

Thrombolytic treatment of intraventricular hemorrhage

Z. Poljaković, J. Ljevak, S. Šupe, V. Matijević, D. Alvir, A. Bazina, A. Mišmaš, V. Peterković¹, B. Malojčić, I. Antončić²

SUMMARY - Standard approach in the treatment of intraventricular hemorrhage (IVH) with developing hydrocephalus is external ventricular drainage combined with conservative symptomatic therapy. Intraventricular thrombolysis with recombinant tissue plasminogen activator (rt-PA) was for the first time introduced for treating this condition about ten years ago. Since then, many clinical studies with different treatment protocols of intraventricular thrombolysis have been reported, all presenting similar results of faster intraventricular clot resolution and improved outcome. We present our first experience with intraventricular thrombolysis in a young male patient with IVH who was treated in the early stage of his illness and finally had an excellent outcome. We also present the accepted Croatian protocol of intraventricular thrombolysis, approved by the ethics committees of two university hospitals in Croatia.

Key words: intraventricular thrombolysis, intraventricular hemorrhage, external ventricular drainage

INTRODUCTION

Intraventricular hemorrhage (IVH) is a frequent life threatening complication of intracerebral hematoma, independently associated with a worse outcome. Routine treatment of IVH is external ventricular drainage (EVD) aiming to treat obstructive hydrocephalus followed by raised intracranial pressure. However, blood clot, formed inside the ventricles, slows clearance of the ventricles and very often leads to obstruction of drainage catheter compromising therapeutic effects of EVD (1,2).

The possibility of intraventricular thrombolysis of blood clot has been introduced for more than 10 years now and the results of several clinical studies show promising results. In all series, patients in the treatment group with thrombolytic agent achieved more rapid clearance of IVH as well as improved outcome compared with controls. In this article,

Intensive Care Unit, University Department of Neurology, Zagreb, Croatia

¹Zagreb University Hospital Center, University Department of Neurosurgery, Zagreb, Croatia

²Rijeka University Hospital Center, Intensive Care Unit, University Department of Neurology, Rijeka, Croatia

we present our first patient with IVH treated with thrombolytic agent (1-3).

CASE REPORT

Our 52-year-old hypertensive patient presented himself to emergency ward with left-sided hemiparesis, mild headache, and dysarthria. Computed tomography (CT) scan revealed a middle-sized typical intracerebral hematoma located in the right thalamic region with clear intraventricular hemorrhage as well, being most prominent in the fourth ventricle. The fourth ventricle appeared already on the first scan larger and rounder than normally expected, and lateral ventricles showed some early signs of hydrocephalus (Fig. 1). Based on the initial diagnosis, age of the patient and neuroradiological characteristics, EVD was considered. Our decision at this time was to treat the developing hydrocephalus. However, being aware of a large amount of blood in the fourth ventricle, we also considered intraventricular thrombolytic therapy after the position of the drainage catheter had been checked by follow up CT scan. As all inclusion criteria were met, without any of exclusion criteria according to our protocol, the patient received 1 mg of Actylise in the left lateral ventricle, followed by another 1 mg after 12 hours. Follow up CT scan performed immediately after the second dosage of recombinant tissue plasminogen activator (rtPA) showed remarkable clot resolution in the fourth ventricle without any radiological or clinical signs of therapy complications (Fig. 2). EVD was removed on the third day of the illness, and the patient was referred to rehabilitation institution 8 days after the treatment without any neurological complications and with clear improve-

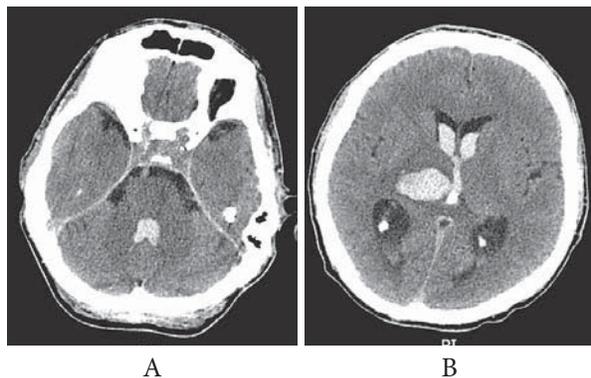


Fig. 1. Initial multislice computerized tomography (MSCT) showing intracerebral haemorrhage (ICH) with blood in ventricular system including lateral ventricles (B) as well as fourth ventricle, which is fulfilled with blood (A)

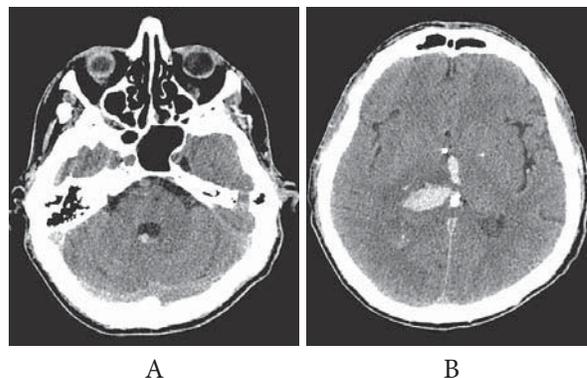


Fig. 2. Follow up MSCT performed after second dosage of rt-PA (14 hours after the initial MSCT scan) showing nearly a complete clot resolution from fourth ventricle (A) and significant reduction of blood in other ventricles (B). Note lack of perifocal edema around ICH as well.

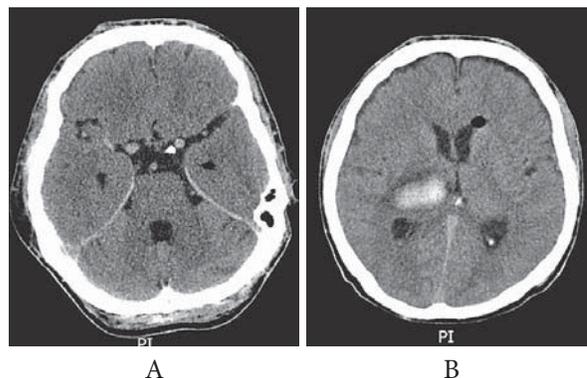


Fig. 3. MSCT on eight day of illness (patients referral to rehabilitation institution). Note complete resolution of blood in ventricular system (A & B) as well as just a mild perifocal oedema around ICH which is partly resolved. A small amount of air still remaining on the top of left lateral ventricle after removing the external ventricular drainage (B)

ment of neurological deficit, as well as marked radiological improvement of intracranial status (Fig. 3).

DISCUSSION

Thrombolytic therapy for IVH has evolved in response to the problems of catheter obstruction and slow IVH clearance, and has been shown to be safe and effective in animal studies and in small clinical case series. A systematic review of published retrospective case series comparing the outcome of conservative treatment, EVD and EVD combined with fibrinolysis in the setting of severe IVH due to subarachnoid hemorrhage or intracerebral hematoma showed that the fatality rate was 78% for conserva-

tive treatment, 58% for extraventricular drainage, and 6% for EVD with fibrinolytic agents. The poor outcome rate was 90% for conservative treatment, 89% for EVD, and 34% for EVD with fibrinolytic agents (1-3).

By now, there is strong evidence suggesting that thrombolytics used for the lysis of blood in the setting of IVH in humans may improve outcomes. The potential clinical benefits include faster reduction of IVH clot size, faster removal of blood from the ventricular system, reduction in the incidence of hydrocephalus, reduced time in coma, and improved outcome (significantly lower mortality rates). This may result in improved patient survival, reduction in the number of patients requiring long term shunting and reduced length of stay at intensive care unit. At this time, there is a clinical consensus that rt-PA is the most commonly used thrombolytic and studies are testing rt-PA in this setting. Future clinical trials using this drug are under way and rt-PA appears to be the drug for which the most accurate information about safety and efficacy will exist (1-3).

According to the protocol which was for the first time used in the Croatian setting (approved by local ethics committees), patients suitable for intraventricular thrombolysis should: 1) have diagnosis of IVH with no angiographic signs of intracranial aneurysm or arteriovenous malformation confirmed on multislice computerized tomography scan (MSCT) and MSCT angiography or magnetic resonance imaging (MRI) and MR angiography; 2) be younger than 65 years; and 3) be free from clinical or laboratory signs of coagulopathy.

There are a number of issues that must be resolved about the use of rt-PA in the setting of IVH, e.g., what dose and period of dosing is safest, when to stop treatment, and in which ventricle should the catheters be placed in order to achieve maximum clot reduction (4). The CLEAR-IVH program is assessing the efficacy of intraventricular rtPA for spontaneous intraventricular hemorrhage (4). This subanalysis assesses the effect of rtPA dose by region on clearance of IVH. Sixty-four patients within 12-24 hours of spontaneous IVH were randomized to placebo, 0.3 mg, 1 mg or 3 mg of rtPA twice daily *via* an extraventricular drain. Twelve subregions of the ventricles were scored 0-4. The effect of dose on IVH clearance to 50% (t50) of baseline score was compared by survival analysis for all regions combined and by subregions. The models including ventricular region, dose and baseline score were compared by Cox-Proportional

Hazards. IVH score reduced faster across all regions with increasing rtPA dose (t50: log-rank $p < 0.0001$; placebo 11.43 days, 95%CI 5.68-17.18; 0.3 mg 3.19 days, 1.00-5.38; 1 mg 3.54 days, 0.45-6.64; and 3 mg 2.59 days, 1.72-3.46). In combined models, the dose and baseline score were independently associated with reduction in IVH score, which was most rapid in midline ventricles, then the anterior half of lateral ventricles, and slowest in the posterior half of lateral ventricles (t50: $p < 0.0001$; rtPA dose: HR=1.47, 1.30-1.67; midline *vs.* anterior-lateral HR=1.71, 1.08-2.71; midline *vs.* posterior-lateral HR=4.05, 2.46-6.65; baseline score HR=0.96, 0.91-1.01), with a significant interaction between dose and ventricular region ($p = 0.005$). According to these results, a conclusion based on the study subanalysis was that rtPA clearly accelerated resolution of intraventricular hemorrhage. This effect is dose-dependent, and greatest in midline ventricles and least in posterior-lateral ventricles (4,5).

In our patient, we followed the Croatian model of treatment protocol (for the first time introduced at Rijeka University Hospital Center), which uses a relatively lower dosage of rt-PA (1 mg) each 12 hours routinely twice, exceptionally 3 times (6). Our patient showed a surprisingly fast and complete clot resolution of IVH, especially considering localization of blood clot (fourth ventricle). This result poses even more questions about correct dosing and timing of drug application (in most studies, the best results were achieved with 3 mg of rtPA every 8-12 hours) as well as about the dynamics of intraventricular fluid (excellent clot resolution in the fourth ventricle with drainage catheter placed in the lateral one). One explanation of our good result of intraventricular thrombolysis might be a very early treatment (less than 6 hours after illness onset), when definite clinical and radiological signs of hydrocephalus had not yet been present. However, in order to be able to make a definite conclusion, much more data in a larger group of patients should be collected.

CONCLUSION

In our report, we witnessed an excellent outcome of a patient with hypertensive intracerebral and intraventricular hematoma after intraventricular thrombolysis. Further investigations in a larger number of patients with similar diagnosis have to be conducted in order to conclude about the efficacy and safety of this therapeutic method.

REFERENCES

1. Naff NJ, Williams M, Keyl PM *et al.* Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the Intraventricular Hemorrhage Thrombolysis Trial. *Stroke* 2011; 42: 3009-16.
2. Naff NJ, Hanley DF, Keyl PM *et al.* Intraventricular thrombolysis speeds blood clot resolution: results of a pilot, prospective, randomized, double-blind, controlled trial. *Neurosurgery* 2004; 54: 577-83.
3. Vereecken KK, Van Havenbergh T, De Beuckelaar W, Parizel PM, Jorens PG. Treatment of intraventricular hemorrhage with intraventricular administration of recombinant tissue plasminogen activator: a clinical study of 18 cases. *Clin Neurol Neurosurg* 2006; 108: 451-5.
4. Staykov D, Wagner I, Volbers B *et al.* Dose effect of intraventricular fibrinolysis in ventricular hemorrhage. *Stroke* 2011; 42: 2061-4.
5. Webb AJ, Ullman NL, Mann S, Muschelli J, Awad IA, Hanley DF. Resolution of intraventricular hemorrhage varies by ventricular region and dose of intraventricular thrombolytic: the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) program. *Stroke* 2012; 43: 1666-8.
6. Dunatov S, Antončić I, Bralić M, Jurjević A. Intraventricular thrombolysis with rt-PA in patients with intraventricular hemorrhage. *Acta Neurol Scand* 2011; 124: 343-8.

Address for Correspondence: Zdravka Poljaković, MD, Zagreb University Hospital Center, University Department of Neurology, Kišpatičeva 12, HR-10000 Zagreb, Croatia

Trombolitičko liječenje intraventrikulske hemoragije

SAŽETAK – Standardni pristup liječenju intraventrikulske hemoragije (IVH) i posljedičnog hidrocefalusa je vanjska drenaža ventrikula kombinirana s konzervativnom simptomatskom terapijom. Intraventrikulska tromboliza s rekombinantnim aktivatorom tkivnog plazminogena (rt-PA) je prvi puta uvedena u liječenje toga stanja prije oko deset godina. Od tada je prikazano mnogo kliničkih studija s različitim terapijskim protokolima intraventrikulske trombolize, koji su svi imali slične rezultate brzog otapanja intraventrikulskog ugruška i poboljšanja ishoda.

Prikazujemo naše prvo iskustvo s intraventrikulskom trombolizom kod mladog muškarca s IVH, koji je bio liječen u ranom stadiju bolesti i ishod bolesti bio je odličan. Osim toga prikazujemo prijedlog hrvatskog protokola intraventrikulske trombolize koji su odobrila etička povjerenstva dviju hrvatskih kliničkih bolničkih centara.

Ključne riječi: intraventrikulska tromboliza, intraventrikulska hemoragija, vanjska ventrikulska drenaža