on mortality.^{16–20} Neuroendoscopy may offer some advantages over more traditional surgical approaches such as EVD placement and intraventricular fibrinolysis and should be considered the gold-standard approach, especially when dealing with elderly patients in poor general health.

Methods

Patient Population

We retrospectively reviewed the demographic, clinical, and outcome data of a series of 96 patients treated for massive IVH between January 1996 and June 2008 (Table 1). All patients presented with spontaneous primary or secondary tetraventricular inundation, acute hydrocephalus, progressive worsening of neurological conditions, and/or coma. A CT scan was obtained within 3 hours of hospital admission, and the blood amount was quantified according

TABLE 1: Demographic and clinical characteristics

Variable	Group A	Group B
sex		
male	28	23
female	20	25
M/F ratio	1.4	0.92
age (yrs)		
mean	57.8	56.4
range	7–80	14–78
etiology distribution (%)		
ICH	39	36
ruptured aneurysm	29	50
pure IVH	17	10
AVM	8	4
posterior fossa hemorrhage	6	0
mean admission Graeb score	9.75	8.5
mean admission GCS score	6.6	7.2
mean duration of EVD placement (days)	12.1	13.9
mean ICU LOS (days)	13	19

to the Graeb score.¹⁴ Angiography was performed when a vascular malformation was suspected. Surgery was always performed in emergency conditions. Forty-eight patients underwent neuroendoscopic surgery (Group A), and the remaining 48 patients underwent EVD placement alone (control Group B). No fibrinolytic agents were used in either group. In patients with a vascular malformation as the likely cause of bleeding, the endoscopic procedure or the EVD placement was performed in close association with endovascular or surgical treatment. In all patients, clinical follow-up was assessed at 1 year according to the mRS score (see Fig. 3).⁷

Group A. Forty-eight patients (28 male and 20 female; male/female ratio 1.4) with a mean age of 57.8 years (range 7–80 years) were treated with endoscopic aspiration of intraventricular blood. All patients exhibited acute hydrocephalus on the initial CT scan as well as blood clots obstructing the third and fourth ventricles.

The IVH was a result of ICH in 39% of patients, a ruptured aneurysm in 29%, primary IVH in 17%, an AVM in 8%, and a posterior fossa hematoma in 6% (Fig. 1). The severity of IVH was graded according to the Graeb scoring system: 65% of patients had a Graeb scale score greater than 10 and tetraventricular clots. The mean Graeb score was 9.75 ± 2.7 ($\pm$ SD). The mean GCS score at the time of admission was 6.6.⁴⁵ Sixty-three percent of patients were treated on the day of admission (within 24 hours from the onset of hemorrhage). The remaining 37% were treated in a delayed fashion (between 48 and 72 hours after onset). Especially in the initial period of training of the last author (P.L.), some of those patients who were admitted overnight were initially managed conservatively with an EVD if the surgeon was not available. Since that time, a second surgeon (A.F.) mastered the technique, and in the past 8 years we have been able to guarantee emergency treatment (within 24 hours) for all patients suitable for undergoing endoscopic aspiration of ventricular clots.

Group B. The records of 48 patients (23 male and 25 female; male/female ratio 0.92) with a mean age of 56.4 years (range 14–78 years) treated with external ventricular drainage for intraventricular blood removal were retrieved and matched from our institutional database as a historical

Fig. 1. Bar graph showing IVH etiology distribution and shunt dependency rates in Group A. pfICH = posterior fossa hematoma; pIVH = primary IVH; rAn = ruptured aneurysm.

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control group. All patients exhibited acute hydrocephalus on the initial CT scan.

The IVH was a result of ICH in 36% of patients, a ruptured aneurysm in 50%, primary IVH in 10%, and an AVM in 4% (Fig. 2). The severity of IVH was graded according to the Graeb scoring system. In 70% of patients the Graeb score was greater than 8 and tetraventricular clots were present; the mean Graeb score was 8.5 ± 1.8 . The mean GCS score at admission was 7.2.

Surgical Procedure

Group A. Despite their clinical condition, all patients with IVH immediately underwent CT scanning, CT angiography, and digital subtraction angiography or MRI when deemed appropriate. Urgent blood work was obtained with special focus on prothrombin time and liver and kidney function. Preoperative management included identification and correction of coagulation disorders, administration of prophylactic anticonvulsants, controlling body temperature, and glycemia correction. The mean arterial pressure should be kept lower than 110 mm Hg and systolic pressure lower than 150 mm Hg. For the endoscopic procedure, 2 types of flexible endoscopes were used with an external diameter of either 2.5 mm (Karl Storz) or 3.9 mm (Codman) and an operative length of 53 cm. The internal diameter of the working channel was 1.2 mm. For aspiration procedures, the entire working channel was used as a sucking device. The access was precoronal, 2 cm from lateral to the midline, through a 12-mm bur hole (Figs. 4 and 5). The access side was chosen as the side of the lateral ventricle containing the largest amount of blood or the largest dilation. In cases with bilateral massive inundation, the access was bilateral. In the presence of a ventricular vascular malformation or aneurysm, an approach from that side was avoided. Lateral ventricle cannulation was achieved using a semirigid peel-away catheter, and systolic blood pressure was maintained at 120 mm Hg. An energetic intermittent manual aspiration was started using a rigid syringe connected to the operating channel of the endoscope. This action breaks down the clot and allows initial visualization in the ventricle. Once the choroidal plexus and Monro foramen were identified, the endoscope was advanced into the third ventricle, preferably into the right-sided bur hole,

Fig. 2. Bar graph showing IVH etiology distribution and shunt dependency rates in Group B.

Fig. 3. Comparison of the 1-year mRS scores in Groups A and B.

and the procedure was repeated. Evacuation of the third ventricle paved the way to the aqueduct and to the fourth ventricle, where the aspiration-irrigation procedures were carefully performed, since the endoscope fills the entire diameter of the aqueduct and potentially dangerous local hypertension might easily be caused by excessive irrigation with Ringer solution. At the end of the procedure, an EVD was left in all patients for ICP monitoring and drainage (with a constant gradient of 15 mm Hg). The mean ICU LOS after the operation was 13 days. Endoscopy was successfully completed in all cases, and each patient received an EVD. There were no intraoperative deaths. The EVD was removed on the same day as the endoscopy procedure in 12 patients and after 1–25 days in the other patients (median 10 days).

Group B. An EVD was positioned in all patients on the 1st day. Bilateral EVDs were positioned in 35 of the 48 patients. The EVD was removed after 8–32 days (median 13.99 days), and all patients underwent catheter substitution 1 or more times during the ICU LOS. In this group, no thrombolysis with rtPA was performed to maintain homogeneity between the 2 groups. The mean ICU LOS after the operation was 19 days.

Statistical Analysis

Statistical models have been fitted to data to describe the specific effect of endoscopy once the effects of sex, age, and admission GCS score were eliminated. We fit a logistic model to measure the effects of available variables on the insertion of a VP shunt, where significant variables were selected by a backward stepwise procedure based on the Akaike information criterion.

Proportional odds models have been fitted to describe a connection between endoscopy and mRS score, which is a scoring variable that is ordinal in that its value increases when outcome is worse. Also in this case we selected significant variables by backward stepwise selection based on the Akaike information criterion. We also considered, as secondary outcomes of interest, the number of days that the EVD was required and the number of days spent in the neuro-ICU. Both these variables are quantitative, nonnegative, and right skew. We used the Box-Cox transformation to select the best function of these outcomes. In both cases the square root transform was chosen. Here too, in both cases, we implemented a backward stepwise procedure

FIG. 4. Preoperative (**upper**) and postoperative (**lower**) CT scans of a spontaneous thalamic hemorrhage with tetraventricular clots.

FIG. 5. Preoperative (**upper**) and postoperative (**lower**) CT scan of an anterior communicating artery aneurysm, treated with emergency coiling and subsequent endoscopic surgery plus external drainage.

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based on the Akaike information criterion to select the significant variables.

Results

A VP shunt was required by 17% of patients in Group A and by 50% of patients in Group B. The 1-year follow-up was recorded according to the mRS. Excellent outcome (mRS Score 0 or 1) was achieved in 29% of patients in Group A and in 37% of patients in Group B. A good outcome (mRS Score 2 or 3) was seen in 27% of patients in both groups. A poor outcome (mRS Score 4 or 5) was recorded in 14% and 23% of patients, and death (mRS Score 6) occurred in 29% and in 13% in Groups A and B, respectively (Table 2). The mRS results in an independent variable when compared with each group (Group A vs Group B, $p = 0.2$; chi-square test).

Backward selection of the logistic model to estimate the effect of endoscopy on the need for a VP shunt revealed that age and admission GCS score were not significant when sex and endoscopy are included in the model. As shown in Table 3, patients who did not undergo endoscopy had an almost 5 times greater probability of requiring a shunt procedure than those who did.

The model describing the effects of endoscopy on mRS score provides different results. Here, only age and admission GCS score result were significant in describing the outcome; the fact that endoscopy was performed did not add any relevant information in predicting the mRS score. The same result of no effect of endoscopy on mRS score was obtained if this variable is recoded in the 4 classes scoring as in Table 2. We also did not find any effect of endoscopy when we relaxed the proportional odds hypothesis by fitting a multinomial model, by not considering the ordinal characteristic of the mRS score. We therefore conclude that there is not a specific effect of endoscopy once age and admission GCS score are considered in predicting the mRS score.

A significant effect of endoscopy is, instead, observed in both models predicting the number of days of external ventricular drainage and neuro-ICU LOS. The presence of endoscopy is significant ($p = 0.038$) regardless of whether the other insignificant variables (sex, age, and admission GCS score) are included. Patients who underwent endoscopy spent about 0.18 days fewer in the ICU than those who underwent EVD placement alone (Table 4).

Similar results were obtained using the model when predicting the LOS in the neuro-ICU. In this case, only age and sex were not significant, whereas admission GCS score had a significant negative effect on this parameter.

TABLE 2: Modified Rankin Scale score distribution

mRS Outcome	No. of Patients (%)	
	Group A	Group B
excellent (score 1)	14 (29)	18 (37)
good (score 2 or 3)	13 (27)	13 (27)
poor (score 4 or 5)	7 (14)	11 (23)
dead (score 6)	14 (29)	6 (13)

Patients who underwent endoscopy had about half a day (0.504) longer stay in the neurological ICU than the others (Table 4).

Discussion

The prognosis of IVH is affected by several factors, including age, sex, GCS score, presence of acute hydrocephalus, coagulopathy, origin of the bleeding, and tetra-ventricular inundation. These factors all play a critical role, but in the first hours after IVH, the sudden increase in ICP associated with initial bleeding may cause a significant reduction in cerebral blood flow, potentially leading to ischemia.²⁸ The obstruction of CSF pathways and the mass effect associated with clots in the satellite hematoma and within the ventricles cause further damage. The fibrinolytic system of the CSF is limited,³² and blood may remain for weeks after hemorrhage.^{6,15,18} Delay of clot resolution leads to obstruction of extraventricular CSF pathways, contributing to the patient's poor clinical status. In the late stage, biochemical changes and blood degradation products are responsible for secondary damage to neurons and white matter.^{41,49} Hematoma and perihematoma regions after intracerebral hemorrhage are biochemically active environments known to undergo potent oxidizing reactions.^{9,11} After ICH, amounts of unconjugated bilirubin in the hematoma can be substantial, as can levels of iron and hemoglobin.¹¹ Oxidation of unconjugated bilirubin to yield bioactive molecules, such as BOXes (bilirubin oxidation products), is an important discovery, expanding the role of bilirubin in pathological processes seen after ICH. Blood degradation products are responsible for oxidative stress in brain surrounding the hematoma, and the spreading through the CSF may be responsible for late damage to the ventricle-facing structures. Thus, the primary goal of acute management for IVH should be the fast removal of intraventricular blood, rapid reversal of ventricular dilation, and normalization of ICP. All of these goals can be achieved immediately using the neuroendoscopic procedure,^{16,25,26,36,37,51} while complications often observed with other traditional approaches are minimized.³³

External Ventricular Drainage

The initial management of IVH has included the placement of 1 EVD or more to allow the egress of blood and CSF from the ventricle system and decrease ICP. However, this approach alone is often not sufficiently effective in improving the poor prognosis of patients with severe IVH.^{4,15,21} Patency of the EVD is frequently difficult to maintain due to occlusion of the catheter by coagulated blood. Optimal treatment should also include removal and dissolution of the intraventricular hematoma itself. This would be expected to decrease ICP, increase cerebral perfusion, and minimize the chance of IVH-induced hydrocephalus resulting from obstruction of CSF drainage from the ventricular system. In selected cases, surgical evacuation of intraparenchymal and intraventricular hematomas has resulted in decreases in mortality rates and disability.¹² However, surgery is invasive and is not always feasible. Survival after primary IVH is common,²⁷ but it is accompanied by considerable morbidity. In general, patients with

TABLE 3: Estimates of the parameters for the final logistic model connecting endoscopy and VP shunt

Parameter	Estimate	exp(estimate)	SE	z Value	p Value
base level (female of Group A)	-1.2284	0.293	0.4424	-2.777	0.005
additional effect for male	-0.7626	0.466	0.4725	-1.614	0.106
additional effect for Group B	1.5771	4.841	0.4894	3.223	0.001

secondary IVH fare worse than those with primary IVH.⁴⁷ When an intracerebral hematoma extends into a portion of the ventricular system, mortality has been reported to be 32%–44%.^{14,22} When IVH extends into all 4 ventricles, mortality has been reported as 60%–91%.^{4,6,12,18,40} With respect to the location of the hematoma causing the IVH, the worst prognosis is found with hematomas located in the thalamus.¹⁸ Predictors of poor outcome are GCS score on presentation and the volume of blood in the ventricle system.^{47,50} The degree of ventricular dilation, independent of the obstruction of CSF flow, has also been found to be a strong indicator for poor outcome.³⁹

Fibrinolytic Agents

Investigators have sought to develop improved methods of treating patients with IVH, trying to expedite the resolution of the ventricular blood clots and improve morbidity and mortality in these patients by administering fibrinolytic agents directly into the ventricular system. The basic rationale for this treatment is to dissolve the blood clot within the ventricular system, since it continues to exert a deleterious effect on the brain. A major reason to consider the use of a fibrinolytic agent is to keep the EVD open so that blood and spinal fluid can continue to drain freely from the ventricular system. In 1990, Shen et al.⁴³ reported on 4 patients with IVH who received [urokinase] u-PA either as an intermittent infusion (n = 2) or continuous infusion (n = 2), into the lateral ventricles through an EVD. All patients underwent bilateral EVD placement. Two patients had a good recovery, 1 had a severe disability, and 1 persisted in a vegetative state. All patients developed meningitis that was likely related to the continuous manipulation of the ventricular catheters. Rainov and Burkert³⁹ reported results of u-PA treatment that were found to be favorable. In their treatment and control groups, respectively, 15 (94%) and 2 (40%) patients had excellent or good outcomes (that is, no deficits or minor neurological deficits), and 1 (6%) and 2 (40%) patients had poor outcomes (that is, permanent vegetative state). No patient in the treatment

group died, and 1 patient (20%) in the control group died. Tush et al.⁴⁸ have been the only authors to report complications encountered with intraventricular u-PA, including 1 case of rebleeding and 2 cases of ventriculitis (in a series of 5 patients). Coplin et al.¹¹ conducted a retrospective cohort study in 1998, which included the largest number of patients thus far treated with intraventricular u-PA under a given protocol. Similar to other reports, the median time for clearance of blood from the third ventricle was 7.0 days and that from the lateral ventricles was 16.0 days. Thrombolytic therapy was found to result in significantly lower mortality (31.8% vs 66.7%; p = 0.03). Previous reports that have included a control group¹¹ or comparison group^{39,43,48} in their analysis have similarly reported that treatment with intraventricular u-PA in patients with IVH reduces mortality by 30%–35%. What is not clear from the literature, however, is whether such treatment results in an improved neurological outcome of the survivors. Shen et al.,⁴³ Akdemir et al.,¹ and Todo et al.⁴⁶ reported good recovery with or without moderate disability in 50%–83% of the patients who received this treatment. However, 1 cohort study found that a larger proportion of the survivors remained in a vegetative state (31.8% treatment group vs 11.1% control group).¹¹ Andrews et al.² concluded that clinical studies of fibrinolytic therapy for IVH have found a 30%–35% reduction in mortality with treatment, but, to date, they have not clearly documented improved neurological outcome of the survivors. Nieuwkamp et al.³⁵ conducted a systematic review to compare conservative treatment, extraventricular drainage alone, and extraventricular drainage combined with fibrinolysis. They reported a poor outcome rate for conservative treatment of 90%; that for extraventricular drainage was 89% (relative risk 0.98 [95% CI 0.75–1.30]) and that for extraventricular drainage with fibrinolytic agents was 34% (relative risk 0.38 [95% CI 0.21–0.68]). In 2002 Lapointe and Haines²³ concluded that there was suggestive and anecdotal evidence that the intraventricular administration of fibrinolytic agents in cases of IVH might be safe and of therapeutic value.

TABLE 4: Summary of the estimates for the final models relating endoscopy to square root of EVD placement and of neuro-ICU LOS

Model	Estimate	SE	t Value	p Value
square root of EVD				
Group A	3.2564	0.1426	22.841	<0.0001
additional effect for Group B	0.4244	0.2016	2.105	0.038
square root of neuro-ICU stay				
base level (Group A)	5.28544	0.50770	10.411	<0.0001
additional effect for each single GCS point at admission	0.16497	0.07093	2.326	0.0222
additional effect for Group B	0.16497	0.27319	2.628	0.0100

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Endoscopic Aspiration

Neuroendoscopic approaches have been reported to produce positive outcomes in patients with IVH.^{8,16,25,36,37,51} In all cases, efficient removal of intraventricular clots was rapidly achieved. However, in 2 of these reports, use of a rigid endoscope required either a cumbersome biportal approach¹⁷ or an ultrasonic aspirator,³⁸ with a high risk (20%) of postoperative rebleeding. The use of a flexible instrument and the freehand technique, albeit offering a narrower operating channel, allows more complete cleansing of the third ventricle and navigation down to the fourth ventricle through the aqueduct. Persistence of blood in the fourth ventricle is related to poor outcomes in patients with IVH.⁴² Complete clearing of the aqueduct and the fourth ventricle is thus an important feature of this treatment because it rapidly establishes the physiological CSF dynamics.

Our experience with flexible endoscopic treatment of severe primary and secondary IVH did not demonstrate any infective complications or rebleeding, showing that this approach can be safe and effective and may favorably compare with more established approaches.³⁴

Conclusions

Our experience with flexible endoscopic treatment of severe primary and secondary IVH shows that once certain measures are taken to minimize the risk of bleeding resulting from ruptured vascular malformations, this approach can be safe and effective and may compare favorably with more established approaches. Similar to other ventricular diseases, IVH can be treated successfully with flexible endoscopes, which may result in a very satisfactory, albeit challenging, approach for experienced neuroendoscopists. Flexible neuroendoscopy in our series was not associated with complications or rebleeding. Neuroendoscopy plus external ventricular drainage reduces shunting rates by 34% when compared with external ventricular drainage alone. Patients who undergo EVD placement have a 5 times higher probability of requiring an internal shunt than those treated with neuroendoscopy plus EVD placement. Neuroendoscopy plus EVD placement together do not significantly improve the 1-year mRS scores when compared with EVD placement alone. Neuroendoscopy plus EVD placement significantly reduces the need for postoperative external ventricular drainage days after surgery, potentially reducing infective complications. The limitation of this study lies in its retrospective nature. However, being aware of the selection biases in determining the treatment group due to differences in time epoch for the 2 treatments, we still think that the data from this study are lacking in the contemporary literature and may prompt a cooperative randomized trial to acquire Level A evidence data that may be adopted as guidelines in the management of an unsolved clinical problem. Reduction of the need for VP shunt procedures encourages the adoption of neuroendoscopic aspiration as a therapeutic tool in cases of massive IVH.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Basaldella, Longatti. Acquisition of data: Basaldella, Marton, Fiorindi, Badreddine. Analysis and interpretation of data: Basaldella. Drafting the article: Basaldella, Marton, Scarpa. Critically revising the article: Basaldella, Marton, Longatti. Reviewed submitted version of manuscript: Basaldella. Approved the final version of the manuscript on behalf of all authors: Basaldella. Statistical analysis: Scarpa. Study supervision: Basaldella, Fiorindi, Longatti.

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Address correspondence to: Luca Basaldella, M.D., Department of Neurosurgery, Treviso Regional Hospital, University of Padova, Piazzale Ospedale Civile 1, 31100 Treviso, Italy. email: lbasaldella@ulss.tv.