PJSS Vol. 74, No. 2, July-December, 2019

PJSS PHILIPPINE JOURNAL OF SURGICAL SPECIALTIES

Technique of External Ventricular Drainage with Intraventricular Administration of Recombinant Tissue Plasminogen Activator for Patients with Secondary Intraventricular Hemorrhage - Case Series in a Single Institution

Kevin Paul B. Ferraris, MD, MBA[1]; Alain James R. Salloman, MD[1]; Kenny S. Seng, MD, FAFN[1,2] and Joseph Erroll V. Navarro, MD, FAFN[1,3]

[1]Section of Neurosurgery, Department of Surgery, Jose R. Reyes Memorial Medical Center
[2]Section of Neurosurgery, Department of Neurosciences, Philippine General Hospital and College of Medicine, University of the Philippines Manila
[3]Section of Neurosurgery, Department of Surgery, University of Santo Tomas Hospital

Introduction: Intraventricular hemorrhage (IVH) as an extension of spontaneous intracerebral hemorrhage is an independent predictor of mortality. The Clot Lysis: Evaluating Accelerated Resolution of IVH phase 3 (CLEAR III) trial is a randomized, double-blinded, placebo-controlled, multiregional trial recently conducted to determine whether external ventricular drainage (EVD) plus intraventricular recombinant tissue plasminogen activator (rtPA, alteplase) improved outcome, in comparison to EVD plus saline. This study is an application of the rationale and principles of management in CLEAR III trial and related literature.

Methods: There are five patients described in this case series. Report followed the PROCESS guidelines.

Results: 30-day mortality in this series is 2 out of 5 while actual all-cause mortality is 4 out of 5. Modified Graeb scores and IVH scores of all subjects have decreased after the intervention. However, good functional status defined as modified Rankin scale (mRS) score of 0-3 has not been achieved with the intervention. Efficacy of completely resolving IVH and hydrocephalus has been achieved in 2 out of 5 which translated to a benefit of survival to one of the two. Shunt dependence has been avoided by the subjects except for the one with the caudate intracerebral hemorrhage. Complications related to the intervention have been noted and discussed.

Conclusion: In this single-institution study, patients for which rtPA was used for intraventricular fibrinolysis of IVH clot in addition to EVD as surgical treatment for hydrocephalus resulted to a 30-day survival of 3 out of 5 in this series, while actual survival is 1 out of 5. The intervention was efficacious in decreasing the Modified Graeb scores and IVH scores of all study subjects at end of treatment. Functional status of mRS 5 is the highest score achieved among survivors.

Keywords: intraventricular hemorrhage, fibrinolysis, external ventricular drainage

Intraventricular hemorrhage (IVH) is a frequent sequelae of intracerebral hemorrhage (ICH), one of the most devastating catastrophic neurologic illnesses to afflict adults. This secondary IVH, usually arising from ICH that are less than 30cc in volume, becomes the significant predictor of 30-day mortality.[1,2] IVH is present in up to 57% of deep-seated ICH located in either the thalamus or basal ganglia. Patients whose ICH have initial IVH are 2.05 to 2.7 times more likely to die or have an unfavorable functional outcome.[3,4]

Casting of the third ventricle and the cerebrospinal fluid (CSF) outflow tracts.[5] From a molecular standpoint, intraventricular blood and its breakdown products cause a cascade of inflammatory response in the ependymal lining of the ventricles, resulting into fibrosis of the arachnoid villi surface.[6,7] Products of clot lysis also are potent nitric oxide (NO) antagonists that deplete NO or inhibit NO synthases. This "sink effect," described in literature relating to aneurysmal vasospasm, increases oxidative stress, myosin phosphorylation, apoptosis and necrosis of neurons, formation of microthrombi, and permanent remodeling of the cerebral wall architecture.[8]

External ventricular drainage (EVD) is a surgical intervention that has become the standard of care for acute obstructive hydrocephalus complicating ICH with IVH according to the American Heart Association/ American

Stroke Association (Class IIa, level of evidence: B).[9] The Japanese Guidelines for the Management of Stroke 2004 and 2009 also recommend emergency surgery via EVD.[10] EVD is mainly used for addressing the problem of increased intracranial pressure caused by IVH. However, the rationale and clinical scenarios surrounding this conventional surgical practice have been reexamined in recent evidence due to the better understanding that has come with new knowledge on IVH. Naff and colleagues presented several points for consideration: 1) EVD alone for CSF drainage does not appear to improve outcomes despite addressing increased ICP; 2) EVD malfunction caused by obstruction of blood that often requires resiting and catheter exchange, hampers its overall efficacy; 3) EVD alone does not accelerate the clot lysis which is the sine qua non for restoration of normal CSF dynamics; and 4) the presence of blood and its degradation products prolongs the duration of EVD, which in turn is the one responsible for the risk of ventriculitis and the development of delayed communicating hydrocephalus. Numerous other studies would posit along similar lines and contribute to literature that would otherwise rule that ventriculostomy has limited benefit, were it not for the addition of intraventricular administration of a fibrinolytic agent via an EVD.[12,13]

A Cochrane review on fibrinolytic therapy for intraventricular hemorrhage in adults. served as foundational high-quality evidence suggesting that the intervention is safe and of therapeutic value.[14] Much later, a randomized, double-blinded, placebo-controlled, multiregional trial was started for the same purpose. The Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) study and the Clot Lysis: Evaluating Accelerated Resolution phase 3 (CLEAR III) trial are landmark studies that served to establish the safety and efficacy of recombinant tissue plasminogen activator (rtPA, alteplase) for clinical use in patients with IVH. The trial was completed on January 2016 with analyzed results published early part of 2017.[15]

To the authors' knowledge, the administration of rtPA for the neurosurgical management of IVH is not routinely done in the local setting. The aim of this study is to present the methods, outcomes and complications of this neurosurgical technique and bridge the gap between the local surgical experience and the current available literature.

Methods

All clinical interventions were conducted according to the principles of the Declaration of Helsinki and was also approved by the Institutional Review Board.

All patients included in this retrospective case series were admitted and managed in the setting of a publicly-funded government hospital in which the investigator is currently affiliated, within the inclusive period of December 2016 to August 2017. Data collection involved chart reviews and phone interviews for follow-up. Participants for the study included patients with IVH and hydrocephalus secondary to either thalamic or caudate ICH who were managed surgically with EVD and subsequent intraventricular administration of rtPA. The inclusion criteria for study subjects were patients who underwent the surgical intervention of EVD as generally indicated for hemohydrocephalus from intracerebral hemorrhage, and whose relatives consented for the additional technique of fibrinolysis via rtPA infusion.

All patients were managed starting at emergency room-level with aggressive hemodynamic support, including, when indicated, intubation and mechanical ventilation. Laboratory tests included routine hematology, chemistry and coagulation studies (i.e., complete blood count, typing, sodium, potassium, blood urea nitrogen, serum creatinine, prothrombin and partial thromboplastin times). Electrocardiogram and chest x-ray were routinely requested and cardiopulmonary risk evaluation prior to surgery also routinely secured. Preexisting co-morbid medical conditions were aggressively managed. The Glasgow Coma Scale (GCS) score was recorded at admission and ictal non-contrast cranial CT scan was done.

The decision to treat an individual patient with EVD was made by the senior neurosurgical resident in consultation with the attending neurosurgeon, based on hydrocephalus as measured by Evan's index of the CT scan. The decision to treat with fibrinolysis using rtPA was made when there is casting of the third ventricle by CT scan, and when 1) modified Graeb score is 9 or above based on the study by Graeb and colleagues[16] and Morgan and colleagues[17] or when 2) the volume of IVH is more than 12-15cc based on the study with normative data by Hallevi and colleagues.[18] At the soonest possible time,

patients for surgery were brought to the operating room, with subsequent note of pre-induction GCS score. The main surgeon for all study participants in this series was the principal investigator of this study.

The surgical interventions were limited to any of the following: single or bilateral frontal horn ventriculostomies through a burr hole at the Kocher's point, or a single occipital horn ventriculostomy through a burr hole at the Frazier's point, whichever method being done under general anesthesia. An improvised EVD was used consisting of sterile feeding tube French 10 as the ventricular catheter, connected to a three-way stopcock and then to a blood transfer bag as CSF repository (Figure 1).

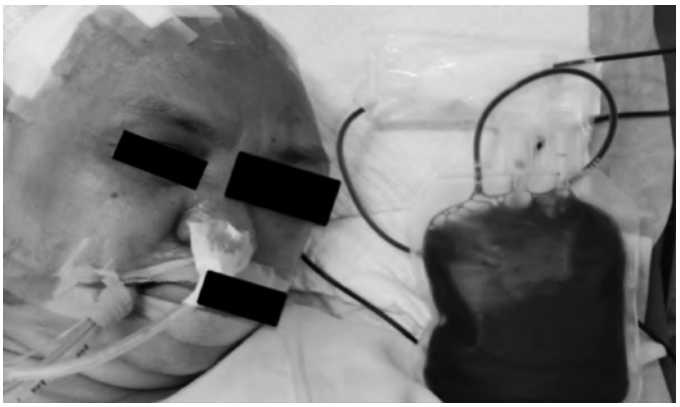

Figure 1. A patient in a typical setup of the EVD with the drainage bag containing CSF with dissolved clot.

After the operation, the patients had non-contrast cranial CT scan at least 6 hours after placement of the EVD. This first postoperative CT scan became the "stability CT scan," described in protocols[16] as the first scan with no catheter-tract hemorrhage or intracerebral hemorrhage growth of >5 cm^3 where any potentially enlarging ICH or IVH might have stabilized. The principal investigator administered alteplase (Actilyse, Boehringer Ingelheim, Germany). Alteplase was reconstituted with 25 mL diluent of plain lactated Ringer's to a create a 2mg/mL solution. This solution was infused by ventricular catheter, then flushed with diluent. The catheter was the closed for an hour, then opened to allow drainage at the level of the external auditory meatus for at least 1 hour. Patients had subsequent repeat CT scans, and altepase administration was continued until the third and fourth ventricles cleared of blood on CT or until the patients expired.

All patients were maintained on mechanical ventilation and followed a stepwise protocol for weaning. A decision for the patient to undergo tracheostomy was made when the patient exceeded two weeks on ventilator support. Admission to the Intensive Care Unit (ICU) was made for the patients should there be an availability; otherwise, they remain at the Post-Anesthesia Care Unit for 48 hours after which they were transferred to the wards.

The goal is a reduction of ventricular hematoma volume and resolution of hydrocephalus seen via CT scan. The degree of hydrocephalus was measured with the Evans' index. For the volume reduction of IVH, the Graeb score and its modified equivalent is the most common scale for predicting short-term prognosis (Appendix 1 and 2). Similarly, the IVH score (IVHS)[18] is another tool for estimating IVH volume and has recently gained widespread acceptance (Appendix 3). Ventricular catheters were removed when there is risk for ventriculitis and/or when there is no shunt dependence. Shunt dependence was assessed as present in the patient when there was neurologic deterioration with elevation of CSF repository, with persistent signs of intracranial hypertension alongside progressive ventricular enlargement.[17] Failing these end points, a ventriculoperitoneal shunt would be placed.

Results

There were 5 cases included in this series. Table 1 summarizes the patient characteristics.

The 30-day mortality in this series is 2 out of 5 (40%) while actual all-cause mortality is 4 out of 5 (80%). Hydrocephalus has decreased across all study subjects, as demonstrated by the decrease in Evans' indices. This resolution of hydrocephalus is attributable to the technique of EVD alone. The additional technique of rtPA administration brought about the decrease in the severity of IVH, evidenced by the demonstration of clearing of the ventricles (Table 2, Figures 2 and 3). The addition of subsequent doses of rtPA showed a trend for increased

Table 1. Patient characteristics, disease severity at presentation, and time elements of intervention.

Patient	A	B	C	D	E
Age/Sex	58/M	67/M	72/F	68/F	56/M
Comorbidities Preexisting In-hospital	 HTN, DM AKI, VAP	 HTN, DM SVT, VAP	S/P Hip surgery HTN, AVNRT HAP	 HTN, DM, CAD	S/P CVD mRS 0 HTN
ICU stay (d)	20	0	16	0	0
Ventilator support (d)	19	59	20	4	4
ICH location	Lateral thalamus, right	Caudate nucleus head, right	Medial thalamus, left	Medial thalamus, right	Lateral thalamus, left
ICH volume (cc)	8.7	15.0	7.8	11.5	18.0
Casting of: 3rd ventricle 4th ventricle	 + +	 + -	 + +	 + +	 + -
Evans' index	0.32	0.39	0.31	0.36	0.26
IVH volume Modified Graeb score IVHS (volume in cc)	 12 17 (30)	 11 16 (24.5)	 12 17 (30)	 9 14 (16.4)	 10 13 (13.5)
Ictus to hospital (h)	17	31	5	3	22
Ictus to first CT (h)	19	32	6	3	24
Ictus to EVD (h)	31	39	12	13	40
EVD to stability CT (h)	22	7	9	24	14
Ictus to first rtPA (h)	216	96	48	32	51

HTN = Hypertension, DM = Diabetes mellitus, AKI = Acute kidney injury, VAP = Ventilator-associated pneumonia, HAP = Hospital-acquired pneumonia, SVT = Supraventricular tachycardia, AVNRT = Atrioventricular nodal reentrant tachycardia.
"Stability CT" refers to the first scan with no catheter-tract hemorrhage or intracerebral hemorrhage growth >5mL.

clearance of IVH initially in the lateral ventricles, followed in the third ventricle, and lastly in the fourth ventricle; although absolute clearance of IVH, defined by clearing of all the ventricles, was not achieved in all of the patients in this series. IVH volume was decreased from a range of volumes of 13-30 cc into 0-6 cc of remaining ventricular blood at end of treatment. Modified Graeb and IVH scores had decreased after the intervention: 0 to 7 and 0 to 9

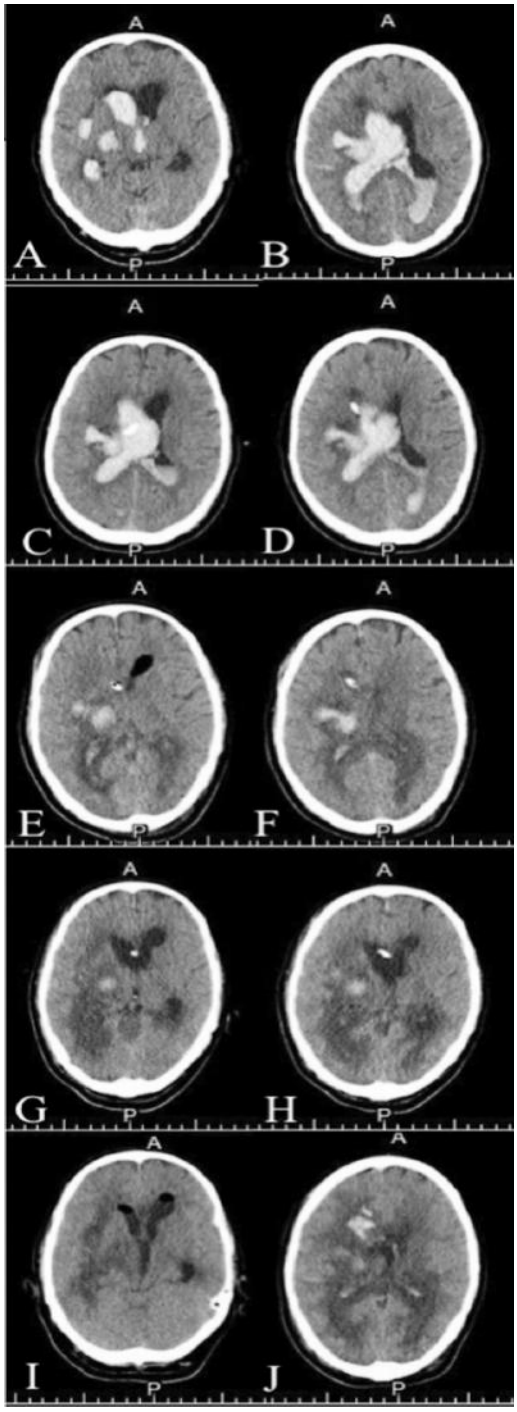

Figure 2.A and B show the ictal CT scan of Patient A. C shows first EVD misplaced to the right. D shows the stability scan after revision EVD. E and F show the scan after giving rtPA. G and H are scans during EVD challenge at end of treatment. I and J show post-removal of EVD with pneumocephalus, catheter-tract hematoma and perihemorrhagic edema.

respectively (Table 2). In this respect, the intervention appeared to be efficacious in resolving IVH. However, good functional status defined as mRS of 0-3 has not been achieved with the intervention. The intervention did not appear to be effective in translating this resolution of IVH into the achievement of good functional status. Nevertheless, the efficacy of the intervention in completely resolving IVH has been achieved in 2 out of 5 (40%) which resulted into a benefit of survival for one of the two. Shunt dependence had been avoided by the subjects except for the one with the caudate ICH. Complications from the intervention were: misplacement of ventricular catheter, pneumocephalus, asymptomatic catheter-tract hematoma, acute subdural hematoma, and perihemorrhagic edema (Figures 2, 3, 4); while ventriculitis was not completely ruled out in all of the subjects. Tables 1 and 2 summarize the patient characteristics and outcomes respectively.

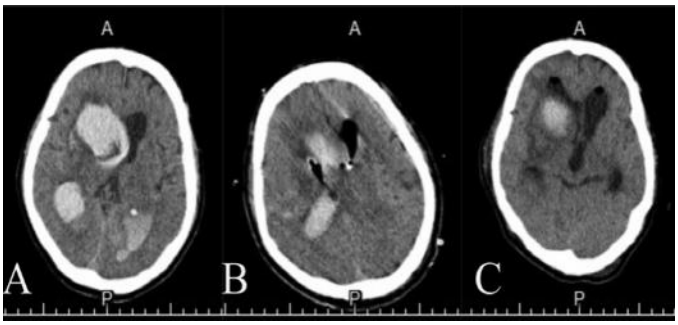

Figure 3. A shows the ictal CT scan of Patient B. B shows the post-rtPA scan with misplacement and pneumocephalus. C shows the end-of-treatment and post-EVD removal CT.

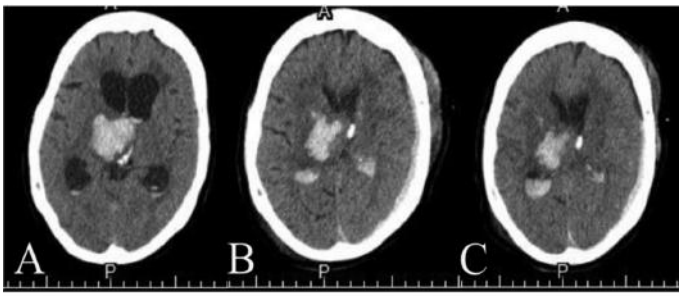

Figure 4. A shows the ictal CT scan of Patient D. B shows the post-rtPA scan with acute subdural hematoma at left frontoparietal convexity. C shows the end-of-treatment scan with the EVD clamped. The acute subdural hematoma remains relatively unchanged.

Table 2. Patient outcomes, complications, and other elements of intervention.

Patient	A	B	C	D	E
rtPA					
Dose per admin (mg)	8	4	6	8, 4	4
No. of doses	3	2	1	1, 2	2
Dual EVD	-	+	-	-	-
Clearing of ventricles					
3rd vent (No. of doses)	3	2	1	2	2
4th vent (No. of doses)	3	N/A	1	1	N/A
All (No. of doses)	3	Not achieved	1	Not achieved	Not achieved
EOT IVH volume					
Modified Graeb score	0	4	0	6	7
IVHS (volume in cc)	0	9 (6.0)	0	6 (3.3)	9 (6.0)
EOT Evans' index	0.28	0.29	0.24	0.28	0.14
Duration of EVD (d)	6	13	13	4*	3*
Complications					
Misplacement	+	+	+	-	-
Pneumocephalus	+	+	-	+	-
Cath-tract hematoma	+	-	-	+	-
Subdural hematoma	-	-	-	+	-
Ventriculitis	-	?	-	?	?
PHE	+	-	-	-	-
Shunt dependence	-	+	-	N/A	N/A
30-day mRS	5	5	5	6	6
30-day mortality	Alive	Alive	Alive	Dead	Dead
All-cause mortality	Dead	Dead	Alive	Dead	Dead

EOT = End of treatment, defined in the CLEAR III protocol as 24 h after the last dose.
PHE = Perihemorrhagic edema, defined as hypodensity in white matter tracts attributable to rtPA.
mRS = modified Rankin scale.
*EVD duration in these cases were until death.
ΩEye opening preceded the intervention of rtPA administration.

The method of alteplase infusion differed slightly from the methodology in the CLEAR-IVH trial. The variation in dosing and schedule is slightly higher and less frequent in the present series than in the trial, i.e., 4-8 mg in only one to three doses as compared to 3 mg twice daily in the trial, but still within the normally-tolerated dosage as found in related non-CLEAR literature. Due to logistical reasons, the interval to the "stability CT scan" varied. The present study setting also limited accessibility to frequent and daily CT scan, and patients never got started with intraventricular rtPA treatment within 24-48 hours.

Discussion

Present results show a trend in the increased clearance of the ventricles and decreased modified Graeb and IVHS scores with every subsequent intraventricular administration of rtPA. Improvement in functional status and good outcome were not achieved in this series of patients.

IVH volume significantly affects the outcomes of morbidity and mortality at 30 days[19] and at a lethal volume of 20cc.[20] Three patients in this study have IVH volume of greater than 20cc and two of them died. Although both modified Graeb score and IVH score reflect the severity of disease process of IVH and should intuitively be consistent, a patient subject (patient B) had a low modified Graeb score at end of treatment and yet, still had a relatively high IVH score. This can be explained by the fact that IVH score incorporates the presence of hydrocephalus in its scoring system, in order to be more predictive of mortality estimates.

In this study, the large proportion of the subjects still suffered mortality regardless of the decrease in the degree of severity of the disease process. It is largely due to the fact that the IVH of the patients in this series were secondarily due to ICH, which portends additional risk for mortality. The patients were uniformly victims of hemorrhagic in their thalami, except for one. The exception is the one with ICH in the caudate nucleus - a location generally regarded to have good prognosis despite the presence of IVH[21] - which probably explains the patient's 30-day survival. Thalamic ICH on the other hand, has notoriety among all the types of stroke. The debilitating effect of its damage is not so much due to its size and volume (mean approximate volume 1.5cm x 2.5cm x 3.5cm) but due to the density of its functions that include being the gateway for pain, sensation, motor control, mental association and consciousness status. In addition, the thalamus is in proximity to other eloquent important structures—the basal ganglia, midbrain, hypothalamus, ventricles and the reticular activating system.[22] To illustrate, thalamic ICH more than 10cc is often destructive to the whole posterior limb of the internal capsule.[23] In and of itself, thalamic ICH notwithstanding IVH, should already portend poor functional status. By subtype and location of thalamic ICH, the medial type in particular has a reported association with poor outcome.[24,25]

Dual EVD is employed in the CLEAR III protocol for the second catheter to be inserted to the side of the dominant IVH, with the intent of addressing the casting, trapping mass effect, and/or shift caused by the IVH. A significant proportion of enrolled subjects in the CLEAR III trial were managed with more than a single EVD.[15] In this series, one patient underwent dual EVD; however, absolute clearance of the ventricles was not achieved. Misplacement of ventricular tip placement and cannulation, e,g., the tip inadvertently crossing the contralateral ventricles as in patient C (Figure 5), also occurred in this series. It may be related in part to the technical difficulty of the procedure when it comes to the disease entity that is IVH, but may largely be due to the learning curve of the trainee neurosurgeon doing the operation. The freehand technique of cannulation may actually be more difficult to accurately achieve, with success rates of around 82%. Rates of malposition of the ventricular catheter range from 4 to 20%, but fortunately, most have not been found to have significant clinical sequelae.[26] Image-guided surgery would very well increase the success rate of dual EVD, or a difficult single EVD insertion for that matter, especially that the clot does not provide the tactile and sensory feedback obtained during insertion, nor does it appear to always lend a fastidious obedience of craniometric points. This series also bore complications of iatrogenic hematoma formation—one had acute subdural hematoma and two had catheter-tract hematoma. The formation of acute subdural hematoma may be due to injury to either a cortical vein during cannulation or to a bridging vein during rapid relaxation of the hemisphere from CSF decompression. Catheter-tract hematoma on the other

hand, is more frequently encountered in the literature,[27] and is differentiated into either symptomatic or otherwise. Symptomatic catheter-tract hematomas are those that are large enough to be clinically significant by causing an attributable focal deficit or change in mental status. In this series however, patients who had catheter-tract hematomas had been consistently awake around the time that these complications were radiologically demonstrated. Ultimately, these hematomas become symptomatic only when they cause mass effect. Similarly, pneumocephalus may be clinically insignificant unless they do not resorb on succeeding scans or when they present as tension pneumocephalus. This complication may be avoided by using devices with drip chambers, meticulous technique in the instillation of fluids, and use of commercial EVD devices.

EVD-related central nervous system (CNS) infection, defined in literature along a spectrum of bacterial ventriculitis, meningitis and non-bacterial ventriculitis, has a rate of 4.4% in the CLEAR III trial versus a 7.9% mean rate in the overall non-CLEAR literature.[31] The CLEAR investigators were also cognizant of the fact that there is wide variability in the literature regarding the definition of infection related to EVD, especially that there are varying degrees of sterile pleocytosis as a reaction to IVH. However, they defined EVD-related infection as culture-positive CSF.[31] Ventriculitis has not been encountered in the two subjects in this study. The limitation of this study however, is that there was failure to rule out infection in all of the other subjects. Considering that there is a considerable wide variation in practice related to the frequency of CSF sampling, in most clinical settings CNS infection is often strictly diagnosed later in the course especially when the patient nevertheless has already been receiving broad-spectrum antibiotics with acceptable blood-brain barrier penetrance or otherwise, for systemic infection of remote focus. Various methods have been proposed to diminish the rates of EVD-related infection,[30] and in this study, care was taken to observe strict sterile conditions for each administration of rtPA, including sterile preparation, antiseptic preparation of the tubing, closed 3-way stopcock syringe technique, and wearing of mask and gown.

Perihemorrhagic edema (PHE), i.e., the varying degrees of both cytotoxic and vasogenic edema of the brain parenchyma surrounding the ICH or IVH for that matter, has been radiologically demonstrated in one of the study subjects, Patient A. PHE has been identified as a possible complication of intraventricular rtPA, hypothesized from animal studies.[22] This is believed to be caused either by an inflammatory response to the proteases of rtPA or the direct toxic effects of the fibrinolytic drugs on brain tissue.[28] However, there is also literature providing evidence for otherwise, stating that rtPA even at high doses of 4mg every 12 hours up to 20 mg, or 1mg every 8 hours up to 12mg does not increase the degree of PHE[29] compared to the natural history[23] of ICH and IVH. Ultimately, it is important to note that rtPA could possibly cause adverse reactions by its very nature as a drug.

The natural history of IVH is also telling of the fact that the obstruction of Pacchioni granulations by the degradation of blood products can eventually result into chronic communicating hydrocephalus, which would require permanent CSF diversion via ventriculoperitoneal shunt surgery.[10] In this study, one patient developed shunt dependence, on the basis of an increase in Evans' index from baseline at the end of treatment or post-removal of EVD. A systematic review comparing conservative management, EVD alone, and EVD plus fibrinolysis has shown that intraventricular fibrinolysis does not appear to have any beneficial effect on arresting the development of hydrocephalus.[30] Fibrinolytic agents such as rtPA cannot reverse hydrocephalus, but the use of rtPA as a causation for hydrocephalus is a different matter altogether. A separate analysis of the CLEAR III results reported that no statistically-significant correlation has been found between the use of rtPA for intraventricular fibrinolysis and permanent CSF diversion. The predictors of shunt dependence were: early elevated intracranial pressure, high CSF output and placement of more than one EVD.[31] In this study, shunt dependence of patient B can be attributed to him having dual EVD.

By using good functional status as the yardstick of a worthwhile intervention, investigators of the CLEAR III trial concluded that *"alteplase at the dose of 1mg every 8h cannot be recommended as an intervention to improve functional outcome in patients with intraventricular hemorrhage."* On the basis of this tall order, use of rtPA for intraventricular administration for the purpose of improving functional status cannot be recommended

prima facie in clinical practice. However, there may be other countervailing factors at work that influence the near-impossibility of achieving good functional outcome. For one, the authors' definition of 'good' functional outcome may be flawed or incomplete. CLEAR III investigators did recommend further research to clarify the divergent picture within the more severe disability segments of mRS.[32]

While the CLEAR III trial results failed to demonstrate that rtPA administration would achieve good functional status, a more nuanced analysis of the results shows that the technique appeared to have averted mortality. Mortality was significantly lower among those who received rtPA; there was a 50% decrease in the odds of being dead (mRS 6) for alteplase versus placebo (adjusted OR 0·50[95% CI 0·31–0·80], p=0·004).[36] It should be noted however, that survivors belonged in the severe disability scale (mRS 4 or 5). Similarly, the patients in this study who survived after 30 days (patients A, B and C) had mRS score of 5. The CLEAR investigators added that fewer neurological, respiratory, and sudden deaths were noted in the treatment group versus the placebo group. They hypothesized that early removal of IVH clot corrects a severe life-threatening cerebral anatomic defect and possibly limits the structural brain injury which in turn limits cardiorespiratory risks inherent with structural brain injury.[36] Based on these results and on the existing literature, the authors hypothesize that for patients with ICH and IVH, the use of rtPA for fibrinolysis of clot in the ventricles will increase their chance of survival, although it may be in a bedridden, totally-dependent state.

Given that this study is a case series, all the relevant biases inherent in this study design are maintained as limitations. Due to the limited availability of rtPA, the time duration of the study is short and the study population is small. At the outset, the main limitation of this study is that it does not intend to analyze the association between response to the surgical interventions and the long-term outcomes of functional status and survival. An analytical study design could be employed if there were to be more cases undergoing this procedure in the future.

Conclusion

In this single-institution study, patients for which rtPA was used for intraventricular fibrinolysis of IVH clot in addition to EVD as surgical treatment for hydrocephalus resulted to a 30-day survival of 3 out of 5 in this series, while actual survival is 1 out of 5. The intervention was efficacious in decreasing the modified Graeb scores and IVH scores of all study subjects at end of treatment. Functional status of mRS 5 is the highest score achieved among survivors. Ventriculitis was not demonstrated in two subjects for which it was ruled out, while shunt dependence was avoided by majority of the patients in the study. Other complications from the intervention considered were: misplacement of ventricular catheter, pneumocephalus, asymptomatic catheter-tract hematoma, acute subdural hematoma, and perihemorrhagic edema.

Acknowledgements

The authors are indebted to Jose C. Navarro, MD, MSc and Jose Carlos S. Alcazaren, MD for their support.

Appendix 1. Original Graeb Score[16]

Lateral Ventricles (x 2)		
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
Third and Fourth Ventricles		
Score:	1 =	Blood present, ventricle size normal
	2 =	Ventricle filled with blood and expanded
Total Score (Maximum = 12)		

Appendix 2.Modified Graeb Score[17]

Scores for each ventricle								
% of blood	R Temp Tip	R Lateral	R Post Tip	L Temp Tip	L Lateral	L Post Tip	IIIrd	IVth
None	0	0	0	0	0	0	0	0
≤ 25%	1	1	1	1	1	1	2	2
> 25% to ≤ 50%	1	2	1	1	2	1	2	2
> 50% to ≤ 75%	2	3	2	2	3	2	4	4
> 75% to 100%	2	4	2	2	4	2	4	4
Expanded	1	1	1	1	1	1	1	1

Appendix 3. The Intraventricular Hemorrhage Score (IVHS)[18]

IVH Score* (IVHS) = 3 x (RV + LV) + III + IV + 3 x H

Lateral ventricle score:
- 0 (no blood or small amount of layering)
- 1 (up to one third filled with blood)
- 2 (one to two thirds filled with blood)
- 3 (mostly or completely filled with blood)

The third and fourth ventricles score:
- 0 (no blood)
- 1 (partially or completely filled with blood)

Hydrocephalus score:
- 0 (absent)
- 1 (present)

* RV = right ventricle; LV = right ventricle; III = third ventricle; IV = fourth ventricle; H = hydrocephalus

IVH volume (mL) = $e^{IVHS/5}$

References

1. Naval NS, Nyquist PA, Carhuapoma JR. Management of spontaneous intracerebral hemorrhage. In select topics on cerebrovascular disease. Neurosurg Clin North Am 2008; 415–42.
2. Adams RE, Diringer MN. Response to external ventricular drainage in spontaneous intracerebral hemorrhage with hydrocephalus. Neurology 1998; 50: 519-23.
3. Witsch J, Classen J, Connolly ES et al. Intraventricular hemorrhage expansion in patients with spontaneous intracerebral hemorrhage. Neurology 2015; 84: 989–94.
4. Mustanoja S, Satopaa J, Meretoja A, et al. Extent of secondary intraventricular hemorrhage is an independent predictor of outcomes in intracerebral hemorrhage: data from the Helsinki ICH study. Int J Stroke 2015; 4: 576–581.
5. Amenta PS, Morcos J. Chapter 375 Nonlesional spontaneous intracerebral hemorrhage. In Youmans and Winn Neurological Surgery Seventh Edition 2017; 3186-97.
6. Pang D, Sclabassi RJ, Horton JA. Lysis of intraventricular blood clot with urokinase in a canine model, part 2: in vivo safety study of intraventricular urokinase. Neurosurgery 1986; 19: 547–52.

7. Mayfrank L, Kim Y, Kissler J, Delsing P, Gilsbach JM, Schroder JM, Weis J. Morphological changes following experimental intraventricular hemorrhage and intraventricular fibrinolytic treatment with recombinant tissue plasminogen activator. ActaNeuropathol (Berl) 2000; 100: 561-7.
8. Ehlert A, Schmidt C, Wölfer J, Manthei G, Jacobs AH, Brüning R, Heindel W, Ringelstein EB, Stummer W, Pluta RM, Hesselmann V. Molsidomine for the prevention of vasospasm-related delayed ischemic neurological deficits and delayed brain infarction and the improvement of clinical outcome after subarachnoid hemorrhage: a single-center clinical observational study. J Neurosurg 2015.
9. Morgenstern LB, Hemphill JC III, Anderson C, Becker K, Broderick JP, Connolly ES Jr, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2010; 41: 2108–29.
10. Teramoto S, Yamamoto T, Nakao Y, Watanabe M. Novel anatomic classification of spontaneous thalamic hemorrhage classified by vascular territory of thalamus. World Neurosurg 2017; 104: 452-8.
11. Naff NJ, Carhuapoma JR, Williams MA, et al. Treatment of intraventricular hemorrhage with urokinase - Effect on 30-day survival. Stroke 2000; 31: 841–7.
12. Coplin WM, Vinas FC, Agris JM, Buciuc R, Michael DB, Diaz FB, Muizelaar JP. A cohort study of the safety and feasibility of intraventricular urokinase for nonaneurysmal spontaneous intraventricular hemorrhage. Stroke 1998; 29:1573-9.
13. Chen CW, Wu EH, Huang J, Chang WT, Ao KH, Cheng TJ, Yang W. Dynamic evolution of D-dimer level in cerebrospinal fluid predicts poor outcome in patients with spontaneous intracerebral hemorrhage combined with intraventricular hemorrhage. J Clin Neurosci 2016.
14. Lapointe M, Haines S. Fibrinolytic therapy for intraventricular hemorrhage in adults. Cochrane Database Syst Rev 2002.
15. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. Lancet 2017; 389: 603–11.
16. Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB. Computed tomographic diagnosis of intraventricular hemorrhage. Etiology and prognosis. Radiology 1982; 143: 91-6.
17. Morgan TC, Dawson J, Spengler D, Lees KR, Aldrich C. Mishra NK, et al. The Modified Graeb Score: An enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. Stroke 2013;44: 635–41.
18. Hallevi H, Dar NS, Barreto AD, et al. The IVH score: A novel tool for estimating intraventricular hemorrhage volume: Clinical and research implications. Crit Care Med 2009; 37(3): 969–e1.
19. Balami JS, Buchan AM. Complications of intracerebral hemorrhage. Lancet Neurol 2012; 11: 101–18.
20. Young WB, Lee KP, Pessin MS, Kwan ES, Rand WM, Caplan LR. Prognostic significance of ventricular blood in supratentorial hemorrhage: a volumetric study. Neurology 1990; 40: 616–19.
21. Hallevi H, Albright KC, Aronowski J. Intraventricular hemorrhage: anatomic relationships and clinical implications. Neurology 2008; 70; 848-52.
22. Tokgoz S, Demirkaya S, Bek S, et al. Clinical properties of regional thalamic hemorrhages. J Stroke Cerebrovasc Dis 2013; 22 (7): 1006-12.
23. Chen M, Wang Q, Zhu W, et al. Stereotactic aspiration plus subsequent thrombolysis for moderate thalamic hemorrhage. World Neurosurg 2012; 77 (1): 122-9.
24. Kwak R, Kadoya S, Suzuki T. Factors affecting the prognosis in thalamic hemorrhage. Stroke 1983; 14: 493-500.
25. Chung CS, Caplan LR, Han W, Pessin MS, Lee KH, Kim JM. Thalamic haemorrhage. Brain 1996; 119: 1873-86.
26. Huang MC, Wang VY, Manley GT. Chapter 15 Intracranial Pressure Monitoring. In Youmans and Winn Neurological Surgery Seventh Edition. 2017; 217-23.
27. Dey M, Stadnik A, Awad I et al. Bleeding and infection with external ventricular drainage: A systematic review in comparison with adjudicated adverse events in the ongoing clot lysis evaluating accelerated resolution of intraventricular hemorrhage phase III (CLEAR-III IHV) Trial. Neurosurgery 2015; 76: 291–301.
28. Fam MD, Zeineddine HA, Eliyas JK, et al. CSF inflammatory response after intraventricular hemorrhage. Neurology 2017; 89:1–8.
29. Volbers B, Wagner I, Willfarth W, Doerfler A, Schwab S, Staykov D. Intraventricular fibrinolysis does not increase perihemorrhagic edema after intracerebral hemorrhage. Stroke 2013; 44: 362-6.
30. Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A. Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. J Neurol 2000; 247(2): 117-21.
31. Murthy SB, Awad IA, Harnof S, et al. Permanent CSF shunting after intraventricular hemorrhage in the CLEAR III trial. Neurology. 2017; 89:1–8.
32. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. Lancet 2017; 389: 603–11.