Intraventricular recombinant tissue plasminogen activator for lysis of intraventricular haemorrhage

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Abstract

A prospective series of 20 patients with moderate to severe intraventricular haemorrhage (IVH) was studied for the effect of intraventricular administration of recombinant tissue plasminogen activator (rt-PA) on reduction of haematoma volume and prognosis. On the day of haemorrhage ventriculostomy was performed and 2 to 5 mg of rt-PA were injected via the external ventricular drainage, followed by drainage closure for two hours. In 14 patients rt-PA treatment was repeated. Computed tomography showed complete clot lysis or substantial reduction of intraventricular haematoma volume in 19 patients within 96 hours; the clearance of the third and fourth ventricle preceded the clearance of the lateral ventricles. Decrease of ventricular enlargement was seen in all but one patient with initial ventricular dilatation. Increase of haematoma volume and ventricular size was found in one patient. Outcome was minor or no neurological deficit in nine patients, disabling neurological deficit in six patients, and vegetative status in four patients. One patient did not survive the IVH. Intraventricular treatment with rt-PA seems effective in rapid lysis of intraventricular haematoma and normalisation of impaired CSF circulation. This treatment may contribute to an improvement in prognosis of moderate to severe IVH.

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Accompanying intraventricular haemorrhage (IVH) aggravates the prognosis of intracerebral and aneurysmal haemorrhage.¹⁻⁴ Haemorrhage extending into all ventricular chambers results in mortalities ranging between 60% and 91%.⁵⁻⁷ Even for partial haematocephaly mortality rates of 32.2% to 44% were reported.^{6,8} Neurosurgical treatment including continuous ventricular drainage and transcortical evacuation of the haematoma was not effective in improving the poor prognosis of IVH.⁹ Serial CT studies showed spontaneous resolution of IVH within three weeks.¹⁰ Recent clinical trials have shown that urokinase and recombinant tissue

plasminogen activator (rt-PA) given intraventricularly achieve reduction of intraventricular haematoma within a few days.¹¹⁻¹³ The present study was undertaken to evaluate how the outcome could be influenced by accelerated intraventricular haematoma resolution and to assess the efficacy and safety of intraventricular fibrinolytic treatment with rt-PA.

Materials and methods

PATIENT POPULATION

Twenty patients with moderate to severe IVH diagnosed by CT were studied. There were 10 women and 10 men (age range 25 to 78 (mean 54)). In eight patients, IVH was due to rupture of an angiographically verified aneurysm of the anterior communicating or internal carotid artery. In nine patients, IVH was the result of penetration of intracerebral haematoma into the ventricles. The spontaneous brain haemorrhage was associated with hypertension in five patients and with arteriovenous malformation in four patients. In two cases the aetiology of the bleeding remained unknown despite angiography and MRI (table 1).

In 14 patients the IVH extended into all ventricles, in five patients the haematoma filled the third and fourth ventricle and a single lateral ventricle. In one patient the blood was distributed in both lateral ventricles and in the third ventricle. The grading system proposed by Graeb *et al* was used to assess the severity of the IVH (table 2).⁶ According to the grading system, nine patients presented with moderate IVH (score 5-8) and 11 patients with severe IVH (score 9-12) (table 1). The ventriculocranial ratio (ratio of the width of the ventricles between the caudate nuclei to the width of the brain at the same level) was calculated for evaluation of the ventricular size. The ratio of 0.155 was considered to be the upper limit of the normal.¹⁴ All but two patients presented with ventricular dilatation (mean 0.23).

All patients were admitted with impaired consciousness and nine were comatose. The Glasgow coma scale (GCS) score ranged from 3 to 14 (mean 8.5).¹⁵ The patient outcome was evaluated 30 to 60 days after IVH according to the Glasgow outcome scale (GOS).¹⁶

TREATMENT PROTOCOL

Informed consent for this study was obtained from or for each of the 20 patients. In all patients continuous ventricular drainage

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Table 1 Demographic and clinical characteristics and summary of results of 20 patients with moderate to severe intraventricular haemorrhage undergoing fibrinolytic intraventricular treatment with recombinant tissue plasminogen activator (rt-PA)

Case No	Age (y), Sex	Cause of IVH	Treatment days	total rt-PA dosage	Graeb score† pretreatment	Graeb score† post-treatment	VCR‡ pre-treatment	VCR‡ post-treatment	Initial GCS	GOS
1	52,M	ICH	1	5	7	2	0.18	0.14	13	3
2	70,F	ICH	2	5	11	3	0.19	0.18	4	3
3	55,F	ICH	2	9	6	1	0.20	0.15	13	2
4	64,M	ICH	1	5	12	12	0.28	0.38	6	5
5	57,M	ICH	3	9	7	2	0.15	0.12	11	2
6	47,M	ACoM aneurysm*	4	20	12	3	0.31	0.20	5	3
7	78,F	ICA aneurysm*	2	10	7	2	0.28	0.22	3	4
8	53,M	ACoM aneurysm*	3	5	9	4	0.20	0.12	3	4
9	40,F	ACoM aneurysm*	2	7.5	12	3	0.25	0.13	4	3
10	48,F	ICA aneurysm*	1	5	10	3	0.22	0.04	4	2
11	63,F	ACoM aneurysm*	3	9	11	3	0.25	0.18	9	3
12	63,F	ACoM aneurysm*	1	5	6	0	0.18	0.15	14	1
13	41,M	ACoM aneurysm*	2	10	8	3	0.28	0.20	3	4
14	25,F	Temporoparietal AVM	2	7.5	12	0	0.24	0.13	9	1
15	58,M	Temporoparietal AVM	1	2	9	1	0.02	0.02	14	1
16	30,F	Thalamic AVM	3	7.5	10	0	0.34	0.21	5	4
17	65,M	Frontoparietal AVM	3	6	11	6	0.25	0.14	13	3
18	43,M	Trauma	3	15	5	3	0.24	0.23	13	2
19	56,M	Unknown	1	5	6	0	0.24	0.19	13	1
20	67,F	Unknown	2	10	8	2	0.24	0.19	11	2

*Definitive haemostasis obtained before fibrinolytic intraventricular treatment with rt-PA.

†Table 2 shows the grading system of Graeb *et al* for assessment of the severity of IVH⁶; VCR = ventriculocranial ratio: for grading system and normative data see text; GCS = Glasgow coma score¹⁵; GOS = Glasgow outcome score.¹⁶

was placed through a frontal twist drill hole immediately after diagnosis of the IVH. The correct intraventricular positioning of the ventriculostomy needle was confirmed in all but one case by CT before rt-PA infusion. Two to 5 mg of rt-PA were slowly injected via the ventriculostomy needle, followed by two hours of drainage closure. After reopening the ventricular drainage, the CSF was drained without a pressure gradient. Computed tomography was performed 16 to 24 hours after injection of rt-PA. The fibrinolytic treatment was continued until appreciable reduction of the haematoma volume in the lateral ventricles and clearance of the third and fourth ventricles were confirmed; in seven patients the rt-PA injections were repeated once, in six patients three injections of rt-PA were required. One patient received four injections of rt-PA. In patients with intraventricular haematoma due to ruptured aneurysm, haematoma lysis was initiated after clipping the aneurysm. In patients with IVH due to arteriovenous malformation, fibrinolytic treatment preceded excision of the angioma. In all patients the rt-PA treatment was started 12 to 48 hours after onset of the symptoms. Coagulation profiles were obtained before and after rt-PA treatment to rule out any systemic coagulopathy.

Table 2 Grading system for assessment of severity of intraventricular haemorrhage⁶

<i>Lateral ventricles (each ventricle is scored separately)</i>	
Trace of intraventricular blood or mild bleeding:	score 1
Less than half of the ventricle filled with blood:	score 2
More than half of the ventricle filled with blood:	score 3
Ventricle filled with blood and expanded:	score 4
<i>Third and fourth ventricles (each ventricle is scored separately)</i>	
Blood present, ventricle size normal:	score 1
Ventricle filled with blood and expanded:	score 2

Maximum score = 12.

Results

Complete removal or substantial reduction of haematoma size in the lateral ventricles was achieved in 19 of 20 patients within one to three days (mean 1.8 days). In the cases of incomplete clearance, the remaining blood did not exert local mass effect. In 19 of 20 patients the blood clots in the third and fourth ventricles were completely lysed in one to two days (mean 1.2 days) after initiation of the intraventricular rt-PA treatment (figure). In all cases the size of the accompanying intracerebral haematoma remained unchanged. Decrease of ventricular enlargement was seen in all but one patient with initial ventricular dilatation. The ventriculocranial ratio improved from a mean of 0.23 (pretreatment) to 0.17 (post-treatment) (table 1). In one patient with IVH extending into all ventricular chambers and rapid neurological deterioration, bilateral ventriculostomy was performed. Without confirmation of uneventful ventriculostomy by CT, 2.5 mg of rt-PA were injected into both lateral ventricles. Computed tomography obtained 16 hours after rt-PA treatment showed an increase in haematoma volume and ventricular ratio. In this patient as well as in the other patients systemic coagulopathy was ruled out. There were no other complications related to intraventricular rt-PA treatment.

In all patients the ventriculostomy needle remained patent during the period of external CSF drainage. The ventricular drain was removed after a mean duration of 23.3 days. Eleven patients developed progressive hydrocephalus after ventriculostomy removal and required ventriculoperitoneal shunt placement.

Four patients recovered completely (GOS 1) and five patients showed only minor neurological deficits (GOS 2). Six patients exhibited incomplete recovery (GOS 3). Four patients became vegetative (GOS 4), and

Computed tomography in a 47 year old man (patient 6) who presented with severe disturbance of consciousness and decorticate posturing. Admission CT showed a severe intraventricular haemorrhage and subarachnoid haemorrhage caused by an angiographically verified aneurysm of the anterior communicating artery. Upper: CT obtained immediately after aneurysm clipping and before first intraventricular injection of 5 mg of rt-PA. Upper, centre: CT obtained 24 hours after aneurysm clipping and first intraventricular injection of 5 mg of rt-PA. Lower, centre: CT obtained 24 hours after second intraventricular injection of 5 mg of rt-PA. Lower: CT obtained 48 hours after the third and 24 hours after the fourth injection of 5 mg of rt-PA showing only traces of blood in both lateral ventricles and appreciable reduction of ventricular size.

one patient did not survive the IVH (GOS 5; table 1).

Discussion

CAUSES AND NATURAL HISTORY OF IVH

Forty six to 62% of intraventricular haematomas result from penetration of a hypertensive or arteriosclerotic intracerebral haemorrhage into the ventricles.^{5 17} Nineteen to 29% of IVHs are caused by rupture of cerebral aneurysms, predominantly arising from the anterior communicating artery and the anterior cerebral artery.^{5 6} Less frequent causes of IVH are periventricular arterio-

venous malformations, head trauma, and tumours.

Intraventricular haemorrhage carries a poor prognosis. The mortality for IVH is related to the amount of intraventricular blood and increases from 32.2% in cases with mild haemorrhage to 91% in cases with complete haematocephalus.^{4 6 9}

PATHOPHYSIOLOGY OF IVH

A consequence of intraventricular bleeding is impaired circulation of CSF. Acute occlusive hydrocephalus and the direct mass effect of the intraventricular haematoma result in dilatation of the ventricular system. The

ventricular enlargement raises the intracranial pressure and reduces the periventricular cerebral blood flow. Mohr *et al* retrospectively studied 91 cases with aneurysmal IVH.³ The degree of ventricular enlargement correlated with the prognosis of aneurysmal IVH, indicating that ventricular enlargement is the major pathophysiological mechanism in IVH.

MANAGEMENT BY VENTRICULOSTOMY

Intraventricular haematomas are managed by external ventricular drainage with or without valve regulation.^{9 18 19} Rapid reduction of ventricular dilatation with consecutive improvement of intracranial pressure and cerebral blood flow is rarely achieved by ventriculostomy because the ventricular drainage usually does not effect the volume of the intraventricular haematoma and only unreliably drains the hydrocephalus because of frequent obstruction with clotted blood.^{9 11} Therefore external ventricular drainage failed to contribute to better outcome in IVH.⁹

FIBRINOLYTIC TREATMENT OF IVH

After successful lysis of experimental subtotal intraventricular haematoma in animal models with urokinase, Shen *et al* reported clot disappearance or its reduction to a minimum within five to six days in four patients with severe IVH after intraventricular injection of urokinase.^{20 13} The results were confirmed by Todo *et al*. They treated six patients with moderate to severe IVH by intraventricular infusion of urokinase; this resulted in clearance of the ventricles seven to eight days after haemorrhage. Eighty three per cent of the patients showed good to excellent outcome.⁷ After studies in primates and clinical trials had shown that intracisternal application of the fibrinolytic agent rt-PA is effective in lysing subarachnoid blood and preventing cerebral vasospasm, intraventricular infusion of rt-PA for treatment of moderate to severe IVH due to ruptured aneurysms and hypertensive intracerebral haemorrhage was performed recently in a small number of patients.^{12 21-27}

Our results show that disappearance of blood clots or clot lysis to a minimum is achieved within 24 to 72 hours after intraventricular injection of 2 to 5 mg of rt-PA per day. The normalisation of the ventricular enlargement (pretreatment mean ventriculocranial ratio 0.23; post-treatment mean ventriculocranial ratio 0.17) indicates that the successful clot lysis results in reduction of the direct mass effect and improvement in the circulation of CSF. The thrombolytic efficacy of rt-PA is higher than that of urokinase.²⁸ Intraventricular injection of 10 000 to 96 000 IU urokinase resulted in haematoma lysis within five to eight days, whereas intraventricular fibrinolytic treatment with 2 to 5 mg rt-PA achieved blood clot disappearance within one to three days.^{7 13} We prefer rt-PA to urokinase for treatment of IVH because the accelerated decrease of ventricular dilatation could help to reduce secondary brain damage.

COMPLICATIONS

In one patient with IVH and hypertensive brain haemorrhage the volume of the intraventricular haematoma increased after initiation of the rt-PA treatment. Because of a deviation from the treatment protocol, uneventful bilateral ventriculostomy was not confirmed by CT in this patient before intraventricular rt-PA injection. It remained unclear whether complication of ventriculostomy or an rt-PA induced rebleed caused haematoma enlargement. In our series as well as in the clinical studies of intracisternal and intraventricular application of rt-PA, systemic fibrinolysis or coagulopathy were not found.^{12 24 26}

Mayfrank *et al* reported one fatal meningitis related to treatment with intraventricular rt-PA.¹²

In our series and in the series of Mayfrank *et al* the volume of accompanying intracerebral haematoma remained unchanged during rt-PA treatment.¹² In the clinical studies of intracisternal application of rt-PA for the prevention of cerebral vasospasm after aneurysmal subarachnoid haemorrhage, epidural haematoma and increase in subarachnoid blood were noted but no intracerebral bleeding complication was found.^{26 29} These findings suggest that the fibrinolytic effect of rt-PA given intraventricularly is predominantly limited to the CSF pathways. Therefore, we believe that definitive haemostasis before the use of intraventricular rt-PA is not necessary in patients with an intracerebral source of bleeding.

PROGNOSIS

Our results suggest that efficacious haematoma lysis improves the poor prognosis of moderate to severe IVH. The mortality of 5% in our series is much lower than the mortalities of 60% to 91% in patients with moderate to severe IVH not subjected to intraventricular fibrinolytic treatment. Hypertensive or arteriovenous malformation associated intracerebral haemorrhage and aneurysm rupture also cause direct brain damage, which contributes to morbidity and mortality of IVH and is not influenced by intraventricular rt-PA treatment. Before accepting intraventricular rt-PA as standard treatment of IVH a placebo controlled randomised clinical study would be necessary to show that rt-PA is truly effective and success is not the consequence of selection criteria. From the ethical point of view a placebo controlled randomised trial is questionable. Fibrinolytic treatment would have to be withheld from severely ill patients to recruit the placebo group even though data highly suggestive of a beneficial effect of rt-PA already exist. To overcome this problem patients from whom informed consent was not obtained could be assigned to the placebo group. Until completion of the randomised trial the lower mortality in our series justifies the continuation of the relatively safe and easy intraventricular fibrinolytic rt-PA treatment for moderate to severe IVH.

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