The safety and efficacy of bridging full-dose IV-IA thrombolysis in acute ischemic stroke patients with MCA occlusion: A comparison with IV thrombolysis alone

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Aims. Early recanalization of the occluded cerebral artery is substantial for clinical improvement in acute ischemic stroke (IS) patients. The rate of achieved recanalizations using IVT is low. The aim of this study was to compare the safety and efficacy of bridging full-dose intravenous-intraarterial (IV-IA) thrombolysis to IVT alone in acute IS patients with occluded MCA.

Methods. Seventy-nine consecutive IS patients with MCA occlusion were treated either with IVT alone (historic controls, Group 1) or with full-dose IV-IA thrombolysis (Group 2). Stroke severity was evaluated using NIHSS, achieved recanalizations using transcranial Doppler (Group 1) or angiography (Group 2). Occurrence of ICH including SICH was evaluated after 24 hours. 90-day clinical outcome was evaluated using modified Rankin Scale (mRS).

Results. Group 1 consisted of 50 patients (24 males, mean age 70.8 ± 10.2 years) and Group 2 of 29 patients (14 males, mean age 67.8 ± 10.0 years). No difference was found in the initial NIHSS (median 16 vs. 17) and other baseline parameters including time from stroke onset to IVT. Patients treated with bridging therapy had a higher number of achieved MCA recanalization (75.9 vs. 32.0%, $P=0.0002$), similar number of SICH (6.0 vs. 6.9%, $P=1.000$) and 34.5% of them achieved mRS 0-2 versus 28.0% of patients treated with IVT ($P=0.546$). Patients with shorter TR had significantly better clinical outcome ($P=0.019$).

Conclusion. Bridging IV-IA thrombolysis seems to be safe and more effective than IVT alone in acute stroke patients with MCA occlusion.

Key words: ischemic stroke, middle cerebral artery, intravenous thrombolysis, intra-arterial thrombolysis, bridging therapy

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INTRODUCTION

Intravenous thrombolysis is considered to be an effective and safe therapy for acute ischemic stroke (IS) patients, and recently its use has been prolonged to the first 4.5 h from stroke onset^{1, 2}. Although, the early recanalization of occluded artery is substantial for clinical improvement and good outcome after IVT, patients presenting with large vessel occlusion have a high probability of poor outcome with low recanalization rates³⁻⁷. Recent retrospective analysis showed only 32.1% of early recanalizations of the occluded MCA after IVT documented by angiography or by transcranial Doppler (TCD) (ref.⁸).

Intra-arterial thrombolysis is more effective than IVT when the MCA main stem is occluded⁹⁻¹⁴. On the other hand, it may be associated with an increased frequency of early SICH, and a special experienced interventional team is required^{9,11}. Moreover, IAT is limited by the “door-to-needle” time, which may be longer than that in IVT because of the catheterisation time. The combination of IVT and IAT allows faster start of thrombolysis using

the IV route and the higher recanalization rate using the intraarterial approach.

The previously reported studies with this “bridging” combined IV/IA approach showed promising results using low-dosed (0.6 mg/kg) IV recombinant tissue plasminogen activator¹⁵⁻¹⁷. Nevertheless, only few studies have reported results with full-dosed (0.9 mg/kg) IV rt-PA (ref.¹⁸).

The aim of our study was to compare the safety and efficacy of a combination of full-dosed (0.9 mg/kg) IV rt-PA followed by IAT to historical controls treated with IVT alone in early recanalization of occluded MCA in acute ischemic stroke patients.

SUBJECT AND METHODS

Patients

A prospective observational single center study was conducted. Consecutive acute IS patients, treated between September 2004 and January 2011 at our stroke center, were included in this study. Before August 2008, all pa-

tients presenting with MCA (M1-2 part) occlusion were treated with IVT according to the valid guidelines¹⁹ and created the Group 1 (historic controls). Patients, who missed the 3-hour time window in this period, were treated with IAT alone. After August 2008, the combination of IVT and IAT was implemented as a treatment approach in patients with MCA (M1-2 part) occlusion documented on baseline magnetic resonance angiography (MRA) or computed tomography angiography (CTA) within 3 h from stroke onset and, within 4.5 h since January 2009 (after the update of ESO guidelines) (ref.²). All patients, who were treated with IV + IA thrombolysis, were enrolled in Group 2. Although since 2010, endovascular treatment using mechanical devices too has been implemented as a rescue therapy at our center, we did not include these patients in the study.

On admission, blood pressure was measured, electrocardiogram was recorded, and blood samples were taken. Clinical status was evaluated using the National Institutes of Health Stroke Scale by a certified neurologist. A brain imaging examination followed immediately. All patients underwent either CT including the CTA (Light speed, General Electrics, MA, USA) or MRI including MRA (Symphony, Siemens, Erlangen, Germany) of arteries of the circle of Willis.

Treatment

All patients received standard full dose IVT according to the valid guidelines^{1,2,19}. From August 2008 (after implementation of bridging therapy protocol), patients are transferred to the angiographic room, where standard digital subtraction angiography (DSA) of the aortal arch and cerebral arteries is performed via the femoral approach. Patients underwent general anesthesia or sedation. If MCA occlusion persisted, IAT was performed using a microcatheter (Progreat 2.7-2.9 F, Terumo Medical Corporate, Somerset, NJ, USA) navigated to the occluded MCA segment in proximity to the thrombus. The microcatheter tip was placed into the thrombus for thrombolytic administration. The presence of the occlusion and the range of collateral circulation was assessed using TICI (Thrombolysis in Cerebral Infarction) scale²⁰. Alteplase was applied in repeated 5-mg doses until arterial recanalization was confirmed by repeat angiography or until the total dose of 20 mg was attained²⁰. Each dose of 5 mg of Alteplase was applied in the form of 5 min lasting infusion. TICI scale was used for the evaluation of artery recanalization grade.

In patients treated with IVT alone, DSA was used for the evaluation of early recanalisation only in 3 of these patients. These were initially indicated for combined therapy and baseline arteriogram showed recanalization. In other IVT patients, transcranial Doppler (TCD) performed with diagnostic duplex 2-MHz was used within 2 h after the end of rt-PA infusion. The recanalization was defined using TIBI classification⁵ as flow grades 3 (partial recanalization, pulsatile signal with normal acceleration, mean flow velocity (MFV) decrease of > 30% compared to normal side and positive end diastolic flow), 4 (complete

recanalization, stenotic flow signal) or 5 (normal flow signal, no significant difference in velocities compared to the normal side).

In all patients, the recanalization status was evaluated after 24 h using CTA or MRA and the occurrence of ICH was assessed on CT or MRI. SICH was defined as a local or remote parenchymal hematoma (PH2 type), associated with an increase in ≥ 4 points in the NIHSS score or leading to death²¹.

Neurological deficit was evaluated using the NIHSS after 24 and 72 h, and the 90-day clinical outcome using the modified Rankin Scale (mRS). The mRS score of 0-2 points was considered a good clinical outcome. The early neurological improvement (ENI) was defined as a NIHSS score of 0 or 1 point at 24 h after treatment or a decrease of ≥ 4 points in NIHSS score 24 h after treatment. The clinical status of all patients was assessed by a certified vascular neurologist with experience in NIHSS and mRS scoring.

For the comparison, patients were divided into two groups; Group 1 (historic control group) consisted of patients treated with IVT only (including 3 patients with achieved completed recanalisation after IVT in "era" of bridging therapy) and Group 2 consisted of patients treated with combination of IVT + IAT.

Statistical analysis

SPSS software version 15.0 (SPSS Inc., Chicago, USA) was used for statistical analysis. Two-group comparison of demographic data was performed using chi-square and Mann-Whitney tests. Baseline clinical data, 24-h, 7-day neurological outcomes and 90-day clinical outcomes comparison was performed using the Mann-Whitney test for non-parametric values. The 90-day clinical outcomes were dichotomized (mRS 0-2 versus 3-6) and compared using the chi-square test. The recanalization rates after thrombolysis were compared using the chi-square test. Fisher's exact test was used for comparison of ICH incidence.

The multivariate logistic regression analysis (LRA) was used for testing the recanalization for the prediction of good clinical outcome (mRS 0-2) and also the following variables: age, sex, presence of diabetes mellitus (DM), normal admission serum level of glucose (≤ 5.6 mmol/L), smoking, presence of atrial fibrillation (AF), prior use of statins (STAT) and antiplatelets (AP), onset-to-treatment interval (OTI), baseline NIHSS and presence of ENI after 24 h.

The Mann-Whitney test was used to compare the recanalization time (RT) between patients with good (mRS 0-2) and poor (mRS 3-6) clinical outcome and between patients with presence or absence of ENI in the group treated with combined approach.

LRA was used for testing the RT for the prediction of presence of ENI after 24 h and for the prediction of good clinical outcome in the group treated with the combined approach.

All tests used alpha level of 0.05 for significance.

Ethics committee approval

Study protocol was in compliance with the Declaration of Helsinki (1975) and was approved by the Ethics Committee of our hospital.

RESULTS

Altogether 365 acute IS patients were treated with IVT between September 2004 and January 2011. The sample consisted of 79 consecutive acute IS patients (39 males, mean age 69.7 ± 10.2 years) with CTA or MRA documented MCA occlusion (M1-2). Fifty of them were treated with IVT only (historic controls, Group 1) and 29 of them were treated with the combination of IVT and IAT (Group 2). Patient demographic and baseline characteristics are shown in Table 1. No significant differences in baseline parameters were found between the groups.

Patients treated with the combination of IVT and IAT had significantly higher recanalization rate (including partial) than patients treated with IVT alone (75.9 vs. 32%, $P=0.0002$) (Table 2). In the IVT group, achieved recanalisation and was documented by TCD in 13 patients and in 3 patients by DSA (patients initially indicated for combined therapy, who had complete recanalization on baseline arteriogram). Complete recanalization was presented in 23.1% of these patients.

In the IVT+IAT group, 9 (31.0%) patients had partial (TICI 2A or 2B) and 13 (44.8%) patients had complete recanalization (TICI 3).

In patients treated with IVT + IAT, the mean recanalization time (interval from stroke onset to achieved recanalisation) was 277.8 ± 56.5 min with a median of 262.5 min (135 - 320 min).

No reocclusion was found on the follow-up CTA or MRA after 24 h.

Only an insignificant trend for a greater number of patients with ENI was found in the IVT + IAT group (Table 2), while no difference was found in NIHSS after 24 h and 7 days (Table 2). Patients in both groups had similar 90-day clinical outcomes including the number of patients with good outcome (mRS 0 - 2) as well as 90-day mortality (Table 2). In patients treated with combined approach, 4 out of 9 deaths occurred within 7 days. The SICH was the cause of death in 2 of them. In the following 2 patients, the brain edema after unsuccessful recanalization was the cause of death and in the others 5 patients, the cause of death was related to the remaining stroke severity associated with serious complications.

No difference was found in SICH occurrence between groups (Table 2). ICH occurrence was higher in patients treated with bridging therapy, but the difference was not significant ($P=0.068$) (Table 2).

The multivariate logistic regression analysis (LRA) showed the recanalization as a strong predictor for good functional outcome (OR: 17.4, 95% CI: 4.6-66.5, $P<0.0001$) (Table 3). In the IVT group, the LRA showed that recanalization was an even stronger predictor with OR: 31.0 (95% CI: 6.0-159.6, $P<0.0001$). Fisher's test

Table 1. Patient demographic and baseline characteristics.

	IVT patients	IVT + IAT patients	<i>P</i>
N	50	29	
Males	24 (48.0%)	14 (48.3%)	0.981
Age (years)	70.8 ± 10.2	67.8 ± 10.0	0.191
Baseline NIHSS (median)	16.0	17.0	0.125
DM	9 (18%)	6 (20.7%)	0.769
GLU	10 (20.0%)	5 (17.5%)	0.763
CHOL	31 (63.3%)	15 (57.7%)	0.637
AP	18 (36.0%)	12 (41.4%)	0.635
STAT	14 (28.0%)	4 (13.8%)	0.147
AF	30 (60.0%)	19 (65.5%)	0.626
Smoking	4 (8.0%)	2 (7.1%)	1.000
Systolic BP (mm Hg)	157.4 ± 16.4	159.0 ± 14.0	0.784
Diastolic BP (mm Hg)	83.6 ± 6.0	81.7 ± 7.9	0.277
OTI (min)	154.9 ± 32.8	168.0 ± 41.7	0.237

AF = presence of atrial fibrillation, AP = prior use of antiplatelet therapy, BP = blood pressure, DM = presence of diabetes mellitus, GLU = normal admission serum level of glucose (≤ 5.6 mmol/L), CHOL = normal serum level of cholesterol (≤ 5.0 mmol/L), NIHSS = National Institutes of Health Stroke Scale, OTI = onset-treatment interval, STAT = prior use of statins

Table 2. Achieved results.

	IVT pts	IVT + IAT pts	<i>P</i>
Recanalizations	16 (32.0%)	22 (75.9%)	0.0002
ENI	13 (26%)	13 (44.8%)	0.135
NIHSS after 24 h (median)	15.5	17.0	0.775
NIHSS at 7 days (median)	12.0	14.0	0.463
MRS (median)	5.0	4.0	0.909
MRS 0-2	14 (28.0%)	10 (34.5%)	0.546
ICH occurrence	11 (22.0%)	12 (41.4%)	0.068
SICH occurrence	3 (6.0%)	2 (6.9%)	1.000
90-day mortality	12 (24.0%)	9 (31.0%)	0.305

ENI = Presence of early neurological improvement after 24 h, ICH = intracerebral hemorrhage, MRS = modified Rankin Scale at 90 days from stroke onset, NIHSS = National Institutes of Health Stroke Scale, SICH = symptomatic intracerebral hemorrhage

Table 3. Results of multivariate logistic regression analysis of baseline variables for the prediction of good functional outcome (mRS 0-2).

Variable	<i>P</i>	OR	95% CI
Age	0.856	0.989	0.881-1.111
Sex	0.445	0.224	0.005-10.416
DM	0.021	0.012	0.003-0.508
GLU	0.711	0.324	0.095-1.102
Smoking	0.271	1.027	0.979-1.072
AF	0.546	0.791	0.382-1.687
STAT	0.603	1.274	0.528-3.070
AP	0.955	0.998	0.975-1.028
OTI	0.431	0.980	0.930-1.030
Baseline NIHSS	0.013	0.513	0.303-0.870
MCA recanalization	0.0001	17.423	4.627-66.564
ENI	0.020	24.127	1.624-354.171

AF = presence of atrial fibrillation, AP = prior use of antiplatelet therapy, CI = confidence interval, DM = presence of diabetes mellitus, ENI = presence of early neurological improvement after 24 h, GLU = normal admission serum level of glucose (≤ 5.6 mmol/L), MCA = middle cerebral artery, NIHSS = National Institutes of Health Stroke Scale, OTI = stroke onset-treatment interval, STAT = prior use of statins

showed significant dependency of good outcome on recanalization ($P < 0.0001$).

From all analyzed baseline variables, LRA showed also the ENI, DM presence and the baseline NIHSS score as predictors of good outcome, but with lower predictive power (Table 3).

In the IVT + IAT group, the patients, who presented with ENI after 24 h, had significantly shorter time to recanalization (TR) (Table 4). Similarly patients, who had a 90-day good outcome (mRS 0 - 2), had significantly shorter RT, than patients with poor outcome (mRS 3 - 6) (Table 4). In this group analysis, LRA showed the RT as a strong predictor for ENI after 24 h (OR: 0.978, 95% CI: 0.957 - 0.9996, $P = 0.046$) and 90day good outcome (OR: 0.976, 95% CI: 0.953 - 0.999, $P = 0.041$).

Three procedure-related significant complications were registered. One patient suffered from subarachnoid hemorrhage after a perforation of cerebral vessel and two patients had transient arterial vasospasms during guiding and manipulation with the catheter, but without follow-up clinical consequences.

DISCUSSION

In the presented study, patients treated with combined full-dose IVT followed by IAT had a significantly higher recanalization rate of occluded MCA compared to historic controls treated only with IVT alone. The recanalization rate after IAT might have also been increased also

Table 4. Impact of recanalization time on presence of early neurological improvement after 24 h and on clinical outcome in patients with achieved recanalization after IVT + IAT.

	ENI	non-ENI	<i>P</i>
N	12	10	
RT (min)			
Mean + SD	223.3 ± 56.1	272.5 ± 36.3	
Median	212.5	265.0	0.019
	mRS 0 - 2	mRS 3 - 6	<i>P</i>
N	10	12	
RT (min)			
Mean + SD	217.5 ± 52.5	269.2 ± 43.0	
Median	212.5	265.0	0.019

ENI = early neurological improvement after 24 h, mRS = modified Rankin Scale, RT = recanalization time (interval between stroke onset and achieved recanalisation), SD standard deviation

by the insertion of the microcatheter tip into thrombus (partial mechanical disruption).

The number of achieved recanalizations after bridging therapy (75.9%) was slightly higher than the reported rates from previous studies with low-dosed IV rt-PA (ref.^{15,22}) and the rate from a recent study with full-dose IV rt-PA followed by IAT (ref.¹⁸). In contrast, in the RECANALIZE study, the recanalization was presented in 87% of patients treated with low-dose IVT followed by IAT (ref.¹⁷).

Although, patients treated with the bridging approach had a significantly higher rate of achieved recanalization compared to the historic controls in the presented study, they did not present with significantly greater number of ENI after 24 h (44.8% of patients) and also they did not have significantly better clinical outcome after 90 days (34.5% of patients). Similar findings were reported from the studies IMS Trial I and II and RECANALIZE study^{12,16,17}, however the absolute number of patients with good outcome was substantially higher in recanalize study compared to the presented results.

Generally lower number of patients with good outcome after bridging therapy (in spite of high number achieved recanalizations), may be affected by the length of RT. Although in our study, LRA showed that recanalization was an expected strong predictor for good functional outcome (Table 3) in patients treated with IVT + IAT, interestingly in the IVT group of historic controls, recanalization was found to be a far stronger predictor (with OR: 31.0, 95% CI: 6.0 - 159.6, $P < 0.0001$). This finding is consistent with the fact that recanalization achieved in the IVT group was earlier, than in the IVT + IAT group and proves that good outcome after successful recanalization is time-dependent²³. This also supports our finding, that IVT + IAT patients presenting with good 90-day outcome had significantly shorter RT, than patients with poor outcome (Table 4).

Concerning the safety outcomes in the presented study, patients treated with bridging therapy had a similar number of SICH compared to IVT alone and the number

of SICH (6.9%) did not differ from the results of previously reported studies¹⁵⁻¹⁸. A greater number of ICH in patients treated with IVT + IAT (41.4%) might be related to more frequent hemorrhagic transformation of ischemic lesion after successful recanalisation and also probably due to intra-arterial application of rt-PA.

Three-month mortality did not differ in IVT + IAT patients from patients treated with IVT alone (Table 2), but the number (31%) exceeded the reported numbers from the IMS trials (16%) and from the RECANALIZE study (17%) (ref.¹⁵⁻¹⁷). Nevertheless, most of our patients (77.8%) presented with unsuccessful recanalization and their cause of death was related to stroke severity with resulting severe complications. Rubiera et al. reported the 3-month mortality as in 50% of patients treated with the combination of full-dose IVT and IAT (ref.¹⁸).

A recently reported metaanalysis, which compared low-dose (0.6 mg/kg) and full-dose (0.9 mg/kg) rt-PA followed by IAT, suggested that using full-dose IV rt-PA prior IAT is safe and might be associated with higher recanalization rates and better functional outcome at 3 months than using of low-dosed rt-PA (ref.²⁴).

Our study has some limitations. Firstly, small study sample size with nonrandomized single center design might induce some bias. However no difference in demographic and baseline parameters was found between compared therapeutic groups. Secondly, two different imaging methods were used for the assessment of achieved recanalization with two different scales for the classification of recanalisation; TIBI scale for IVT patients and TICI scale for IVT + IAT patients.

CONCLUSION

The results showed, that bridging full-dose IV-IA thrombolysis significantly increased the recanalization rate of occluded MCA in acute ischemic stroke patients without increased SICH occurrence compared to IVT

alone. Shortening the recanalization time increased the chance for good clinical outcome. Results from large randomized trials are needed to confirm these findings.

ABBREVIATIONS

IAT, Intra-arterial thrombolysis; IVT, Intravenous thrombolysis; ICH; Intracerebral hemorrhage; LRA, Logistic regression analysis; MCA, Middle cerebral artery; NIHSS, National institutes of Health Stroke Scale; RT, Recanalization time (time to stroke onset to recanalization); SICH, Symptomatic ICH.

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