Intraarterial Thrombolysis with r-tPA for Treatment of Anterior Circulation Acute Ischemic Stroke

Technical and Clinical Results

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Summary

To investigate factors effecting the safety and recanalization efficacy of local intraarterial (IA) recombinant tissue plasminogen activator (r-tPA) delivery in patients with acute ischemic stroke.

Eleven patients with anterior circulation acute ischemic stroke were treated. The neurological status of the patients were graded with the Glasgow Coma Scale (GCS) and National Institute of Health Stroke Scale (NIHSS). All patients underwent a computed tomography (CT) examination at admission. In addition four patients had diffusion-weighted and one patient had a perfusion magnetic resonance (MR) examinations. Patients were treated within six hours from stroke onset. Immediate, six hours, and 24 hours follow-up CT examinations were performed in order to evaluate the haemorrhagic complications and the extent of the ischemic area. The Rankin Scale (RS) was used as an outcome measure.

Two of the 11 patients had carotid "T" occlusion (CTO), nine had middle cerebral artery (MCA) main trunk occlusion. Four patients had symptomatic haemorrhage with a large haematoma rupturing into the ventricles and subarachnoid space. Of these, three patients died within 24 hours. The remaining seven patients had asymptomatic haematomas that were smaller compared to symptomatic ones, and showed regression in size and density on follow-up CTs. At third month five patients had a good outcome and three patients had a poor outcome.

In acute ischemic stroke, local IA thrombolysis is a feasible treatment when you select the right patient. Haemorrhage rate does not seem to exceed that occuring in the natural history of the disease and in other treatment modalities.

Purpose

Acute stroke is the third most common cause of death after cardiovascular diseases and cancer [1]. Strokes of ischemic origin are mostly secondary to arterial embolic occlusions and 75% occur in the carotid artery territory [2]. Brain tissue has low tolerance for ischemia. Cellular death in acute stroke depends on the vascular collaterals and not the occlusion itself. In the acute phase, the necrotic core is surrounded by a layer –ischemic penumbra- where cells have lost their function but not their viability. The possibility of saving these cells would mean the prevention of further neuronal cell death.

The success achieved in the treatment of acute myocardial infarction with thrombolytic therapy has brought this treatment in the field of cerebral diseases. Following the use of intravenous (IV) r-tPA, IA use, which theoretically provides more effective recanalization, has been put to use. The risk of haemorrhage, the uncertainty in the choice of suitable patients, technical and infrastructural insufficiencies

however, has forced local IA treatment to be used in a limited number of patients.

The purpose of this study is to use IA thrombolysis in suitable patients with acute stroke and to present our experience about the safety, dosage and timing of this agent, technical manipulations and equipment used.

Material and Methods

Eleven patients were treated by intraarterial thrombolysis between May 1999 and September 2002. Nine patients were female and two were male with an age range of 44-80 (mean 64). The demographical and clinical information about the patients are presented in table 1. Information about the procedure, the risks and benefits of the treatment were clearly explained to the families and written consent was obtained.

The GCS of the patients at presentation, the neurological grading by NIHSS, and RS were evaluated. The results of the procedure were followed up by immediate evaluation after treatment, at six and 24 hours, and then daily examinations. NIHSS and RS were used in the follow-up of results. A RS of 0-2 was considered good, and 3-5 as bad outcome, whereas 6 meant the patient was dead.

Non-contrast CT scan was performed for all patients to evaluate the presence of haemorrhage and ischemic signs. The CT scan was repeated for same purposes right after treatment and at six and 24 hours. The haemorrhages observed on the CT scans were classified as symptomatic and asymptomatic. Symptomatic haemorrhages were visible on CT, occured in the first 36 hours, and caused deterioration in the clinical situation of the patient (a rise of at least 4 points of NIHSS). Asymptomatic haemorrhages were visible on CT but caused no change in the clinical condition of the patient.

The CT findings that were considered to be due to acute ischemic changes were; hyperdense MCA, obscuration of margin of the lentiform nucleus, loss of insular ribbon, sulcal effacement, and presence of parenchymal hypodensities. Patients with parenchymal hypodensities were excluded from thrombolytic treatment except one patient with CTO who

Table 1 **Demographic data about the patients, angiography findings, and treatment results**

No	Sex-age	Time to arrive	Neurological status at arrival (GCS-NIHSS)	Angiography findings	Time to start thrombolysis (hr)	Recanalization n time (hr)	r-tPA Dose (mg)	Recanalization on result	Bleeding complications	Clinical results (RS)	
										24. hr	3. mo
1	F-76	2	12-20	L MCA	3,5	5	20	TR	SH	6	-
2	F-80	1,5	14-16	R MCA	3,5	5,5	20	TR	SH	6	-
3	F-76	2	15-15	R MCA	3	- (bleeding)	5	NR	SH	6	-
4	M-54	2	12-22	L MCA	2,5	3,5	18	TR	ASH	2	0
5	F-47	2	12-22	CTO	2,5	6,5	20	TR	ASH	5	4
6	F-63	2,5	10-21	R MCA	3	4,5 (plaque)	20	PR	ASH	4	4
7	M-44	4	13-17	CTO	4,5	6,5	30	TR	ASH	4	0
8	F-70	2	9-20	L MCA	3,5	5,5	25	TR	ASH	4	2
9	F-60	0,5	15-20	R MCA	2,5	4,5	20	TR	ASH	4	0
10	F-72	2	15-16	L MCA	3,5	- (plaque)	15	NR	SH	5	4
11	F-62	0,5	13-17	R MCA	1	2	10	TR	ASH	2	0

F: female, M: male, hr: hour, mo: month, L: left, R: right, GCS: Glascow coma scale, NIHSS: National Institute of Health Stroke Scale, MCA: middle cerebral artery, CTO: carotid "T" occlusion, TR: total recanalization, NR: no recanalization, PR: partial recanalization, SH: symptomatic haemorrhage, ASH: asymptomatic haemorrhage, RS: Rankin score

presented with a limited area of hypodensity in the frontoparietal area. The time for starting the intraarterial infusion instead of the time passed since the admission to the hospital was taken into account, and it was decided that no thrombolytic therapy would be administered beyond six hours following the stroke onset.

Diffusion MRI was also performed in four, and perfusion MRI in one patient following CT. After the thrombolytic therapy, early, 6 and 24 hour control diffusion MRI to the same four and control perfusion MRI to the same patients were performed to evaluate the new infarction areas and the perfusion after thrombolysis.

Angiography was only performed to patients who were selected as suitable for IA thrombolysis by clinical, CT, and MRI findings. On the concern of time, the study was directed to the vessel where the embolic occlusion was suspected to be. The diagnostic procedure was ended on the demonstration of the embolic area, and the other vessels were demonstrated after the end of the thrombolytic treatment.

Thrombolytic Procedure

After the diagnostic angiography, a 6F guiding catheter with continuous pressure infusion of isotonic saline was placed either in the common carotid artery (CCA) or in the internal carotid artery (ICA). A bolus dose of 2500 IU at the beginning of the procedure then 1000 IU hourly dose of heparin injection was administered to the patients. Rapid Transit microcatheter (Cordis, Johnson & Johnson, IS, FL) and Terumo 0.016 microwire (Terumo, Japan) combination was passes through the guiding catheter to reach the thrombus. Microcatheter was pushed to the distal end of the thrombus. Contrast was injected to visualize the exact localization and size of the thrombus and the condition of the vascular bed distal to the thrombus. The tip of the microcatheter was then pulled back into the thrombus and pressure infusion of isotonic saline and microwire manipulations were used to disintegrate the thrombus. The aim in this procedure was to try to maximize the area of thrombus facing the thrombolytic agent that was going to be applied later on.

Thrombolytic agent used was r-tPA (Actilyse, Boehringer Ingelheim) for all patients. The average dose used was 18.5 mg (range 5-30 mg). The procedure was ended in one patient when active haemorrhage was observed in the control angiography after 5 mg r-tPA was administered. In five cases, r-tPA was used at a standart concentration of 1 mg/ 1 ml, and with a dose of 1 ml/ 1 minute with pulse doses by 2 ml injectors. In six cases, the standart r-tPA concentration was diluted 10 to 1 with isotonic saline, and then given in the same way at a rate of 5 ml /minute. After every 5 mg infusion and three minutes of waiting time, control angiography was performed through the guiding and the microcatheter.

Thrombolytic therapy was ended when one of the following conditions were noticed: total recanalization, 30 mg r-tPA dosage, or a time of more than six hours had passed since the start of the acute attack. If there was a sign of haemorrhage in the control CT studies, no heparin infusion was used within the first 24 hours.

Results

The angiographic findings, treatment results, and clinical follow-up information are presented in table 1.

The mean time of hospital admission was 1,9 hours (range 0.5-4). GCS range was 9-15 (mean 12.7) and NIH score range was 15-22 (mean 18.7). Hyperdense MCA (n=5), loss of insular ribbon (n=10), lentiform nucleus contours (n=10) were common CT findings. Hypodensity in the hemispheric cortex was present in only one case with CTO. In three out of four patients that had a diffusion MRI, ischemia was only present in the basal ganglia, and in one patient it was located in the basal ganglia and the frontoparietal area (figure 1B). The same patient had a larger defect in the perfusion MRI (figure 1C). Two cases had CTO (figure 1,2). Five patients had right MCA and four patients had left MCA main trunk occlusions (figure 3).

Recanalization Results

The average time between hospital admission and the start of the angiography was 1.05 hours (range 0.5-2 hours). The procedure was terminated in one patient when active bleeding was detected. In two cases, recanalization of the MCA M1 segment displayed atherom plaques causing a vessel occlusion 60% and over 90% respectively. In these two cases, the procedure was ended without angioplasty, since the at-

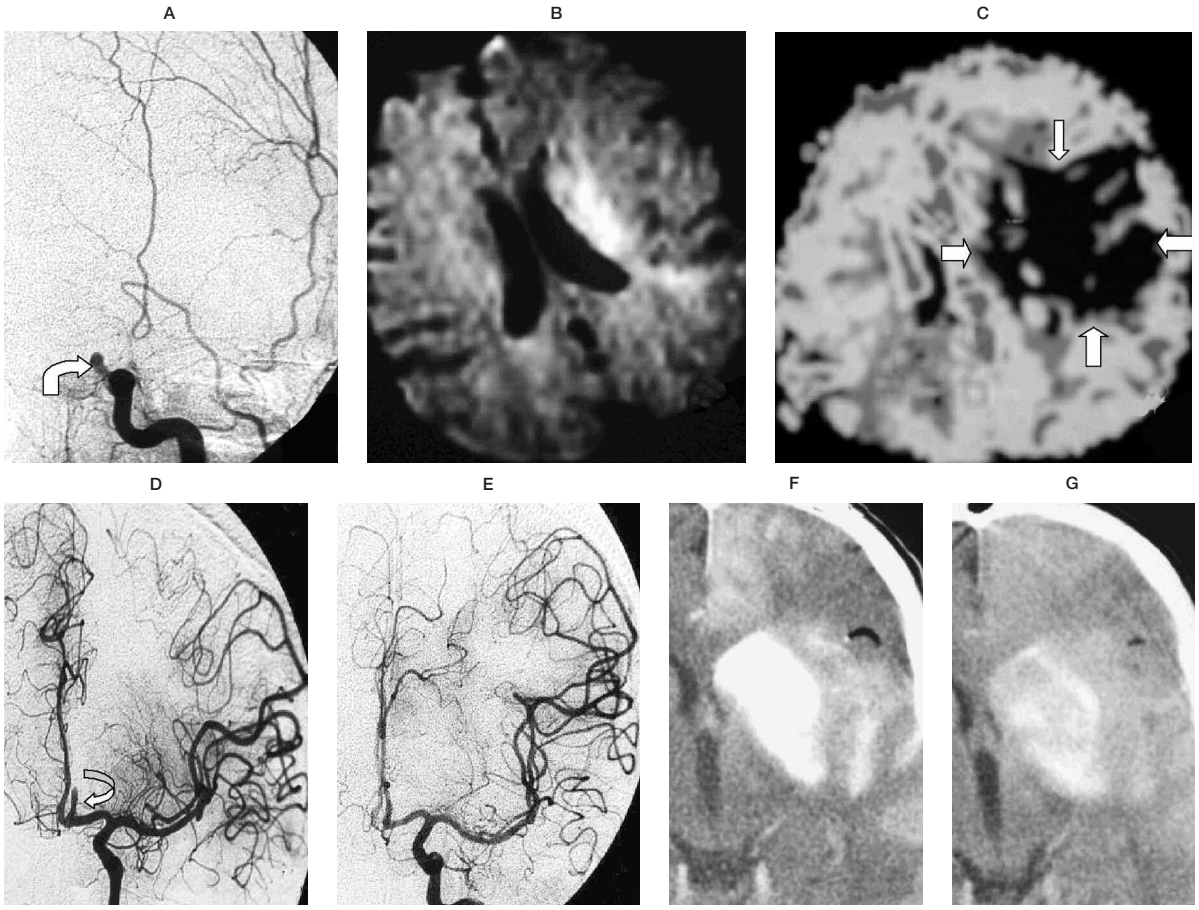

Figure 1 Case 5 A) Left internal carotid artery is totally occluded after the origin of the ophtalmic artery (right curved arrow). B) Diffusion-weighted MR examination (SE EPI TR/TE: 10000/102msn, B: 1000s/mm^2). Hyperintense ischemic area near the left lateral ventricle at the level of corona radiata. C) Blood flow volume mapping perfusion MR examination (SE T2* EPI TR/TE: 2000/60msn, ET: 1.2). Perfusion defect in a larger area (arrows). D) After 20 mg r-tPA at 6th hour of the attack MCA and contralateral ACA is recanalized, but the A2 segment of the ipsilateral ACA is still occluded (left curved arrow). E) After manipulations with microguidewire, A2 segment of the ipsilateral ACA is recanalized. F) Post-procedural CT examination. Hyperdense lesion at the level of the basal ganglia consistent with parenchymal haematoma associated with subarachnoid haemorrhage. G) Control CT examination after 6 hours. The original opacity is mainly due to contrast media. As the contrast media is absorbed, the density of the haematoma is decreased and haemorrhagic infarct area is visible.

herom plaque was located at the bifurcation and the vessel calibration was narrow. In the patient with severe stenosis, MCA was reoccluded after control angiography. The patient with moderate stenosis showed adequate filling of distal branches both in the control DSA and MR angiographies. In two cases with CTO and six cases with MCA main trunk occlusions, complete recanalization was achieved. The mean recanalization time after the start of thrombolytic therapy was 1.9 hours (range 1-4 hours).

Clinical Results

Three out of four patients that developed symptomatic bleeding during the procedure died within 24 hours (RS=6). The remaining eight patients 24 hour evaluations showed good outcome in two patients (RS=2); bad outcome in six patients (four patients RS=4, one patient RS=5). The 3-month controls of the living eight patients showed good outcome in five patients (four patients RS=0, one patient RS=2), bad outcome in three patients (RS=4).

Complications (Haemorrhage)

The immediate post procedural CT examination showed haemorrhagic complications in the area of the occluded vessel. Symptomatic haemorrhage was seen in four patients. All of these patients had intraparenchymal haematomas at the level of basal ganglia, rupturing into the ventricle and the subarachnoid space.

The mean maximum diameter of the haematomas was 5.6 cm (range 5-6 cm). The follow-up CT examination at 6 hours showed no significant change in the diameter of the haematomas (mean 5.3 cm) in three of these patients. One patient was lost peroperatively and had no follow-up examination. The average r-tPA dose for these four patients was 15 mg (range 5-20 mg), and the mean age was 76 (range 72-80). In patients with asymptomatic haemorrhage, six basal ganglia and one temporal lobar haematomas were seen. The mean maximum diameter of the haematomas was 2.5 cm (range 1-4.5 cm). The follow-up CT examination at 6 hours showed mean maximum diameter of the haematomas to decrease to 1.8 cm. Four of these seven patients had regression of the haematoma size, but there was a significant decrease in the density in all patients. The reason for this is the resorption of the contrast material that extravasated with blood. The post-procedural NIHSS in three of these patients was unchanged and in four patients the score showed a decrease. The average r-tPA dose for these patients was 20.4 mg (range 10-30 mg), and the mean age was 57.1 (range 44-70 years). The mean recanalization time in the patient group with symptomatic haemorrhage was 5.25 hours after the acute attack (range 5-5.5 hours), and it was 4,7 hours (range 2-6.5 hours) in the asymptomatic group. There was no difference between the two groups when the early ischemic signs on CT were concerned.

Discussion

Pre-procedural Patient Evaluation

The cerebral pathophysiological changes that occur in patients with acute stroke differ from case to case and within time. There is no clinical benefit in restoring perfusion in nonviable tissue. The risk of haemorrhagic transformation, which is the main complication of ischemic brain tissue, increases with reperfusion [3]. This is the reason why patient selection is the main issue in planned studies or personal case treatments by administering either IV or IA thrombolytic therapy.

The two largest studies performed by using IV thrombolysis are ECASS (European Cooperative Acute Stroke Study) and NINDS (The National Institute of Neurological Disorders and Stroke) and they treat patients in the first 6

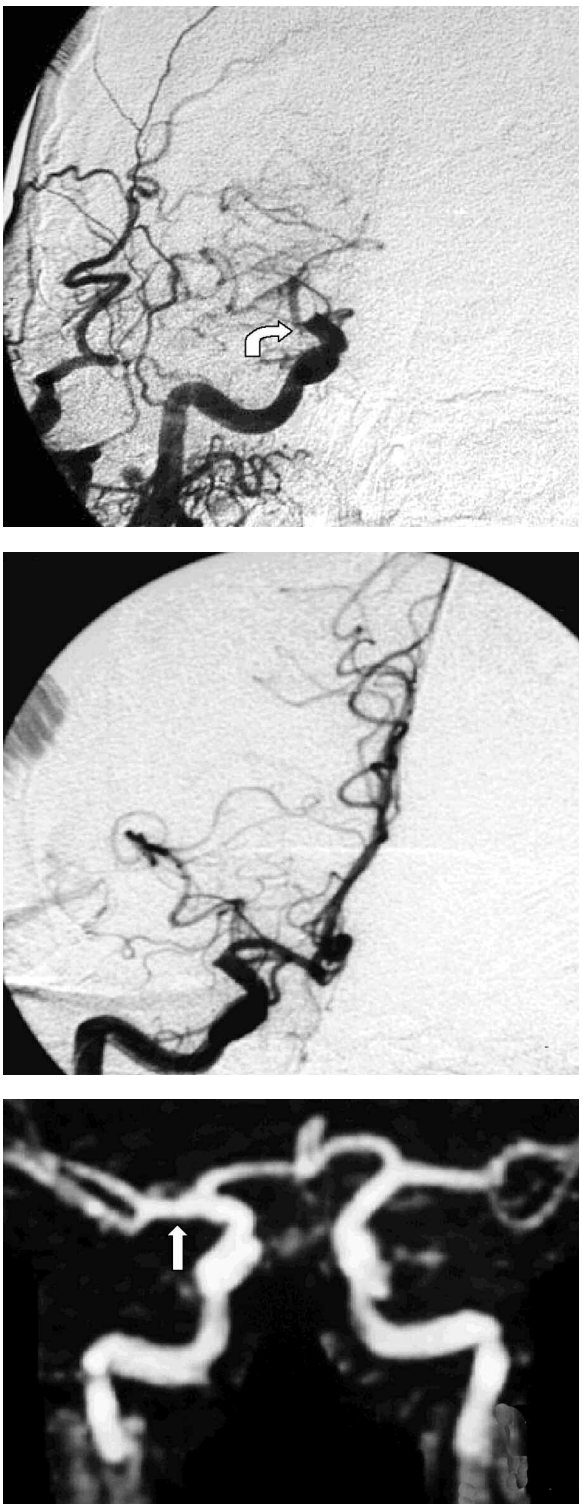

Figure 2 Case 7 A) Internal carotid artery is totally occluded distal to the ophtalmic artery origin (curved arrow). B) After 30 mg of r-tPA, only anterior cerebral artery is recanalized. There is no filling in the middle cerebral artery. C) Control MR angiography 6 hours after thrombolysis. The middle cerebral artery is recanalized (arrow).

hours and 3 hours respectively [4,5]. We accepted 6 hours as the last point to use r-tPA in our study.

CT is the first choice in evaluating the cases with acute stroke since it is widespread and quickly performed. It is used in planning antiaggregant and thrombolytic treatments because it has a high rate of successfully differentiating haemorrhagic and ischemic stroke cases. The mean time for CT examination to be performed was 2 hours (range 0.5-4 hours) after stroke onset in our cases. All but one case demonstrated hypodensities in the basal ganglia and loss of contour. Only one case had hypodensity in the hemispheric cortex. Data analysis of the NINDS study demonstrated that the arrival NIHSS along with the edema in CT and mass effect are two important factors for bad prognosis [6]. Von Kummer stated that hypodensity in more than 1/3 of the MCA area helps in determining grave prognosis and that this is an early sign of major ischemia [7]. In cases with parenchymal hypodensities in more than 1/3 area of the MCA, two out of 31 cases treated with r-tPA, and three out of 21 cases where placebo was used showed good prognosis. Five cases in the r-tPA group had fatal bleeding where there was none in the placebo group.

The early signs of ischemia on CT are usually indefinite, dependent on the quality of the examination, and it is usually not possible to correctly quantify the extent of the ischemia. The CT examination may be completely normal in the early phase of cerebral ischemia. Fast MR sequences like diffusion weighted MR are highly sensitive to the early changes in ischemia and has a high sensitivity and specificity in making the diagnosis. Changes in the diffusion-weighted sequences occur in minutes after the ischemic injury. The lesions are markedly separated from the surrounding normal brain tissue and older infarct areas. The therapeutic time window differs from patient to patient, and every patient might respond differently to the same treatment method independent of the time since the start of the attack. If diffusion weighted examination is used together with perfusion imaging, more rational patient selection can be made for thrombolytic therapy in acute stroke. Use of CT together with MRI however, is time consuming and more expensive. CT is invaluable in ruling out haemorrhagic causes of stroke. The findings about the accurate diagnosis of acute intraparenchymal haemorrhage by susceptibility-weighted GE or echo-planar T2-weighted sequences still remains to be proved [8]. In our practice, we use diffusion-weighted examination along with CT since our equipment has been updated. Although this provides extra cost, it is a fast sequence and does not cause a significant loss of time. We could perform perfusion imaging in only one patient. The remaining three patients lacked cooperation and perfusion imaging could not be performed.

Clinical Results

Conservative treatment of non-haemorrhagic stroke patients result in serious neurological deficit or death. The 30-day and five year mortality rates of anterior system territory stroke cases are 17% and 40% respectively [9]. Saito et al reported 78% mortality or serious neurological deficit rate and 9% good prognosis rate in their study of 33 cases with M1 occlusion [10].

NINDS study has an average patient age of 67, and pre-procedural average NIH score of 14. The third month controls showed good prognosis (RS=0-1) in 39% of cases [5]. ECASS study has an average patient age of 67, and pre-procedural average NIH score of 13 [4]. The third month controls showed good prognosis (RS=0-2) in 36% of cases. The mortality rates at 30 days are 17% and 13% respectively. Trouillas reported good prognosis (RS=0-1) rate of 45% in his study on 100 patients treated with IV r-tPA [11].

A high rate of recanalization is reported in the relatively small sized studies in the carotid artery system where the thrombolytic agent is administered directly into the thrombus intraarterially [12-14]. The rate of minimal or no neurological deficit is reported to be 15-75% in these patients. This wide range is thought to be due to a variety of different reasons. These include difference in grading system for prognosis, type of the thrombolytic agent and its dose, difference in patient demographics, and localization of the arterial occlusion.

The results of the first multicenter randomized trial, where a comparison of intraarterial recombinant prourokinase and placebo treatment is made, including patients with acute MCA stroke with angiographicaly proven M1 and M2 occlusions was reported in 1998 [15]. Clinical results were evaluated after 90 days and the good prognosis (RS=0-1) rate of 21% in the placebo group was found to be 31% in the

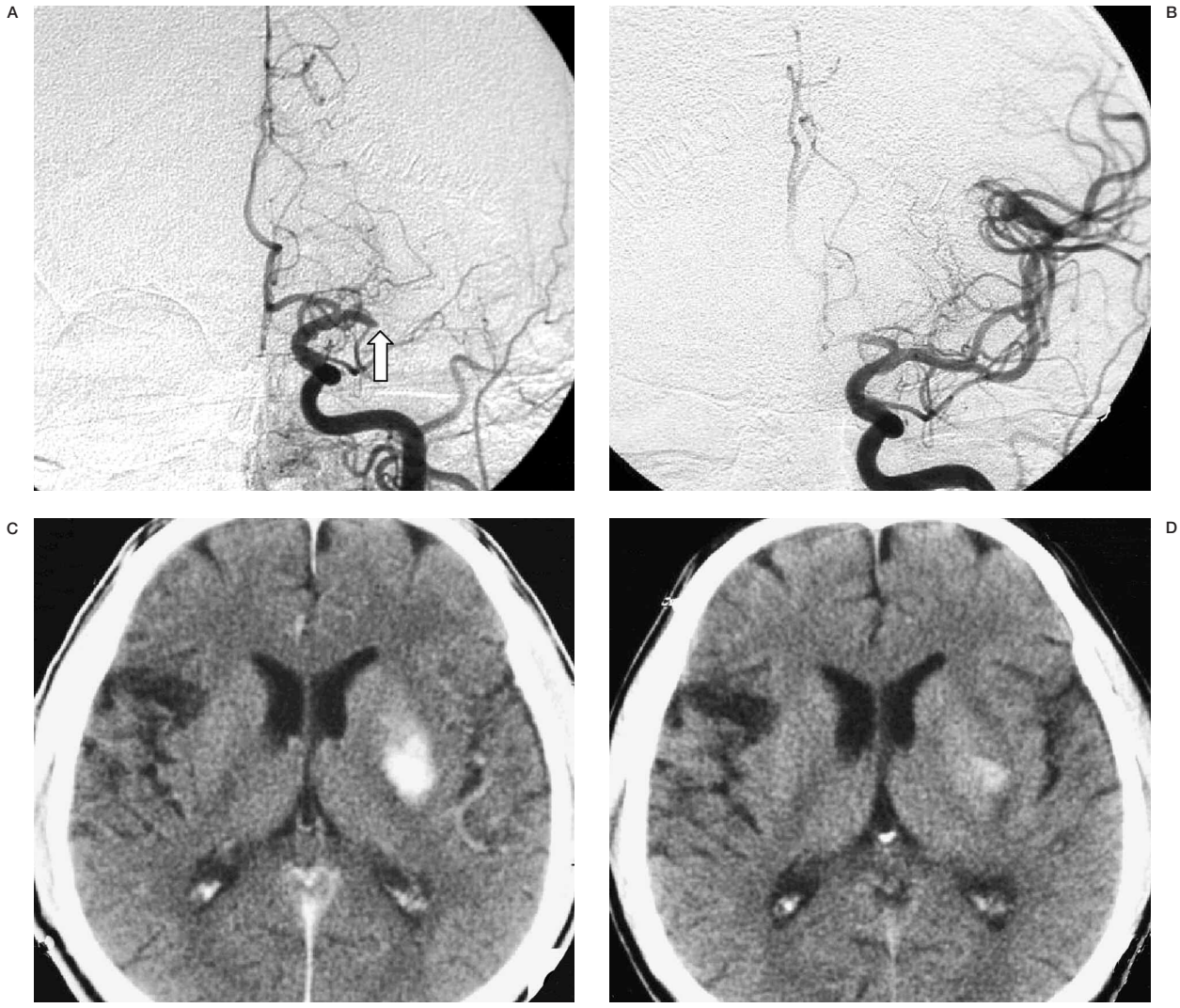

Figure 3 Case 4 A) Left sided middle cerebral artery main trunk occlusion (arrow). B) After 18 mg of r-tPA, middle cerebral artery and its cortical branches are recanalized. C) Early post-procedural CT examination. Hyperdense lesion in the lentiform nucleus consistent with haemorrhage. D) Control CT examination 6 hours after the procedure. The actual haemorrhage area is much smaller.

group receiving thrombolytic therapy. Jahan et al reported good prognosis (RS=0-2) in 48% of 26 patients with follow-up where they performed IA urokinase [16]. They stated that bad results and mortality risk increases with age (patients with good prognosis had a mean age of 48, patients with mortality had a mean age of 78). Keris reported a good result rate of 54% at 3 months in his study where he used IA and IV r-tPA concomitantly [17].

The mean pre-procedural NIH score of 11 patients in our study was 18,7 (range 15-22). In five cases (45%), prognosis at three months was good (RS=0-2), and in 3 cases the prognosis was bad. Three patients were lost in the first 24 hours after treatment due to intraparenchymal haemorrhage. It is difficult to assess our results because the size of our series is small. On the other hand, the neurological deficits of our patients are either worse or equal to the work published in the literature and the results are comparable. The mortality rate for carotid artery area stroke patients is reported to be 5-45% [18,19]. Our mortality rate is 27% and it is not any higher than other IA thrombolytic treatment studies in the literature [13,20,21]. As Jahan reported in his study, the main factor affecting mortality is patient's age. The mean age of pa-

tients who are alive is 59, whereas the mortal patients' mean age was 77. There was no significant difference between the mean age of patients with good and bad prognosis (58 vs. 60).

Kucinski et al reported CTO as the clinical condition with the worst prognosis [22]. Herniation secondary to brain oedema and haemorrhage secondary to thrombolytic therapy is more frequent in these patients. Zeumer reported that all eight patients with CTO died in his study where he compared occlusion types and clinical results [13]. Jansen reported death in 53% of his patients and bad prognosis in 31% of patients [20]. One of two patients in our group is in a totally independent condition with RS=0 at three months (figure 2). The other patient, although having a successful recanalization with hyperintensities limited to basal ganglia and neighboring frontal and parietal lobes on diffusion MRI, had to undergo decompression surgery 12 hours after the procedure due to oedemal herniation. The patient is dependent (RS=4) at three months (figure 1).

Recanalization

The primary aim in the treatment of stroke patients is to reestablish blood flow to limit the infarct area. The results of a metaanalysis state that early recanalization affects prognosis in a favorable way [23]. There are multiple time frames in these patients after the start of the attack for which the treatment team can interact to shorten: arrival at the hospital, evaluation at the emergency service, evaluation at the radiology unit, performing the diagnostic angiography, placement of the guiding catheter, infusion of the thrombolytic agent, and recanalization.

In the prospective randomized PROACT study comparing IA recanalization with conservative treatment, 58% (15/26) of patients showed partial or full (5/26) recanalization with IA treatment at 2 hours, where the same rate is 14% (2/14) in the placebo group (15). All of these cases are either M1 or M2 segment occlusions and there are no CTOs. Jahan reported a 42% recanalization rate with urokinase treatment (16). Only one of the 5 CTO cases was successfully recanalized.

Complete recanalization was achieved in 8 out of 11 (73%) of our cases. One of the two cases with atherom plaque in the MCA had restenosis in the early phase after recanalization and the procedure was ended with partial recanalization in the other patient. Balloon dilatation was not used in both of these cases due to technical reasons. Total recanalization was achieved in two cases with CTOs. The r-tPA dose was up to 30 mg in one case and after 6.5 hours, there was no recanalization in the MCA where the anterior cerebral artery was recanalized. The control MR angiography 6 hours after the procedure showed recanalization in the MCA (figure 2C). The r-tPA infusion was stopped at 20 mgs in the other patient when the 6-hour limit was passed. Although there was recanalization only in the A1 and M1 segments, there was partial recanalization in the distal branches. The procedure was continued with mechanical recanalization by microguidewire and at 6.5 hours total recanalization was achieved in the distal branches. (figure 1E). For this reason, we believe that the treatment should be more aggressive in CTO cases since the natural prognosis is poor.

Haemorrhage

Haemorrhage is the most important complication of the thrombolytic therapy that has an effect on the clinical results whether it is done by IA or IV ways. Although bleeding is classified as parenchymal haematoma and haemorrhagic infarction in most studies, it is better to name it symptomatic or asymptomatic to express their effects on the prognosis. In our patient group, all symptomatic haemorrhages ruptured into the ventricle and subarachnoid space. The mean maximun diameter of the haemorrhages in the symptomatic group were also bigger when compared to the asymptomatic group (5.6 vs 2.5 cm). The most important difference between IA and IV treatment methods is the evaluation of the haemorrhagic areas on CT. The contrast agent used during IA treatment may cause the haemorrhagic areas to appear more exaggerated, bigger, and denser. Some haemorrhagic infarct areas may present as parenchymal haematomas due to contrast agent extravasation (figures 1F,1G, 3C,3D). Major changes in the shape and density of the haemorrhage can be seen in follow-up examinations. Therefore, the bleeding types should better be evaluated according to the clinical results rather than morphological criteria. Early postoperative CT examination can be omitted unless the patient develops neurological deterioration with suspected massive haemorrhagical origin.

Endothelial damage occurs together with the neural parenchymal injury as a result of the ischemia in the infarct area. Reperfusion causes extravasation from the damaged vessel wall. Therefore the rate of haemorrhage increases as the recanalization rate increases. This is one of the reasons why haemorrhagic complication rates in patients treated with IA thrombolysis are higher since there is a higher rate of recanalization.

There is a lot of data in many of the studies about haemorrhage rates and effects on mortality, where thrombolytic treatment is performed. In the NINDS, symptomatic haemorrhage rate is 6.4% in the treated group compared with 0.6% in the placebo group [6].

In the ECASS data, it is stated that there is no significant difference in the rate of haemorrhagic complications between the treated group and the placebo group – 44% and 37% respectively-, but parenchymal haematomas are more frequent in the r-tPA group -19.4% against 6.8%-, and haemorrhagic infarcts are more frequent in the placebo group [4]. The rate of haemorrhage in the carotid artery area after IA thrombolysis is reported as 17%-56%. Symptomatic haemorrhage rate is 12 % in Jahan's study [16]. In PROACT, the bleeding rate in the prourokinase group is 42% (15% symptomatic) and the same rate is 7% in the placebo (a patient with symptomatic bleeding) [15]. The mortality rates of patients with haemorrhagic complications are high. Jahan reported a death rate of 62% in these patients compared with 23% in the non-haemorrhagic ones [16]. Another study states 65% haemorrhagic transformation rate in mortality cases compared with 26% in the survivors (22). The NINDS gives a 73% (16/22) mortality rate at 3 months in the symptomatic haemorrhage group. In our study, we experienced symptomatic haemorrhage in four (36%) patients and three of them were lost. There was no mortality in the seven patients with asymptomatic haemorrhage.

Because of the poor prognosis of patients with haemorrhage, establishing the predisposing factors can have aid in planning interventional procedures. The focal hyperdense area that can be seen on CT is reported to be the sign of haemorrhagic transformation, but there is no unity on this subject. The data from the ECASS proves that r-tPA treatment and advanced age increases the risk for parenchymal haematoma and the early signs of ischemia seen on CT and deterioration in neurological status increases the risk for haemorrhagic infarction [24].

The NINDS states that with the brain edema and mass effect seen on arrival CT, the poor neurological state of the patient at arrival (NIHSS>20) increases the risk of haemorrhage [6]. The PROACT proved similar results and all hypodensities covering more than one third of the MCA area had haemorrhage [15]. Kucinski and Wolpert on the other hand stated that early CT hypodensity has no value in approximation of damage [22,25]. When the patients with symptomatic and asymptomatic haemorrhage were compared in our study, there were no significant differences when arrival CTs, neurological status, treatment time, and r-tPA doses were compared. The only independent variable between the two groups was the patient age. The mean age for the group with symptomatic haemorrhage was 76, where it was 56.3 for the group with asymptomatic haemorrhage. This finding needs to be further studied for a possible future age limit for thrombolytic treatment administration. Urokinase, r-tPA, and recombinant prourokinase were used in different studies as thrombolytic agents.

Urokinase, when compared to r-tPA, has been used for a longer period of time and the safe doses are better known. There have not been sufficient randomized studies to provide safe doses for r-tPA. For this reason, it is difficult for us to determine the effect of the r-tPA doses on the haemorrhagic complications as independent variables. A dose of 20-40 mg has been suggested to be between safe limits in some studies [13,26].

We have tried not to exceed a r-tPA dose of 20 mg (mean 18.5 mg). One patient with CTO received a dose of 30 mg r-tPA because of the severity of the clinical condition without any haemorrhagic complications. However, a dose of 5 mg r-tPA have caused massive bleeding in one of our patients. Therefore, a certain level of safe dose of r-tPA can not be given for each individual patient.

Zeumer stated that 20 mg r-tPA is equivalent to 750 000 U urokinase on effect and safety (13). Cross et al reported a bleeding rate of 75% and 15% for patients with basilar artery thrombosis who are treated with r-tPA (4 cases) and urokinase (20 cases) respectively [27].

The doses used were 20-50 mg for r-tPA, and

250000-1750000 U for urokinase. They have used the ratios given in Zeumer's study when converting urokinase doses to r-tPA, and they have decided r-tPA to be unsafe in these doses.

Conclusions

IA thrombolysis is a challenging new treatment in acute stroke. Obviously, treating the wrong patient results in an unacceptably high rate of complications.

The most important factor affecting prognosis is the haemorrhagic complications. Therefore it is important to decide which patient will benefit from treatment and which patient has a high risk of haemorrhage. We can state with our limited number of cases and the information published in the literature that patient age is the most important independent variable for haemorrhagic complications. In cases with CTO where the mortality rate is high, the treatment should be more aggressive.

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