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ORIGINAL RESEARCH

MR Imaging–Based Localized Intra-Arterial Thrombolysis Assisted by Mechanical Clot Disruption for Acute Ischemic Stroke due to Middle Cerebral Artery Occlusion

K. Imai
T. Mori
H. Izumoto
M. Watanabe
T. Kunieda
N. Takabatake
S. Yamamoto

BACKGROUND AND PURPOSE: LIT-MCD is used in our institution for acute stroke due to MCA occlusion, with the goal of reducing symptomatic intracranial hemorrhage by maintaining recanalization of the occluded vessels. The purpose of the study was to investigate the safety and efficacy of LIT-MCD and to identify factors associated with a poor outcome in patients undergoing this procedure.

MATERIALS AND METHODS: LIT-MCD for MCA occlusion was performed in 90 of 1907 consecutive patients with acute stroke admitted to our institution. Radiographic data and clinical outcome were evaluated in the 90 patients, and factors predictive of a poor outcome (3-month mRS score, 3–6) were investigated by multivariate analysis.

RESULTS: Recanalization was achieved in 73 of the 90 patients (81%); symptomatic intracranial hemorrhage occurred in 7 (8%); procedure-related complications, in 9 (10%); and a favorable clinical outcome (3-month mRS score, 0–2), in 48 (53%). A high baseline NIHSS score (≥20), a low preprocedural ASPECTS on MR imaging (≤7), proximal M1 occlusion (in the horizontal segment of the MCA at or proximal to the lenticulostriate arteries), and no recanalization were significant predictors of a poor clinical outcome.

CONCLUSIONS: LIT-MCD is a safe and effective treatment for acute stroke due to MCA occlusion. However, further intervention is needed to improve the outcome of patients with proximal M1 occlusion.

ABBREVIATIONS: ASPECTS = Alberta Stroke Program Early CT Score; CFGS = collateral flow grading system; CI = confidence interval; DWI = diffusion-weighted imaging; ICH = intracranial hemorrhage; LIT = localized intra-arterial thrombolysis; LIT-MCD = MR imaging–based LIT using a low dose of urokinase and assisted by MCD; M1 = horizontal segment of the MCA; M2 = insular segment of the MCA; MCA = middle cerebral artery; MCD = mechanical clot disruption; MRI = MR imaging; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; rtPA = recombinant tissue plasminogen activator; TICI = Thrombolysis in Cerebral Infarction

LIT is regarded as an effective therapy that is mainly used for patients with stroke who are ineligible for intravenous administration of rtPA. Recently, LIT has also been attempted in cases resistant to intravenous rtPA.[1] In several case series,[2-9] MCD has been attempted in cases resistant to LIT alone to promote recanalization and shorten the time for completion of recanalization. Currently, another endovascular strategy, embolectomy, is the common clinical approach to recanalization therapy,[10] but MCD is still used with pharmacologic thrombolysis for an occluded lesion at a distal site or a lesion resistant to embolectomy. However, there are few data available for assessment of the efficacy of MCD in a relatively large and homogeneous population.

In Japan, LIT was the only method of recanalization therapy until intravenous administration of rtPA was approved in October 2005. Up to this time at our institution, LIT-MCD had been performed for acute stroke due to MCA occlusion. The purpose of the current retrospective study was to investigate the safety and efficacy of LIT-MCD for acute ischemic stroke due to MCA occlusion and to identify predictive factors for a poor clinical outcome to clarify the limitations of LIT-MCD and the need for further interventions.

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From the Department of Emergency Medicine (K.I.), Acute Stroke Center of Kyoto First Red Cross Hospital, Kyoto, Japan; Department of Stroke Treatment (T.M., H.I., T.K., N.T., S.Y.), Shonan Kamakura General Hospital, Kanagawa, Japan; and Department of Neurology (M.W.), Kumamoto University School of Medicine, Kumamoto, Japan.

Please address correspondence to Keisuke Imai, MD, Department of Emergency Medicine, Acute Stroke Center of Kyoto First Red Cross Hospital, 15–749 Honmachi Higashiyama Kyoto, 605-0981, Japan; e-mail: keisuke@qb4.so-net.ne.jp

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Materials and Methods

Patient Population

Of 1907 consecutive patients with acute ischemic stroke admitted to Shonan Kamakura General Hospital from April 2000 to January 2006, 90 (4.7%) with MCA occlusion fulfilling our inclusion criteria underwent LIT-MCD. A retrospective review of these patients was conducted. The study was approved by the institutional ethics committee.

Inclusion Criteria for LIT-MCD

Our criteria for use of LIT-MCD for MCA occlusion included patients who met the following criteria: 1) They were expected to receive the procedure within 6 hours of stroke onset; 2) they presented with neurologic symptoms defined by a baseline NIHSS score ≥5; 3) they had neither cerebral hemorrhage nor extensive infarction on T2-

weighted imaging and DWI; and 4) they had symptom-related MCA occlusion suspected from 3D time-of-flight MR angiography (TR/TE/flip angle, 28 ms/6.9 ms/20°) and proved by cerebral angiography.

LIT-MCD Procedure

The LIT-MCD treatment was approved by the institutional ethics committee, and informed patient or proxy consent was obtained before initiation of the procedure. After a diagnostic angiogram was obtained, systemic anticoagulation was initiated by intravenous administration of a bolus of 5000 U of heparin. A 6F guiding catheter was placed in the cervical segment of the ipsilateral internal carotid artery and a 0.016-inch microguidewire was advanced up to the occluded segment of the MCA. A microcatheter with a single end-hole was navigated over the wire into or close to the thrombus. Urokinase (60,000 U) was then injected manually through the microcatheter. If clot lysis occurred after administration of the first 60,000 U, an additional injection of urokinase was performed at the same position. The injection was repeated up to 240,000 U only when clot lysis occurred satisfactorily. At that time, if sufficient recanalization (TICI perfusion category of grade 2b)[11] was achieved and some residual clots were seen, an additional injection was administered up to a maximum dose of 420,000 U of urokinase with neither an injection of urokinase distal to the clots nor MCD.

If there was no clot lysis after the first or additional administrations of urokinase, LIT from a proximal site was interrupted and penetration of the thrombus was attempted with a microguidewire followed by the microcatheter, though this manipulation itself was not regarded as MCD. At the distal position, an additional injection of 60,000 U of urokinase was performed and LIT was continued if some clot lysis occurred. However, if further clot lysis did not occur with the additional injection of 60,000 U of urokinase or sufficient recanalization (TICI grade 2b)[11] had not been achieved when the dose of urokinase reached 240,000 U, MCD was performed by maceration with the microcatheter or angioplasty with a balloon catheter. For vessels of <2-mm diameter, maceration alone was attempted by passing the microcatheter tip back and forth through the thrombus over the microguidewire several times. When diagnostic angiograms after the procedure showed no or partial recanalization (TICI grade 0–2a)[11] an additional injection of 60,000 U of urokinase distal to the occlusion followed by maceration was repeated in an identical fashion up to a maximum dose of 240,000 U of urokinase, about half that of the maximum dose for LIT alone.

For vessels with a diameter of ≥2 mm, angioplasty with a balloon catheter was attempted instead of maceration. A 300-cm (0.014-inch) microguidewire and a low-profile 1.5- to 2.0-mm balloon catheter (Stealth, Maverick, or Gateway; Boston Scientific, Natick, Massachusetts) were used. The balloon was inflated slowly for 60–120 seconds, kept inflated at the target size for 10–15 seconds, and then deflated. Unless sufficient recanalization (TICI grade 2b)[11] was achieved with angioplasty, further MCD was attempted by moving the deflated balloon catheter back and forth through the thrombus over the long microguidewire and an additional 60,000 U of urokinase was subsequently injected through the end-hole of the balloon catheter at a site distal to the thrombus. Angioplasty, maceration with the balloon-catheter, and injection of urokinase distal to the thrombus were repeated in an identical fashion up to a maximum dose of 240,000 U of urokinase. In summary, the maximum dose of urokinase allowed was 420,000 U in patients treated with LIT alone, while it was 240,000 U in those treated with LIT followed by MCD.

The procedure was considered complete if angiography revealed the following: complete recanalization (TICI grade 3[11] in LIT alone, TICI grade 2b or 3 in LIT followed by MCD), the dose of urokinase reached a maximum (in LIT alone) and several attempts of MCD failed, the total time of the procedure was >2 hours, or severe procedural complications occurred. After the procedure, each patient was monitored closely in the intensive care unit for 24 hours. Systolic blood pressure was maintained at <180 mm Hg. Cranial CT was performed immediately, after 24 hours, and 7 days after the procedure. Therapy with 10,000 U per day of heparin was started after ruling out intracranial hemorrhage in the 24-hour cranial CT.

Pre- and Postprocedural Clinical and Radiographic Evaluations

Preprocedural neurologic deficits and brain damage were evaluated by NIHSS score and DWI, respectively. An NIHSS score ≥20 was taken to indicate a significant neurologic deficit. The degree of damage on DWI was analyzed by using the ASPECTS,[12] with ≤7 defined as a low ASPECTS on MR imaging.[13]

The location of occlusion in the MCA was determined by angiography and was categorized as proximal M1 (horizontal segment of the MCA), distal M1, and M2 (insular segment of the MCA). A proximal M1 occlusion was defined as at or proximal to the lenticulostriate arteries.[11] Development of collateral flow was evaluated angiographically by using grades 0–4 in the CFGS.[11] The degree of recanalization was evaluated angiographically by using TICI perfusion grades 0–3.[11] On the TICI scale, no recanalization, recanalization, and complete recanalization are defined as grades 0 and 1; grades 2a, 2b, and 3; and grades 2b and 3, respectively. Intracranial hemorrhage was diagnosed by cranial CT within 24 hours and was considered symptomatic if associated with clinical deterioration based on a change in NIHSS score of ≥4 points. All intracranial hemorrhage was defined as both symptomatic and asymptomatic. Clinical outcome at 90 days after the procedure was evaluated independently by doctors from another institution by using a mRS, on which 0–2 indicates a favorable outcome and 3–6 indicates a poor outcome.

Evaluation of Efficacy and Safety of LIT-MCD

Medical records and imaging studies were reviewed for the 90 patients in the study. The incidences of procedure-related complications and symptomatic intracranial hemorrhage and the rates of angiographic recanalization and favorable clinical outcome were determined to analyze the safety and efficacy of LIT-MCD, respectively.

Statistical Analysis

To identify predictive factors of poor clinical outcome in patients receiving LIT-MCD, we classified the 90 patients into 2 groups based on poor or favorable clinical outcome. The significance of intergroup differences was assessed by using a χ^2 test or Fisher exact test for categoric variables and an unpaired *t* test or Mann Whitney *U* test for continuous variables. After univariate analysis of potential predictors, multivariable analysis with logistic regression was performed to identify predictors of a poor clinical outcome. Variables with a univariate association of $P < .1$ were included as candidates in the multivariate logistic regression model and then were removed by backward stepwise selection to maximize sensitivity. Predictors that were significant at $P < .05$ were retained in the multivariate model. Associations are presented as ORs with corresponding 95% CIs. The Statistical Package for the Social Sciences, Version 10 for Windows (SPSS, Chicago, Illinois), was used for all analyses.

Results

The mean age of patients was 73 ± 10.5 years; and the mean onset-to-door, door-to-procedure, and onset-to-procedure times were 63 ± 59, 142 ± 35, and 205 ± 63 minutes, respectively. The median baseline NIHSS was 18 (range, 7–26). Occlusion at M1 was found in 49 patients (54%), including 20 and 29 cases at the proximal and distal M1s, respectively. The preprocedural TICI was grade 0 in 75 patients and grade 1 in 15, and the collateral flow was grade 1 in 8, grade 2 in 76, and grade 3 in 6 patients.

In the procedure, the median dose of urokinase was 240,000 U. MCD was used in 62 patients (68.9%), with maceration and balloon angioplasty performed in 14 and 48, respectively. Angioplasty was not performed in 2 patients: The microguidewire could not be passed across the occluded lesion in 1 patient and the balloon catheter could not be advanced due to severe atherosclerotic changes proximal to the occlusion in the other. The angiographic results showed postprocedural TICI grade 0 in 13, grade 1 in 4, grade 2a in 37, grade 2b in 23, and grade 3 in 13 patients. The rates of recanalization and complete recanalization were 81% and 40%, respectively. In the 36 cases of complete recanalization, 17 were achieved by LIT alone, and residual stenosis requiring additional angioplasty did not occur in any of the 17 patients. Recanalization was achieved in 13 of 20 (65%) patients with proximal M1 occlusion; 23 of 29 (79%) with distal M1 occlusion; and 37 of 41 (90%) with M2 occlusion. Complete recanalization was achieved in 6 of 20 (30%), in 11 of 29 (38%), and in 19 of 41 (46%) vessels with proximal M1, distal M1, and M2 occlusion, respectively.

Procedure-related complications occurred in 9 patients (10%). Vessel injury due to manipulation occurred in 5 patients. All occurred in MCD, during maceration in 1 patient, angioplasty in 2, and attempted angioplasty in 2. Extravasation in a recanalized region was diagnosed by angiography in 2 of the 5 patients and by CT immediately after the procedure in the other 3 patients. In the 2 patients diagnosed by angiography, protamine sulfate was administered intravenously and the procedure was aborted. The 4 other complications included clot migration to regions beyond the recanalization area in 1 patient during maceration and in 2 during angioplasty and extracranial bleeding at the puncture site requiring a blood transfusion in 1 patient.

Intracranial hemorrhage was detected in 27 patients (30%), including symptomatic intracranial hemorrhage in 7 (8%): after angioplasty in 5, after LIT alone by using 420,000 U of urokinase in 1, and during attempted angioplasty in 1 (a procedure-related complication). All 7 patients received conservative treatment because their family members refused a rescue operation; 5 of the 7 died of brain herniation resulting from hematoma, massive hemispheric infarction, or both within 7 days after the procedure.

mRS scores of 0–1 and 0–2 at 90 days were found in 25 (28%) and 48 (53%) patients, respectively. Eleven of the 90 patients (12%) died within 90 days after the procedure: Six deaths were due to brain herniation; 2, to pneumonia; and 1 each, to acute coronary syndrome, pulmonary embolism, and pancreatic cancer. Comparisons between patients with poor and favorable clinical outcomes are shown in Tables 1 and 2, and predictive factors for a poor clinical outcome in multivariate logistic regression analysis are shown in Table 3.

Table 1: Univariate statistics of background and intracranial hemorrhage for patients with poor clinical outcome and favorable outcome

	Clinical Outcome at 90 days		
	Poor (mRS, 3–6)	Favorable (mRS, 0–2)	*P*
No. of patients	42	48	
Age (yr, mean)	74.4 ± 8.9	72.3 ± 11.6	.313[b]
Sex (male)	28 (67%)	30 (63%)	.680[c]
OTP time[a] (min, mean)	209.2 ± 75.2	201.7 ± 50.2	.575[b]
Hypertension	25 (60%)	26 (54%)	.609[c]
Diabetes mellitus	11 (26%)	11 (23%)	.718[c]
Hyperlipidemia	7 (17%)	10 (21%)	.614[c]
Coronary disease	10 (24%)	8 (17%)	.398[c]
Peripheral arterial stenotic diseases	3 (7%)	2 (4%)	.661[d]
Previous stroke	11 (26%)	6 (13%)	.098[c]
Side of lesion (left)	30 (71%)	27 (56%)	.136[c]
B-NIHSS[e] (points, median)	20 (9–26)	14.5 (7–24)	.001[f]
No. of patients with high score of B-NIHSS (≥20 points)	24 (57%)	13 (27%)	.004[c]
Stroke etiology: cardiogenic embolism	32 (76%)	37 (77%)	.920[c]
ASPECTS on MRI (points, median)	7 (5–10)	8 (5–10)	<.001[f]
No. of patients with low ASPECTS (5–7)	27 (64%)	8 (17%)	<.001[c]
Administration of free radical scavenger	31 (74%)	33 (69%)	.597[c]
Symptomatic ICH within 24 hours	6 (14%)	1 (2%)	.047[d]
All ICH within 24 hours	17 (40%)	10 (21%)	.042[c]

[a] Onset to procedure time.
[b] Unpaired *t* test.
[c] χ^2 test.
[d] Fisher exact test.
[e] Baseline NIHSS
[f] Mann Whitney U test.

Discussion

Comparison with Previous Studies for LIT Alone or LIT Assisted by MCD

An indirect comparison with results from randomized trials with LIT alone for MCA occlusion[14,15] suggests a lower incidence of symptomatic intracranial hemorrhage (8%), a higher incidence of recanalization (81%), and a favorable clinical outcome (53%) in the present study. Differences in patient selection, vessel regions, and methods of recanalization limit comparison of our results with previous studies with LIT assisted by MCD or direct angioplasty for MCA occlusion,[2-9] but the baseline characteristics in this and the previous studies are similar. Procedure-related complications (10%), symptomatic intracranial hemorrhage (8%), recanalization (81%), and favorable outcome (53%) in our patients were similar to those found in previous studies, though the rate of complete recanalization (40%) was lower. Therefore, our results suggest that LIT-MCD can be used for recanalization of MCA occlusion in patients with acute stroke with acceptable safety and efficacy.

Table 2: Univariate statistics of angiographic results and methods of LIT-MCD for patients with poor clinical outcome and favorable outcome

	Clinical Outcome at 90 Days		
	Poor (mRS, 3–6)	Favorable (mRS, 0–2)	*P*
No. of patients	42	48	
Location of occlusion			
Proximal M1[a]	17 (41%)	3 (6%)	<.001[b]
Distal M1	12 (29%)	17 (35%)	.488[b]
M2[c]	13 (31%)	28 (58%)	.009[b]
No. of patients with			
Preprocedural TICI of grade 0	38 (90%)	37 (77%)	.089[b]
Poor collaterals (CFGS, grade 1)	6 (14%)	2 (4%)	.139[d]
Moderate collaterals (grade 2)	35 (83%)	41 (85%)	.786[b]
Ample collaterals (grade 3)	1 (2%)	5 (10%)	.209[d]
Dose of urokinase ($\times 10^3$ U) (mean)	237 ± 9.1	265 ± 10.0	.172[e]
Use of low dose of urokinase (≤240,000 U)	37 (88%)	33 (69%)	.028[b]
Use of mechanical clot disruption	37 (88%)	25 (52%)	<.001[b]
No recanalization (TICI grade 0 + 1)	15 (36%)	2 (4%)	<.001[b]
Postprocedural TICI grade			
0	12 (29%)	1 (2%)	<.001[b]
1	3 (7%)	1 (2%)	.336[d]
2a	18 (43%)	19 (40%)	.753[b]
2b	7 (17%)	16 (33%)	.071[b]
3	2 (5%)	11 (23%)	.015[b]
Procedure-related complications	5 (12%)	4 (8%)	.729[d]

[a] Indicates occlusion of the horizontal segment (M1) of the MCA at or proximal to the lenticulostriate arteries.
[b] χ^2 test.
[c] Insular segment of the MCA.
[d] Fisher exact test.
[e] Unpaired *t* test.

Table 3: Multivariable ORs and 95% CIs for predictive factors of poor clinical outcome

Variable	OR	95% CI	*P*
High score of baseline NIHSS (≥20)	4.67	1.44–15.12	.01
Low preprocedural ASPECTS (≤7)	5.8	1.81–18.64	.003
Proximal M1 occlusion[a]	8.78	1.83–42.24	.007
No recanalization (TICI 0–1)	15.41	2.54–93.48	.003

[a] Indicates occlusion of the horizontal segment of the MCA at or proximal to the lenticulostriate arteries.

Rationale for the LIT-MCD Approach

Older patients are often treated with recanalization therapy in Japan,[16] and these patients are reported to have a high risk for symptomatic intracranial hemorrhage after this therapy.[17] Therefore, the LIT-MCD protocol was designed to reduce the risk of symptomatic intracranial hemorrhage through patient selection based on DWI and restriction of the maximum dose of urokinase. Careful selection of candidates for recanalization therapy is essential to reduce the risk of symptomatic intracranial hemorrhage,[17] and DWI is an effective technique for decision-making in thrombolytic therapy.[18] Indeed, no apparent relationship was found between onset-to-procedure time and clinical outcome in the present study. Limiting urokinase is also important to reduce the risk of symptomatic intracranial hemorrhage,[17] and the median dose of urokinase in the present study was lower than that in a previous randomized study using LIT alone.[15]

One concern with restriction of urokinase is that it may simultaneously reduce the chance of recanalization. Therefore, to maintain a good rate of recanalization, MCD was introduced for an occluded lesion that was probably resistant to LIT alone. In a review of MCD, Nesbit et al[19] described its role in establishing rapid blood flow by fragmenting the thrombus and increasing cerebral perfusion when emboli created by MCD are small enough to pass through the distal circulation. Another role of MCD may be to increase the surface area of the thrombus exposed to thrombolytic agents,[19] and these 2 potential roles were the main reasons why we combined MCD with LIT. However, MCD may cause vessel injury during complex manipulation and may have deleterious downstream effects on the branches of the MCA or concomitant collaterals. Therefore, in the present study, MCD was not performed aggressively when sufficient recanalization was likely to be achieved by LIT alone.

Predictive Factors for a Poor Clinical Outcome of LIT-MCD

A high baseline NIHSS score (≥20), a low preprocedural ASPECTS on MR imaging (≤7), proximal M1 occlusion, and no recanalization were identified as significant predictive factors of a poor clinical outcome. Predictors of clinical outcome after MCD have not been analyzed, but factors associated with outcome after LIT alone have been evaluated in previous studies. Gönner et al[20] found that a good outcome at 3 months in 45 patients was associated with a baseline NIHSS score of <20, improvement by ≥4 NIHSS points within 24 hours, and vessel recanalization. Ueda et al[21] showed that poor outcome at 6 months in 76 patients was predicted by an NIHSS score of >20, cardioembolic infarction, low perfusion on single-photon emission CT, incomplete recanalization, and older age. The high baseline NIHSS score and no recanalization identified as predictive factors for a poor outcome in the present study are consistent with these findings. The low preprocedural ASPECTS on MR imaging reflects severe primary brain damage due to ischemia, similar to a previous finding that a low ASPECTS on CT reflected such damage.[12] In patients with such damage, clinical recovery will not be achieved even if early recanalization after LIT-MCD is established; therefore, this predictive factor may suggest an over-indication in the present study. Indeed, Kimura et al[22] suggested that patients with a DWI ASPECTS of >5 should be considered eligible for intravenous administration of rtPA.

Proximal M1 occlusion was identified as a predictive factor for poor clinical outcome in the present study. This finding might be due both to the extensive region of low perfusion resulting from proximal M1 occlusion and to the lower rate of complete recanalization in patients with such occlusion. This rate was 30% in these patients compared with 79% and 90% for distal M1 or M2 occlusion, respectively, in our study, and lower than the rate for M1 occlusion in previous studies.[2-9] The reason for the lower recanalization rate for proximal M1 occlusion was not clear, but the high volume of the thrombus in the proximal M1 may make it difficult to achieve complete recanalization with LIT with a low dose of urokinase assisted by MCD. Therefore, additional intravenous administration of rtPA[1] or mechanical embolectomy[10] may be needed to improve the outcome of patients with proximal M1 occlusion through faster and more complete recanalization.

Limitations

Our study has several limitations: The study design was retrospective in nature, there was no randomized comparison group, and our sample size was small. Evaluation of NIHSS, MR imaging, CT, and angiograms was not performed by blinded operators, and the decision to perform additional MCD was made at the operator's discretion in each case. Thus, the findings for LIT-MCD may not be generalizable to other settings; the safety, efficacy and exact predictive factors for a successful outcome of LIT-MCD were not completely established by this study. However, our results suggest that LIT-MCD is technically feasible and may provide more clinical benefit than LIT alone. This warrants further study of LIT-MCD with or without other interventions in larger numbers of patients.

Conclusions

Patients with acute stroke due to MCA occlusion can be treated with LIT-MCD with acceptable safety and efficacy. To improve clinical outcome after LIT-MCD, especially in patients with proximal M1 occlusion, combination with interventions such as intravenous administration of rtPA or mechanical embolectomy is required.

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