

Research Article

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Treatment of Intraventricular Hemorrhage (IVH) by Injection of Recombinant Tissue-type Plasminogen Activator (rtPA) – Single Institution Experiences with 80 Patients

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Abstract

Introduction: The aim of our study was to present the results of intraventricular injection of recombinant tissue-type plasminogen activator (rtPA) in patients suffering from intraventricular hemorrhage (IVH).

Material and methods: Patients with spontaneous IVH were enrolled in the study during 2006-2010. A rigid external ventricular drainage (EVD) was implanted via left or right sided frontal burr holes. 3 mg rtPA was injected each day over the EVD for three consecutive days. Hemorrhage size was determined by daily CT scanning. Classification of IVH was done using the IVH scoring system. The clinical condition was classified using the Glasgow coma scale (GCS) and Glasgow outcome scale (GOS). Statistical analysis (Fisher's exact and χ^2 -Test) was done for various parameters to analyze their impact on outcome.

Results: Eighty patients were included to the study (45 male, 35 female). At time of admission 49 patients (56.3%) were in a poor (GCS ≤ 8), 14 (17.5%) in an intermediate (GCS 9-12) and 17 (21.3%) in a good condition (GCS ≥ 13). In the majority of all cases clot lysis could reach a reduction of over 66%. However, clot lysis alone did not lead to a statistically significant reduction of morbidity and mortality ($p > 0.05$). Poor GCS grade and age > 70 years were statistically significant for poor outcome.

Conclusion: Intraventricular application of rt-PA as a minimal invasive treatment modality seems to be suitable for clearance of the blood clots from the ventricles. Despite our mainly good and successful volume reduction, clot lysis alone did not influence the outcome positively. Its usage should be considered in view of different predictive factors. Large Prospective and randomized trials are necessary to answer the open questions.

Keywords: Intraventricular hemorrhage; Clot lysis; rt-PA application; Outcome

Introduction

Spontaneous intraventricular hemorrhage (IVH) occurs most frequently in line with aneurysmal rupture and arterial hypertension. Less frequently IVH is associated with ruptured arteriovenous malformations (AVM) and tumors [1,2]. In absence of any treatment IVH is known to be a high grade and independent risk factor for morbidity and mortality above 80% [3].

A meta-analysis by Gaberel et al. has shown that involvement of the ventricles in cases of spontaneous intracerebral hemorrhage (ICH) has a significant higher impact on poor outcome compared to parenchymal ICH alone with mortality rates of 51.2% and 19.5% respectively [1,4,5].

Pathophysiological constellations like obstructive hydrocephalus, mass effect, toxicity of blood-breaking products and development of chronic hydrocephalus accompanied with IVH are well known and extensively described [4,6].

IVH is usually treated by an external ventricular drainage (EVD) to flush out the blood and to control intracranial pressure (ICP). With regard to the hypothesis that accelerated clot resolution might have a positive effect and improve the outcome in affected patients, several studies dealt with the intraventricular application of recombinant tissue-type plasminogen activator (rtPA) [7-10]. These studies conclude that the use of rt-PA for intraventricular clot lysis has an acceptable safety profile, increases lysis rates and might improve the outcome.

The aim of the presented study is to demonstrate and discuss our results and experiences of intraventricular clot lysis with rt-PA with the special focus on the association of the degree of intraventricular clot clearance with good outcome.

Material and Methods

Patients with spontaneous, non-traumatic IVH ($n=80$) and those with associated small intracerebral hemorrhage $< 35 \text{ cm}^3$ (ICH), which were treated in our department during 2008-2012 were included in this study. The cut-off size of 35 cm^3 was chosen in view of a parallel study of treatment of basal ganglia hemorrhage with rt-PA.

Diagnosis was made by CT scanning within 24 hours after onset. A rigid external ventricular drainage (EVD) was implanted via frontal burr hole at the dominant side of the hemorrhage. Cranial CT scanning documented the correct position of EVD. All patients were

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Received February 21, 2013; **Accepted** April 11, 2013; **Published** April 11, 2013

Citation: Maslehaty H, Ntoulas G, Petridis AK, Bitter A, Niklewski F, et al. (2013) Treatment of Intraventricular Hemorrhage (IVH) by Injection of Recombinant Tissue-type Plasminogen Activator (rtPA)–Single Institution Experiences with 80 Patients. J Neurol Disord 1: 113. doi:10.4172/jnd.1000113

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treated in the neurosurgical ICU with continuous measurement of the arterial blood pressure (systolic limit value: 150 mmHg), pulse rate, oxygen saturation, and continuous recording of electrocardiogram. The neurological condition in the continuing course was assessed by the physician at the ICU closely. Mechanical ventilation was obtained in cases with respiratory insufficiency.

According to earlier dose finding examinations at our institution and based on the published data on this topic with recommendation of low dose application of rt-PA, 3 mg rt-PA was injected (bolus injection) each day over the EVD for three consecutive days by using the three-way stopcock which is connected to the EVD system. After injection, EVD was closed for 2 hours and was re-opened. Hemorrhage size was monitored by daily CT scanning. Classification of IVH size was done using the IVH scoring system developed by Hijdra et al. for each ventricle: 0, no blood; 1, small amount of blood; 2, moderately filled with blood; or 3, completely filled with blood. Maximal score: 12 [11].

The total amount of hemorrhage reduction after third injection is given in percentage. Four subgroups have been created: volume reduction <25%, 25-50%, 51-75% and >75%. For statistical analysis we made a cut off value of 50%. The size of associated ICH was calculated using the ABCs of measuring method [12].

The clinical condition of the patients at time of admission and discharge was classified using the Glasgow coma scale (GCS) and Glasgow outcome scale (GOS). For simplify the overview and for further analysis the clinical condition of the patients were divided into three sub-groups: poor: GCS ≤ 8; intermediate: GCS 9-12 and good: GCS ≥ 13. The GOS grades were summarized into two groups with poor outcome (GOS 1-3) and good outcome (GOS 4 and 5).

Furthermore, according to our previous studies, we made a cut off age of 70 years for statistical analysis [13]. Statistical analysis was done using the Fisher's exact test and Chi-square with Yates' correction. The p-value was calculated with two tails. Statistical significance was estimated as p-value <0.05.

Results

In total we analyzed the data of 80 patients (45 male, 35 female; male to female ratio: 1.3:1). The contribution of the patients to the age groups showed a predominance for the age group >70 years (Figure 1). Six patients were in a good clinical condition at time of onset (GCS ≥ 13, 7.5%), 25 patients belonged to the intermediate group (GCS 9-12, 31.3%) and 49 patients had a poor clinical condition (GCS ≤ 8, 61.3%). The total mortality rate was 22.5% (n=18).

Fourteen patients (17.5%) received antithrombotic treatment with acetylsalicylic acid (ASA) and 17 patients (21.3%) with

phenprocoumon. The Hijdra score of IVH at time of onset in patients with ASA and phenprocoumon was 7.6 and 7.12 respectively. In patients without antithrombotic treatment the Hijdra score was 8.78. The Hijdra score after third injection of rt-PA in patients with ASA and phenprocoumon was 2.17 and 2.61 respectively. The score in patients without antithrombotic treatment was 2.67.

Considering complications, infection associated to EVD like local wound infection or meningitis and to the stay at the ICU like pneumonia or infection of the urinary tract occurred in n=12 patients (15%). Re-bleeding occurred in 4 cases (5%), chronic hydrocephalus with necessity of permanent shunting in 17 patients (21.3%).

The total volume reduction percentage of all patients after third injection was 68.64%. GCS-Subgroup-divided the mean percentage was 67.2% in the poor GCS group, 72.5% in the intermediate group and 63.4% with good GCS (Table 1).

The total mean Hijdra score at time of admission and after 3rd injection was 8.2 and 2.5 respectively. Division of the Hijdra score in the poor GCS group was 8.4/2.7, in the intermediate group 7.8/2 and in the good GCS group 8.6/2.8.

Forty-nine patients presented with associated small ICH. Mean ICH volume was 11.7 cm³.

The total mortality was estimated with 22.53% (n=18). The outcome distribution was as follows: GOS 2: n=7 (8.8%), GOS 3: n=28 (35%), GOS 4: n=14 (17.5%), GOS 5: n=13 (16.3%).

Different factors (age, gender, GCS, antithrombotic therapy, complications, bleeding source and degree of clot lysis) were assessed in univariable analysis for associations with good outcome (GOS 4 & 5). The results are displayed in table 2.

Discussion

Since it is proven that untreated IVH has a significant higher rate of morbidity and mortality and by considering the hypothesis that early removal of ICH has a positive effect on the brain recovery due to the reduction of intracranial pressure and edema, as well as improvement of the brain perfusion and decrease of the toxicity of blood breaking products [14-18], it is assumed that intraventricular clot lysis might have a similar effect. Several studies have focused on this topic [19-22]. The CLEAR IVH trial randomized 48 patients with IVH for rt-PA or placebo application and came to the conclusion that has an acceptable safety profile compared to placebo and can reduce ventricular blood clots effectively and can control ICP in the affected patient group [7]. Other studies concluded that application of rt-PA speed up the clearance of IVH compared to EVD alone and improved outcome [8-10].

According to this, the results of our study show that the application of rt-PA has the potential to reduce intraventricular blood clots within a short time period sufficiently (Figures 2-4). The mean volume reduction was estimated with 68.64% after three days.

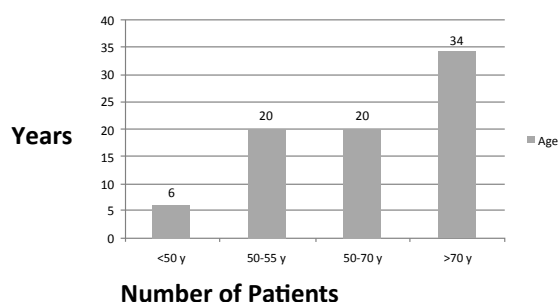


Figure 1: Age distribution.

Volume reduction in relation to the GCS group			
Volume/GCS	Poor GCS (n=49)	Intermediate GCS (n=25)	Good GCS (n=6)
<25%	1 (2%)	0	0
<50%	7 (14.3%)	6 (24%)	1 (16.7%)
<75%	23 (44.9%)	7 (28%)	4 (66.7%)
>75%	18 (36.7%)	13 (52%)	1 (16.7%)
Mean volume reduction	67.2%	72.5%	63.4%

Table 1: Volume reduction in relation to the GCS groups.

Statistical analysis			
	Poor (n)	Good (n)	p-value
Age			
<70y	24	22	0.047*
>70y*	26	8	
Gender			
Male	31	14	0.472
Female	22	13	
GCS			
≤ 8*	39	10	0.003*
<8	14	17	
Antithrombotic therapy			
Phen	13	4	0.325
ASA	10	4	0.603
Complication			
Infection	8	4	0.854
Re-bleeding	4	0	0.357
Shunt	12	5	0.837
Bleeding source			
Aneurysm	16	7	0.890
HTN	37	20	
Clot lysis			
<50%	10	5	0.969
>50%	43	22	

Table 2: Statistical analysis, Bold text: statistically significant, Poor: GOS 1-3, Good: GOS 4 and 5, Phen: phenprocoumon, ASA: Acetylsalicylic acid, HTN: Hypertension.

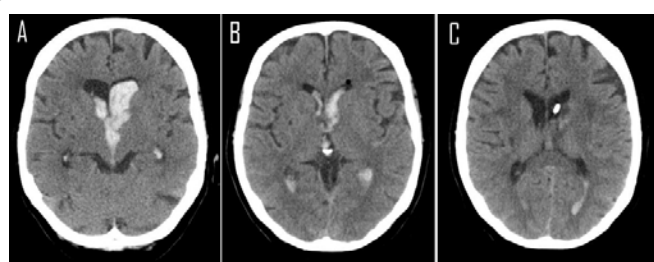


Figure 2: Illustrated case 1, A: First CT scan after onset, B: CT scan after first rt-PA application, C: CT scan after third rt-PA application.

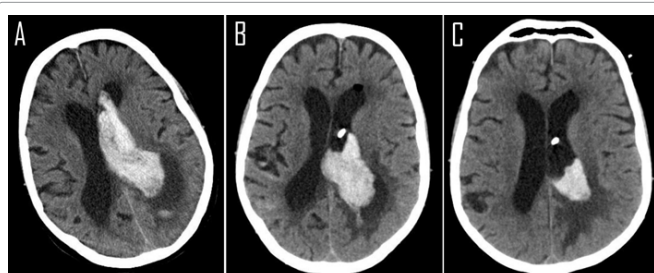


Figure 3: Illustrated case 2, A: First CT scan after onset, B: CT scan after first rt-PA application, C: CT scan after third rt-PA application.

However, Webb and co-workers postulate that clearance of IVH with rt-PA and its success is dose-dependent which has the most impact in the midline ventricles [23].

From the analyzed parameters, only age >70 years and poor GCS grade at time of admission (GCS ≤ 8) were statistically highly significant factors for poor outcome. Gender, postoperative infection, necessity of shunting and the source of hemorrhage, whether aneurysmal or hypertensive, were statistically not significant parameters for poor

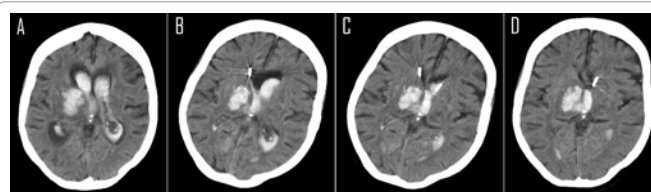


Figure 4: Illustrated case 3, A: First CT scan after onset, B: CT scan after first rt-PA application, C: CT scan with bi-frontal EVDs and second rt-PA application, D: CT scan after third rt-PA application.

outcome. Other studies postulate that clot lysis with rt-PA may have a benefit for younger patients or those in poor clinical conditions [8].

The total mortality in our study was 22.5% and is in the range to the CLEAR IVH trial with 19% [9]. Feared re-bleeding due to application of rt-PA occurred in 4 cases (5%) and led to a high mortality rate of 75% in our series and is in a range of other studies on this topic [7,8]. Although the total incidence is low, the high morbidity and mortality rate due to re-bleeding should be taken into account.

The level of intraventricular clot lysis itself did not have a statistically significant influence on outcome. A significant association with GOS 4-5 by a high rate of clot lysis could not be demonstrated. Furthermore, a high IVH score at time of admission did not correlate with the severity of the clinical condition at time of onset. We observed nearly the same IVH score in the poor, intermediate and good GCS groups. Interestingly, the IVH score at time of onset was lower in patients with antithrombotic treatment. However, the success of intraventricular clot lysis was most sufficient in the patient group with ASA medication, which appears consequential due to the impaired blood clotting by this drug.

Considering the question, if intraventricular clot lysis prevent delayed post hemorrhagic hydrocephalus, Jaffe and co-workers postulate that this treatment method has no effect on this issue [9]. However, rt-PA lysis might play an important role in prevention of acute occlusive hydrocephalus. Through our analysis and results we are not able to bring any clarification on this issue, so that this question requires separate consideration.

Despite rapid clearance of blood clots from the ventricles with rt-PA, IVH remains a devastating disease with high morbidity and mortality rates. However, application of rt-PA seems to have a benefit compared to EVD alone by reviewing the literature on this topic and historical controls. Hence its application seems reasonable in cases with severe IVH to control at least ICP.

Nevertheless, it is important to take different factors like clinical condition, age and the bleeding source into account when performing rt-PA lysis to provide an adequate prognosis assessment. Further large multi-centre series with homogeneous patient groups concerning size of hemorrhage, clinical condition, bleeding source etc. are needed to prove the efficacy of intraventricular clot lysis adequately. Maybe the ongoing CLEAR IVH phase III trial is able to answer the open questions.

Conclusion

Intraventricular application of rt-PA as a minimal invasive treatment modality seems to be suitable for clearance of the blood clots from the ventricles. Despite our mainly good and successful volume reduction, clot lysis alone did not influence the outcome positively. Its usage should be considered in view of different predictive factors.

Large Prospective and randomized trials are necessary to answer the open questions.

Conflict of Interest Disclosure

We declare that we have no conflict of interest.

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Citation: Maslehaty H, Ntoulis G, Petridis AK, Bitter A, Niklewski F, et al. (2013) Treatment of Intraventricular Hemorrhage (IVH) by Injection of Recombinant Tissue-type Plasminogen Activator (rtPA)—Single Institution Experiences with 80 Patients. *J Neurol Disord* 1: 113. doi:[10.4172/jnd.1000113](https://doi.org/10.4172/jnd.1000113)

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