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Incomplete mechanical recanalization of middle cerebral artery occlusions facilitates endogenous recanalization within 5 h

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Abstract

Background and purpose—Successful revascularization can often improve functional outcome after large intracranial arterial occlusions. However, incomplete or unsuccessful recanalization is often the end result after attempted mechanical thrombectomy. A study was undertaken to determine whether partial recanalization of proximal isolated middle cerebral artery (MCA) occlusions facilitates endogenous thrombolysis and spontaneous recanalization.

Methods—We retrospectively analyzed consecutive patients with acute ischemic stroke undergoing mechanical thrombectomy using the Merci Retriever System for occlusions involving any portion of the M1 segment of the MCA. Only those patients with a residual obstruction of the proximal MCA segments were included. The rates of facilitated endogenous recanalization (FER₅) by imaging within the 5 h following intervention were compared in patients with partial proximal recanalization and those in whom recanalization was unsuccessful.

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Results—Forty-two patients were included in the analysis. Twenty-six patients had good recanalization of the proximal aspect of the target lesion with an arterial occlusive lesion score of 2 or 3 but a residual partial or total occlusion of the MCA, while 16 patients failed to recanalize any portion of the target occlusion. Twelve patients (46%) in the first group and only one (5.9%) in the second group had facilitated endogenous recanalization on interval imaging 5 h after intervention (OR 12.9, 95% CI 1.5 to 112.2). Nine patients with proximal recanalization had good clinical outcomes at discharge (mRS = 2) compared with none without recanalization ($p=0.01$), but FER did not have a relationship with clinical outcome.

Conclusions—Despite initially incomplete proximal mechanical thrombectomy, nearly half of all patients with residual M1 occlusions will undergo further endogenous recanalization within the subsequent 5 h.

INTRODUCTION

Large intracranial arterial occlusions are associated with high morbidity and mortality. In patients who are ineligible for or fail intravenous thrombolytic therapy, endovascular revascularization is often the only method that can potentially improve functional outcome.^{1–3} Although a good arterial occlusive lesion (AOL) score represents good or excellent target vessel recanalization and is associated with favorable clinical outcomes,²⁴⁵ it does not necessarily equate to tissue revascularization. Incomplete recanalization and thus poor reperfusion can be the end result after attempted endovascular intervention. We recently demonstrated that partial proximal flow restoration in simultaneous concomitant internal carotid artery-middle cerebral artery (ICA-MCA) occlusions resulting in residual MCA occlusions promotes further endogenous recanalization, in most cases within 5 h of intervention. Our hypothesis is that partial proximal restoration of flow in proximal MCA occlusions may similarly augment antegrade perfusion pressure and flow, thereby improving endogenous thrombolysis at the face of any residual thrombus. This may be sufficient to facilitate endogenous recanalization in the immediate post-thrombectomy period.

METHODS

All consecutive patients undergoing mechanical thrombectomy using the Merci Retriever System for acute large artery ischemic stroke were prospectively entered into our institution's database according to a protocol approved by our local Institutional Review Board. We retrospectively analyzed only M1 (horizontal, pre-bifurcation) segmental occlusions of the MCA from December 2002 to January 2008. Only those patients with a residual obstruction of the MCA were included. Because they were analyzed in our previous study, ICA terminus occlusions involving the M1 segment and tandem ICA-MCA occlusions were excluded. In order to evaluate post-thrombectomy recanalization, all patients had to undergo non-invasive MR or CT angiography performed per protocol at our institution within 5 h after endovascular intervention.

We grouped patients with regard to the final revascularization of the primary AOL score obtained from review of the digital subtraction cerebral angiogram. This scoring system has been described previously.²⁵ In this grading system a score of 0 represents no recanalization, 1 represents incomplete or partial recanalization with no distal flow, 2 represents incomplete

or partial recanalization with any distal flow and 3 represents complete recanalization with any distal flow.

Two reviewers independently reviewed all angiograms to determine the location of the initial and residual thrombus. The proximal M1 occlusion was defined as the absence of contrast filling in any of the cortical or lenticulostriate branches of the M1 segment of the MCA, while a mid-M1 occlusion failed to opacify the MCA bifurcation although some (but not all) lenticulostriate or early temporal branches could be visualized. Distal M1 occlusions comprised those patients with MCA occlusions where the thrombus was thought to be immediately proximal to or involving the MCA bifurcation, as suggested by microcatheter injections distal to and guide catheter injections proximal to the thrombus. This group included occlusions where all the lenticulostriates and/or some of the M2 branches opacified.

Patients with initial primary AOL scores of 2 or 3 and any residual M1 occlusion were compared with those in whom little or no recanalization was achieved (AOL score 0 or 1). Baseline age and sex and clinical variables were compared between the two groups. We contrasted the angiographic aspects of the time to first retrieval attempt and initial location of occlusion following MERCI thrombectomy. We also explored possible differences in the concomitant use of intravenous or intra-arterial recombinant tissue plasminogen activator. The primary comparison between these two groups was the rate of further endogenous recanalization as demonstrated on post-intervention MR or CT angiography within 5 h after intervention (FER₅). In order to classify by FER, the reviewers were aware of the degree of post-intervention residual occlusion. FER was categorically designated when flow or contrast enhancement was noted in vessels beyond the residual occlusion on the 5 h post-intervention CT or MR angiogram.

Hemorrhagic transformation (HT) was classified into clinical categories of HT as asymptomatic, symptomatic (defined as a decline in NIH Stroke Scale score of ≥ 4 points)⁶⁷ or fatal. We then compared the rate of HT in patients between the groups with and without FER₅ as well as between groups with and without successful partial proximal recanalization. We also compared rates of good clinical outcome (modified Rankin Scale (mRS) ≤ 2) at time of discharge.

RESULTS

A total of 42 patients were identified who met the criteria to be included in the analysis. Thirty patients (71%) were women and the mean age was 64 ± 19 years. Good or excellent recanalization of the proximal lesion was achieved in 26 patients and recanalization failed in 16. There were no differences in the baseline demographics in either group, with a similar time to intervention between the two groups. There was a similar distribution of occlusion locations on presentation (table 1).

In the primary comparison, 12 of the 26 patients (46%) in whom we were able to achieve some proximal recanalization had FER₅ on interval non-invasive angiographic imaging compared with one of the 16 (6.3%) in whom mechanical thrombectomy was completely

unsuccessful. Patients with successful proximal recanalization were 13 times more likely to have FER₅ than those in whom we were unable to achieve any recanalization (OR 12.9, 95% CI 1.5 to 112.2).

Multiple demographic comparisons were made (table 1) in the patients within groups (dichotomized by success of proximal recanalization) and between groups (dichotomized by FER₅).

The within-group comparison in gender showed no difference with respect to successful proximal recanalization (81% vs 56%, $p=0.16$), while the between-group comparisons showed fewer women achieving FER₅, regardless of proximal recanalization status (31% vs 72%, $p=0.02$). There was no age difference with respect to proximal recanalization status (65 ± 20 vs 63 ± 18 , $p=0.79$) or FER₅ (70 ± 15 vs 62 ± 20 , $p=0.18$). With respect to clinical variables, the only difference noted was that patients with premorbid cardiac disease more often experienced FER₅ (85% vs 38%, $p<0.01$), while there was a trend toward more patients with presumed cardioembolic sources of their stroke achieving successful proximal recanalization (88% vs 63%, $p=0.06$). Within-group and between-group comparisons on the time to MERCI intervention showed no difference ($p=0.5$ and $p=0.3$, respectively).

With regard to good clinical outcome at discharge (mRS ≤ 2), nine patients with proximal recanalization (39%) achieved this clinical endpoint compared with none in the group without recanalization ($p=0.01$). There was no relationship between FER and clinical outcome at discharge (2 (18%) vs 7 (28%), $p=0.69$).

There was no difference in the distribution of patients who collectively received or underwent concomitant adjunctive therapies including intravenous or intra-arterial thrombolysis and intracranial angioplasty and/or stenting. Of the patients in whom proximal partial recanalization was successful but with incomplete reperfusion, seven received and failed intravenous thrombolysis, three underwent adjuvant intra-arterial thrombolysis and three underwent intracranial transluminal balloon angioplasty. Of the patients in whom we failed to achieve any proximal recanalization, four received and failed intravenous thrombolysis, one underwent adjuvant intra-arterial thrombolysis and two underwent intracranial transluminal balloon angioplasty (all individual comparisons $p=1$; composite of any therapy, $p=1$). Of note, all four patients in this cohort who received adjuvant intra-arterial thrombolysis (three with successful partial proximal recanalization and one without) went on to FER₅ (31% vs 0%, $p<0.01$).

Nineteen patients experienced HT. Fourteen of 26 patients (54%) with proximal recanalization had HT, not different from the 5 of 16 patients (31%) in whom proximal recanalization was unsuccessful (OR 2.6, 95% CI 0.7 to 9.5). Rates of any HT also did not differ between patients with and without FER₅ (57% vs 38%; OR 1.4, 95% CI 0.4 to 5.3). Only one fatal or symptomatic HT occurred in this cohort. This patient received intra-arterial thrombolysis and was the only patient in whom we were unable to achieve any successful proximal mechanical recanalization but experienced FER₅.

DISCUSSION

The present study suggests that any proximal flow restoration after mechanical thrombectomy for acute MCA occlusions can facilitate endogenous recanalization within 5 h. A previous study using serial transcranial Doppler revealed that early (<6 h) spontaneous recanalization occurs in 18% of patients with cardioembolic strokes in the MCA territory, and that delayed (6–36 h) spontaneous recanalization occurs in 52% of such patients.⁸ This rate was confirmed in the PROACT study where angiographically-confirmed spontaneous recanalization at 6–8 h after onset of stroke occurred in 18% of placebo patients receiving intravenous heparin for acute MCA occlusions.¹⁹

MR angiography has also been used to document delayed recanalization. In 82 patients with MCA occlusions there was a higher delayed recanalization rate 24 h after symptom onset following intravenous thrombolysis compared with placebo. Partial and complete recanalization (TIMI 2 and 3) occurred in 24% of patients receiving placebo and in 38.5% of those receiving intravenous thrombolysis.¹⁰

In our study, FER within 5 h after stroke onset occurred in 5 of 11 (45%) patients following MERCI thrombectomy with adjunctive therapy and 7 of 15 (47%) of those patients not undergoing concomitant adjunctive therapies. This study differs from the previous studies by its exclusive selection of patients ineligible for or failing intravenous thrombolytic therapy and also in the distinct manner of direct removal or disruption of clot from the target AOL. This result suggests that mechanical thrombectomy with or without adjunctive therapy for acute ischemic stroke can obtain immediate vessel recanalization, as demonstrated by the MERCI and Multi MERCI trials,^{311–14} and it may also enhance the likelihood of further spontaneous post-intervention recanalization when reperfusion is initially incomplete. Figure 1 is an example of FER occurring 5 h after intervention.

We first coined the term ‘facilitated endogenous recanalization’ to reflect the direct effect of partial thrombectomy on perfusion pressure, flow and thus the circulation of fresh blood across the proximal face of and microchannels within the residual thrombus.¹⁵ We intentionally did not apply the term ‘spontaneous’ because of the presumed effect that the primary modality of thrombectomy has on the thrombus, even if overall perfusion is not immediately restored.¹⁶¹⁷ The presumptive mechanism through which partial recanalization facilitates fibrinolysis is through increased flow and arterial wall shear stress, shown to enhance plasminogen release and circulation across the clot in vitro,¹⁸ in vivo¹⁶ and in healthy humans.¹⁷

The presence of residual thrombus at the conclusion of mechanical thrombectomy signals a technically suboptimal procedure. It is possible that our cohort of residual MCA occlusions incorporates cases selected through operator bias. These may be cases where the operator felt that aborting further therapy was appropriate based on the subjective interpretation of adequate reperfusion. Although we reviewed all procedural reports to assess the validity of this concern, none reflected this interpretation.

The phenomenon of higher facilitated recanalization with partial flow restoration may be induced by the augmentation of endogenous thrombolysis resulting from the successfully

recanalized primary AOLs. However, the potential relationship of pretreatment collateral flow with subsequent spontaneous recanalization must also be considered. These aspects need to be further studied.

One interesting finding is the unequal distribution of intra-arterial thrombolysis usage. All four patients receiving this adjuvant therapy experienced FER, regardless of the success of proximal recanalization. To investigate whether intra-arterial thrombolysis was in fact a contributor to our overall findings, we excluded these four patients in a post hoc analysis. The results were similar to the primary comparison: 9 of 23 patients who were partially recanalized experienced FER compared with none of the 15 in whom recanalization was unsuccessful ($p=0.006$). This, however, does not exclude the possibility that adjuvant intra-arterial thrombolytic agents independently promote FER.

Although we observed improved clinical outcomes in patients with proximal flow restoration, experiencing FER did not predict a better functional outcome. It is possible that proximal recanalization in itself is beneficial, regardless of FER. An alternative explanation is that FER is only beneficial if the underlying tissue remains viable until the time of FER, and is thus dependent on factors such as cellular metabolism and collateral flow. An alternative explanation is the high prevalence of complete or near-complete infarct of the basal ganglia (M1a pattern) in this cohort.¹⁹ As expected of a cohort composed entirely of MCA occlusions, 63% (20/33) of patients had an M1a pattern, which has been established as a predictor of poor outcome. In combination with the small cohort size, it is possible that we could not detect an effect of FER on outcome because of an overwhelming M1a effect. Another important factor beyond our control is the degree to which the stroke neurologist or neuro-intensivist was vigilant for FER and whether it was addressed through blood pressure reduction or other clinical means. As this study is the first to describe FER, it has not had a routine effect on the post-intervention care at our institution. As a novel descriptive finding, it is possible that identifying FER and adjusting post-intervention hemodynamics accordingly may in fact improve long-term clinical outcome.

This study has several limitations. Although there is an association between a good AOL score and favorable 3-month clinical outcome,²⁵ the impact of FER after MERCI thrombectomy on the long-term clinical outcome was not assessed in this study because of the small study population. The sample size also impaired our ability to detect small between-group differences. Because there was only one instance in our cohort, we could not determine if FER had any relationship with symptomatic or fatal hemorrhage. The small cohort size also prevented further analysis of the impact of intra-arterial thrombolysis, which deserves further exploration.

CONCLUSION

This study re-confirms that restoration of proximal but partial perfusion enhances the endogenous dissolution of downstream residual occlusions. As we established with simultaneous concomitant ICA-MCA occlusions including both tandem extracranial ICA-MCA and contiguous intracranial ICA-MCA thrombi, proximal restoration of ICA flow after endovascular therapy may augment antegrade perfusion and collateral flow. This

principle appears to hold true with singular MCA occlusions. Although attempts at acute endovascular stroke therapy should strive to completely reperfuse salvageable tissue, flow restoration is incomplete in a minority of attempted endovascular interventions. Our study suggests that such suboptimal overall anatomic results should not be discouraging, and that routine angiographic imaging should be performed, possibly within 5 h following intervention, to help guide blood pressure management and anticoagulant/antithrombotic decisions.

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Figure 1.

An example of facilitated endogenous recanalization in an acute right middle cerebral arterial (MCA) occlusion. (A) Pre-intervention MR angiogram showing absence of flow beyond the proximal aspect of the MCA (arrowhead). (B) Initial anteroposterior (AP) arteriogram of the right internal carotid artery confirms the obstruction, seen as an abrupt flow cut-off. (C) AP arteriogram of the right internal carotid artery following three passes with the MERCI retriever; there is proximal recanalization of flow in the MCA stem to the bifurcation (arrow) but most of the MCA secondary divisions (M2) are not seen. (D) MR angiogram obtained 5 h after intervention showing near-complete reperfusion with flow into the M2 branches.

Table 1

Comparison of demographic, clinical and interventional variables in the study cohort

	Proximal recanalization		
	Yes (n=26)	No (n=16)	p Value
Female gender, n (%)	21 (81)	9 (56)	0.16
Age in years, mean $\pm$ SD	65 $\pm$ 20	63 $\pm$ 18	0.79
Clinical history, n (%)			
Cardiac disease	16 (62)	6 (38)	0.20
Hypertension	16 (62)	10 (63)	1
Diabetes	4 (15)	6 (38)	0.14
Prior stroke	1 (4)	3 (19)	0.15
Peripheral vascular disease	2 (8)	0	0.52
Chronic renal insufficiency	2 (8)	1 (6)	1
Current use of antiplatelets	5 (19)	2 (13)	0.69
Current use of statins	6 (23)	3 (19)	1
Presumed cardioembolism	23 (88)	10 (63)	0.06
Admission glucose (mmol/l)	7.1 $\pm$ 1.6	8.4 $\pm$ 4.2	0.14
Pre-intervention M1a pattern on MR	15 (68)	5 (50)	0.44
Location of initial occlusion			
Proximal M1	13 (50)	7 (44)	0.76
Middle M1	8 (31)	5 (31)	1
Distal M1	5 (19)	4 (25)	0.71
Interventional variables			
Time to intervention (min)	422 $\pm$ 142	408 $\pm$ 242	0.82
Adjuvant intravenous rt-PA	7 (27)	4 (25)	1
Adjuvant intra-arterial rt-PA	3 (12)	1 (6)	1
Intracranial angioplasty and/or stenting	3 (12)	2 (13)	1
Any adjuvant therapy	11 (42)	6 (38)	1
Hemorrhagic transformation			
Asymptomatic	14 (54)	5 (31)	0.21
Symptomatic (including fatal)	0	1 (6)	0.38
Fatal	0	1 (6)	0.38
Facilitated endogenous recanalization at 5 h	12 (46)	1 (6)	0.01
Median outcome at discharge, mRS (IQR)	4 (1–5)	4 (4–5)	0.21
Good outcome at discharge (mRS $\leq$ 2)	9 (39)	0 (0)	0.01

mRS, modified Rankin scale; rt-PA, recombinant tissue plasminogen activator.