ORIGINAL RESEARCH

External Ventriculostomy and Intraventricular Instillation Of Recombinant Tissue Plasminogen Activator For Management Of Spontaneous Intra-Ventricular Hemorrhage: A Prospective Study

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Abstract
Aim: To evaluate external ventriculostomy and intraventricular instillation of recombinant tissue plasminogen activator for management of spontaneous intra-ventricular hemorrhage.
Material and method:The present non-randomized prospective study was done in the Department of Neurosurgery among 30 patients who underwent external ventriculostomy and intraventricular instillation of recombinant tissue plasminogen activator at Bangur Institute Of Neurosciences & SSKM HOSPITAL, IPGME&R, KOLKATA between April 2020 – August 2021. Various parameters studied were GOSE SCORE: 7 days------>30days------>90 days, Ventriculitis: (0-180days) (y/n), 30 days survival (y/n), worsening hemorrhage during t/t till 72 hr. of last dose (y/n), worsening hemorrhage during t/t > 72 hr. of last dose (y/n), hydrocephalus during follow up (y/n) and Qol (EQ5D) at 1 month and 3 months.
Results: Mortality was reported among 33.33% of the subjects after 3 months. After seven days, good recovery was not found in any of the subject but after 1 month and 3 month, good recovery was reported among 4 (13.33%) and 9 (30%) of the subjects respectively. After 3 months; vegetative state, severe disability and moderate disability was found in 2, 7 and 2 subjects respectively. There was significant decrease in clot volume (cc) after the intervention of external ventriculostomy and intraventricular instillation of recombinant tissue plasminogen activator i.e. it decreases from 38.23 to 8.11 after 5 days.
Conclusion:rtPAwas efficacious in decreasing the modified GOSE scoresand clot volume of all study subjects at end of treatment. Ventriculitis was demonstrated only in six subjects.
Keywords: IVH, rtPA, Mortality, Ventriculitis

Introduction: Intraventricular hemorrhage (IVH) is a frequent complication of subarachnoid hemorrhage (SAH) and intracranial hemorrhage (ICH)[1].Respectively, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) account for about 15% and 5% of the 750,000 strokes occurring yearly in the United States, totalingmore than 45,000 patients per year[2-4].

About 45% of spontaneous ICHs and 25% ofaneurysmal SAHs extend into the ventricles[2,5-6]. For patients with both ICH andintraventricular hemorrhage (IVH), the expected mortality is 50% to 80%[7-8]. Patientswith IVH are twice as likely to have poor outcomes (a modified Rankin scale [mRS] scoreof 4–6 at hospital discharge) and nearly three times more likely to die than their cohortswithout IVH[9].

Risk factors for IVH include older age, higher baseline ICH volume, mean arterial pressure values >120 mm Hg, and location of the primary ICH[8]. Deep, subcortical structures tend to bemost at risk for IVH; frequent locations include the putamen (35%–50%), lobes (30%),thalamus (10%–15%), pons (5%–12%), caudate (7%), and cerebellum (5%)[9]. Whereassome authors have focused on the volume of the original ICH as the predictor of pooroutcome, others have used sophisticated volumetrics to define a threshold volume of IVH (20 mL) as particularly ominous[10]. Hallevi et al[11] correlated larger ICH volume withthe presence of IVH, as well as location near the ventricular system, which likely leads toearly intraventricular rupture.

External ventricular drainage (EVD) is a surgicalintervention that has become the standard of care for acuteobstructive hydrocephalus complicating ICH with IVHaccording to the American Heart Association/AmericanStroke Association (Class IIa, level of evidence: B)[12]. TheJapanese Guidelines for the Management of Stroke 2004and 2009 also recommend emergency surgery via EVD.[13]EVD is mainly used for addressing the problem ofincreased intracranial pressure caused by IVH.

Numerous other studies would posit along similar lines and contribute to literature that would otherwise rule thatventriculostomy has limited benefit, were it not for the addition of intraventricular administration of a fibrinolytic agent via an EVD.[8,14]

A Cochrane review on fibrinolytic therapy forintraventricular hemorrhage in adults served asfoundational high-quality evidence suggesting that theintervention is safe and of therapeutic value[15]. Muchlater, 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: EvaluatingAccelerated Resolution phase 3 (CLEAR III) trial arelandmark studies that served to establish the safety andefficacy of recombinant tissue plasminogen activator(rtPA, alteplase) for clinical use in patients with IVH.The trial was completed on January 2016 with analyzedresults published early part of 2017[16].

To the authors' knowledge, the administration of rtPA forthe neurosurgical management of IVH is not routinely donein the local setting. The aim of this study is to present themethods, outcomes and complications of this neurosurgicaltechnique and bridge the gap between the local surgicalexperience and the current available literature.

Material and Methods: The present non-randomized prospective study was done in the Department of Neurosurgery among all the patients who underwent external ventriculostomy and intraventricular instillation of recombinant tissue plasminogen activator at Bangur Institute Of Neurosciences & SSKM HOSPITAL, IPGME&R, KOLKATA between April 2020 – August 2021 were included in this study. The patients undergoing traumatic IVH were excluded from this study.

Sample size: 30 cases

Inclusion criteria:
1) Age 18-80
2) Symptom onset less than 24 hrs prior to diagnostic CT scan
3) Spontaneous ICH less than or equal to 30 cc or primary IVH
4) IVH obstructing 3rd and/or 4th ventricles
5) ICH clot stability at 6 hours or more post IVC placement
6) IVH clot stability at 6 hours or more post IVC placement
7) Catheter tract bleeding stability 6 hours or more post IVC placement
8) EVD placed per standard medical care
9) SBP less than 200 mmHg sustained for 6 hours prior to drug administration
10) Historical Rankin of 0 or 1

Exclusion criteria:
1. Suspected or untreated ruptured cerebral aneurysm, AVM, or tumor
2. Presence of a choroid plexus vascular malformation or Moyamoya
3. Clotting disorders
4. Platelet count less than 100,000, INR greater than 1.4
5. Pregnancy
6. Infratentorial hemorrhage
7. SAH at clinical presentation
8. ICH/IVH enlargement that cannot be stabilized in the treatment time window
9. Ongoing internal bleeding
10. Superficial or surface bleeding
11. Prior enrolment in the study
12. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated
13. Planned or simultaneous participation (between screening and Day-30) in another interventional medical investigation or clinical trial.
14. No subject or legal representative to give written informed consent

Outcome:
Various parameters were studied under following headings –
1) NIHSS SCORE: at admission ---------->7 days
2) GOSE SCORE: 7 days------>30days------>90 days
3) VENTRICULITIS: (0-180days) (y/n)
4) 30 days survival (y/n)
5) Worsening hemorrhage during t/t till 72 hr. of last dose (y/n)
6) Worsening hemorrhage during t/t > 72 hr. of last dose (y/n)
7) Hydrocephalus during follow up (y/n)
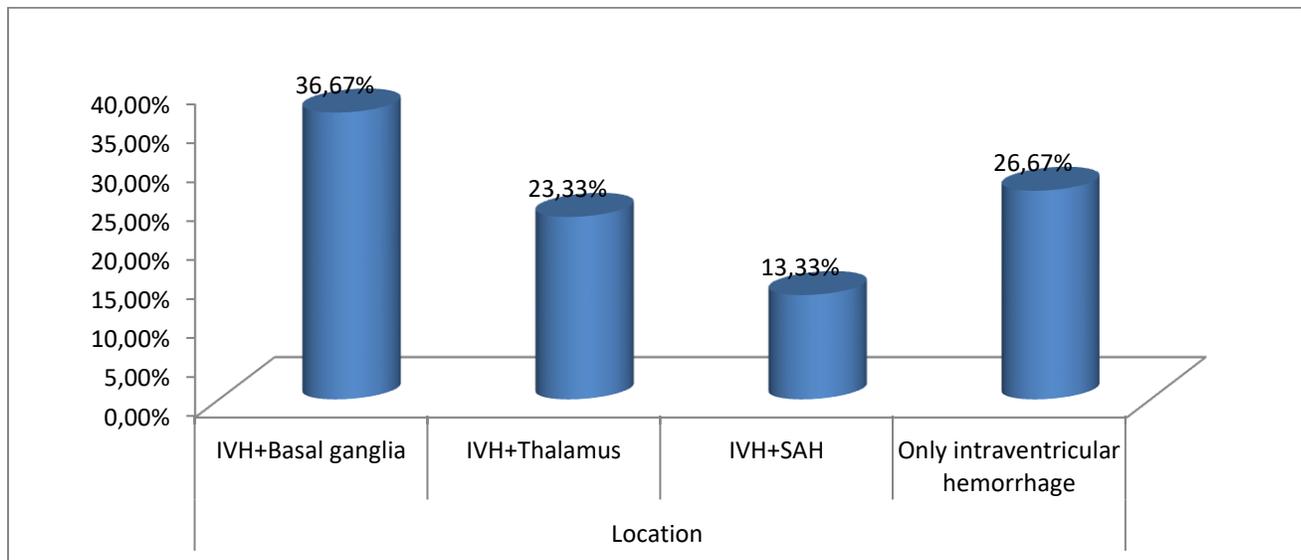8) Qol (EQ5D) at 1 month and 3 months

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p < 0.05$.

Results: Out of 30 subjects, 21 (70%) were males and 9 (30%) were females. Hence there was male dominance in our study. Maximum subjects were from the age group of 51-60 years (43.33%) followed by 61-80 years (23.33%). Most of the subjects had GCS score of 3-8 at the time of admission.

Table 1: Gender, age, GCS score at admission distribution among the study subjects

Gender	N	%
Male	21	70
Female	9	30
Age Group (in years)		
18-30	2	6.67
31-40	3	10
41-50	5	16.67
51-60	13	43.33
61-80	7	23.33
GCS Score		
3-8	17	56.67
9-12	9	30
13-15	4	13.33

Bleeding at solely on intraventricular hemorrhage (IVH) was revealed in 26.67% of the subjects. Bleeding at IVH+Basal ganglia, IVH+Thalamus and IVH+SAH was reported among 36.67%, 23.33% and 13.33% of the subjects respectively (graph 1).

Graph 1: Location of bleed among the study subjects

ICU stay (in days) among the study subjects was 24.68±30.73 days with minimum and maximum of 4 and 164 days. Hospital stay (in days) among the study subjects was 47.42±56.20 days with minimum and maximum of 16 and 230 days (table 2).

Table 2: Operative parameters among the study subjects

Variables	Minimum	Maximum	Mean	SD
ICU Stay (in days)	4	164	24.68	30.73
Hospital Stay (in days)	16	230	47.42	56.20

Mortality was reported among 33.33% of the subjects after 3 months. After seven days, good recovery was not found in any of the subject but after 1 month and 3 month, good recovery was reported among 4 (13.33%) and 9 (30%) of the subjects respectively. After 3 months; vegetative state, severe disability and moderate disability was found in 2, 7 and 2 subjects respectively. When GOSE scale was compared at different intervals using chi square test, significant improvement was found as $p<0.05$ (table 3).

Table 3: GOSE scale

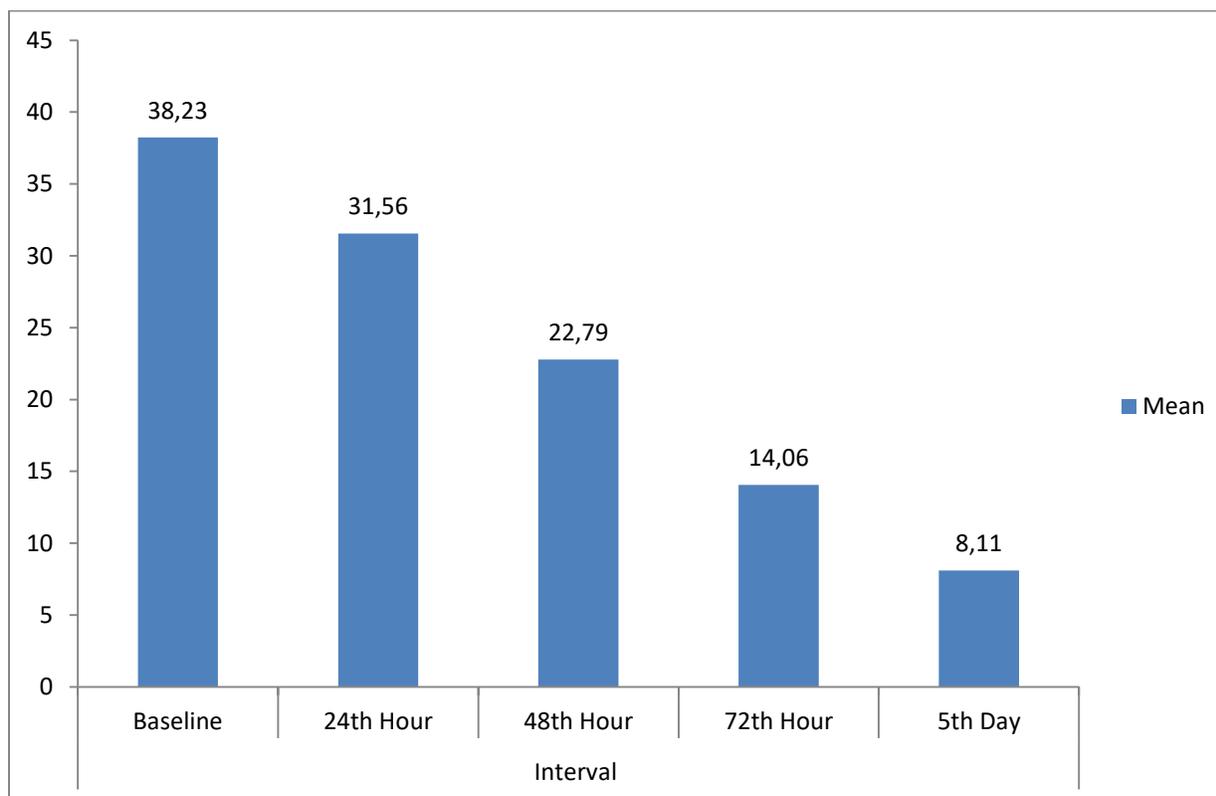| GOSE Scale	7 Days		1 Month		3 Month		p value
	N	%	N	%	N	%	
Death	4	13.33	6	20	10	33.33	
Vegetative State	3	10	2	6.67	2	6.67	
Severe Disability Lower	9	30	7	23.33	4	13.33	
Severe Disability Upper	6	20	5	16.67	3	10	
Moderate Disability Lower	5	16.67	4	13.33	1	3.33	
Moderate Disability Upper	3	10	2	6.67	1	3.33	
Good Recovery Lower	0	0	2	6.67	4	13.33	0.003*
Good Recovery Upper	0	0	2	6.67	5	16.67	

*: statistically significant

After one month of external ventriculostomy and intraventricular instillation of recombinant tissue plasminogen activator, mean EQ5D (QoL) score was 36.5 which further increased to 53.89 after three months. Hence there was significant improvement in QoL among the study subjects as $p<0.05$ (table 4).

Table 4: Mean EQ5D (QOL) score at 1 month and 3 months

Interval	EQ5D		p value
	Mean	**SD**	
1 Month	36.5	11.32	0.008*
3 Month	53.89	14.80	

*: statistically significant

There was significant decrease in clot volume (cc) after the intervention of external ventriculostomy and intraventricular instillation of recombinant tissue plasminogen activator i.e. it decreases from 38.23 to 8.11 after 5 days (graph 2).

Graph 2: Clot volume (cc) at different intervals among the study subjects

At the end of study; ventriculitis, worsening hemorrhage, hydrocephalus and mortality was reported among 20%, 13.33%, 6.67% and 33.33% of the subjects respectively (table 5).

Table 5: Outcome among the study subjects

Outcome	N	%
Ventriculitis	6	20
Worsening Hemorrhage	4	13.33
Hydrocephalus	2	6.67
Mortality	10	33.33

Discussion: Recombinant tissue plasminogen activating factor has long been shown to be safe and effective in declotting vascular catheters that become clotted with hematologic material. It stood to reason that the samemechanism should provide for increased efficiency of clot resolution in body spaces to which surgical accessis gained. Of particular interest in this study are clots consequent to intra ventricular hemorrhage in patients who had external ventricular drains placed for intracranial pressure monitoring and management and clotevacuation[17].

Out of 30 subjects, 21 (70%) were males and 9 (30%) were females. Hence there was male dominance in our study.V.A. Kiran Kumar et al[18] and Mark Krelet al[17] in their study revealed similar male dominance.

3-8, 9-12 and 13-15 GCS score at admission was found among 56.67%, 30% and 13.33% of the subjects respectively. Hence most of the subjects had GCS score of 3-8 at the time of admission.Similarly Mark Krelet al[17] in their study revealed that GCS on arrival ranged from four to14 with mean intake GCS of eight. GCS at the time of admission was 3-8 (low) in 39 patients (57%), 9-12 in 23patients(33%) and 13-15 in 7 patients (10%) as stated by A. Kiran Kumar et al[18] in their study.

Bleeding at solely on intraventricular hemorrhage (IVH) was revealed in 26.67% of the subjects. Bleeding at IVH+Basal ganglia, IVH+Thalamus and IVH+SAH was reported among 36.67%, 23.33% and 13.33% of the subjects respectively in our study.Similarly V.A. Kiran Kumar et al[18] in their study mentioned that major site of hemorrhage was basal ganglia in 24 (35%), thalamus in 13 (19%), cerebellum in 5 (7%), brain stem in 3, frontal/temporal in2 patients.SAH with IVH was noted in 12 patients (17%) and only IVH was noted in10 patients (14%).

In our study; ICU stay (in days) among the study subjects was 24.68±30.73 days with minimum and maximum of 4 and 164 days. Hospital stay (in days) among the study subjects was 47.42±56.20 days with minimum and maximum of 16 and 230 days. In a study by Mark Krelet al[17], length of stay in ICU ranged from five to 160 days with a mean of 21.82 days. Thetotal duration of hospitalization ranged from nine to 224 days with mean 44.14 days. These findings are similar to our study. This may be due to the fact that patients who present with low GCSalso tend to have more severe medical comorbidities that require more protracted hospital courses.

Review of existing literature on length of stay with intracranial hemorrhage shows that patients who present with GCS10 or better have shorter stays and seven or worse have significantly longer stays (average 12 for > 10, 31 for <seven) (in the setting of intracranial hemorrhage). When IVH is co-morbid, that increases the length of staybut not significantly.

Furthermore, the average length of stay ranges from nine to 22 days. Many of thepatients in this study had more protracted stays than this reported average, however, this may beattributable to the patient population our safety-net hospital serves and the concomitant difficulty in safedisposition after inpatient hospitalization inherent to this population[19].

There was significant decrease in clot volume (cc) after the intervention of external ventriculostomy and intraventricular instillation of recombinant tissue plasminogen activator i.e. it decreases from 38.23 to 8.11 after 5 days in our study.Speed of clot evacuation has been demonstrated widely to be significant at aphysiologic level (i.e. to return biochemical and biophysical processes of cerebral metabolism and CSFcirculation to pre-incident baseline) and has been postulated to be of clinical importance, however, athorough discussion of this point is outside the scope of the present study.[20]

This is in agreement with the work of Jaffeand colleagues whose work demonstrated laterality, in and of itself, had no bearing on intraventricular clotevacuation, but that the catheter being placed within the largest volume of the clot does increase the speed of clot evacuation[21].

Clot resolution, inherently, is an important part of reestablishing physiologic CSF circulation and will, in this way, assist in weaning the EVD. It is not, however, the sole factorresponsible for the ability to wean. For this reason, we elected to use overall EVD duration as a marker forclinical progress rather than strictly CT resolution of intraventricular hemorrhage as, often, this wasinsufficient to wean the EVD and, in some cases, patients with CT resolution of IVH still required VPS placement. Other authors have proposed a pathologic mechanism for this involving fibrosis of the basalleptomeninges or impaired CSF absorption due to fibrosis of arachnoid villi leading to communicatinghydrocephalus even in the face of resolution of the presenting acute obstructive hydrocephalus.[20]

At the end of study; ventriculitis, worsening hemorrhage, hydrocephalus and mortality was reported among 20%, 13.33%, 6.67% and 33.33% of the subjects respectively in our study.

Anecdotally, several neurosurgeons have trepidation with initiating transcatheter medication administration that requires multiple, repeated pushes of fluid directly into the ventricular space due toincreased risk of ventriculitis. Previous data indicate an overall rate of ventriculitis with EVD catheters of 8.8% while in the present study, the rate of ventriculitis in this study was 6%.[22]Certainly, this is anotable and clinically important rate increase. Care should be taken to minimize the risks of ventriculitis andfuture work will define strict protocols for optimized sterility of administration. The fear of ventriculitis,however, should not preclude implementation of transcatheterintraventricular administration of rt-PA toresolve acute intraventricular hemorrhage[17].

According to Mark Krelet al[17], four patients enrolled in the study developed ventriculitis. Of those, one developed ventriculitis prior tocommencement of rt-PA protocol.While the CLEAR III trial (Murthy SB et al[23]) results failed to demonstratethat rtPA administration would achieve good functionalstatus, a more nuanced analysis of the results shows thatthe technique appeared to have averted mortality. Mortalitywas significantly lower among those who received rtPA;there was a 50% decrease in the odds of being dead (mRS6) for alteplase versus placebo (adjusted OR 0·50[95%CI 0·31–0·80], p=0·004).The CLEAR investigators added that fewerneurological, respiratory, and sudden deaths were notedin the treatment group versus the placebo group. They hypothesized that early removal of IVH clot correctsa severe life-threatening cerebral anatomic defect andpossibly limits the structural brain injury which in turnlimits cardiorespiratory risks inherent with structural brain injury[24].

Based on these results and on the existingliterature, the authors hypothesize that for patients withICH and IVH, the use of rtPA for fibrinolysis of clot in theventricles will increase their chance of survival, althoughit may be in a bedridden, totally-dependent state.

All the relevantbiases inherent in this study design are maintained aslimitations. Due to the limited availability of rtPA, the timeduration of the study is short and the study population issmall. At the outset, the main limitation of this study is that it does not intend to analyze the association betweenresponse to the surgical interventions and the long-termoutcomes of functional status and survival. An analyticalstudy design could be employed if there were to be morecases undergoing this procedure in the future.

Conclusion:In this single-institution study, patients for which rtPAwas used with EVD, clot resolution are seen. The intervention wasefficacious in decreasing the modified GOSE scores, NIHSS score and clot volume of all study subjects at end of treatment. Ventriculitis was demonstrated only in six subjects. Hence our results argue strongly in favor of larger prospective trials of rt-PA protocol inception in addition to EVD forpatients presenting with acute intraventricular hemorrhage.Therefore rt-PA is a safe and effective adjuvant therapy for transcatheterintraventricular administration in the setting of intraventricular hemorrhage.

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