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Repeated Mechanical Endovascular Thrombectomy for Recurrent Large Vessel Occlusion: A Multicenter Experience

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Stroke

ORIGINAL CONTRIBUTIONS

Repeated Mechanical Endovascular Thrombectomy for Recurrent Large Vessel Occlusion

A Multicenter Experience

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BACKGROUND AND PURPOSE: Mechanical thrombectomy (MT) is now the standard of care for large vessel occlusion (LVO) stroke. However, little is known about the frequency and outcomes of repeat MT (rMT) for patients with recurrent LVO.

METHODS: This is a retrospective multicenter cohort of patients who underwent rMT at 6 tertiary institutions in the United States between March 2016 and March 2020. Procedural, imaging, and outcome data were evaluated. Outcome at discharge was evaluated using the modified Rankin Scale.

RESULTS: Of 3059 patients treated with MT during the study period, 56 (1.8%) underwent at least 1 rMT. Fifty-four (96%) patients were analyzed; median age was 64 years. The median time interval between index MT and rMT was 2 days; 35 of 54 patients (65%) experienced recurrent LVO during the index hospitalization. The mechanism of stroke was cardioembolism in 30 patients (56%), intracranial atherosclerosis in 4 patients (7%), extracranial atherosclerosis in 2 patients (4%), and other causes in 18 patients (33%). A final TICI recanalization score of 2b or 3 was achieved in all 54 patients during index MT (100%) and in 51 of 54 patients (94%) during rMT. Thirty-two of 54 patients (59%) experienced recurrent LVO of a previously treated artery, mostly the pretreated left MCA (23 patients, 73%). Fifty of the 54 patients (93%) had a documented discharge modified Rankin Scale after rMT: 15 (30%) had minimal or no disability (modified Rankin Scale score ≤2), 25 (50%) had moderate to severe disability (modified Rankin Scale score 3–5), and 10 (20%) died.

CONCLUSIONS: Almost 2% of patients treated with MT experience recurrent LVO, usually of a previously treated artery during the same hospitalization. Repeat MT seems to be safe and effective for attaining vessel recanalization, and good outcome can be expected in 30% of patients.

Key Words: arteries ■ atherosclerosis ■ ischemic stroke ■ standard of care ■ thrombectomy

In 2015, mechanical thrombectomy (MT) became the standard of care for the treatment of acute ischemic stroke due to large vessel occlusion (LVO) within 6 hours.[1,2] In 2018, the treatment window was expanded up to 24 hours from acute ischemic stroke symptom onset.[3,4] On average, the 5-year risk of acute ischemic stroke recurrence is 24% for women and 42% for men, with most of the risk within the first 2 weeks after the index event.[5,6] With estimates of 65 000 to 90 000 patients meeting MT criteria annually in the United

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Nonstandard Abbreviations and Acronyms

iMT	index mechanical thrombectomy
LVO	large vessel occlusion
mRS	modified Rankin Scale
MT	mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale
rLVO	recurrent LVO
rMT	repeat mechanical thrombectomy

States, the number of patients who may experience a recurrent LVO (rLVO) requiring repeat MT (rMT) may be substantial.[7]

The literature on the safety and outcomes of rMT, especially in the same vascular territory, is limited. Fandler et al[8] showed that successful rMT could be achieved in a patient with recurrent early reocclusion of the same artery within 24 hours. Bouslama et al[9] reported on 14 patients with rMT and showed that there were no statistically significant differences in demographics, stroke severity, time from last known normal to groin puncture, reperfusion rates, hemorrhagic complications, good functional outcomes, or mortality between patients who underwent rMT and those who were treated with a single thrombectomy.

The cause of rLVO is also not well described. Up to 20% of LVO is caused by atherosclerosis because of plaque rupture leading to vessel thrombosis or artery-to-artery embolism.[10] A population-based study showed that atherosclerotic large vessel disease carried the highest risk of stroke recurrence.[11] This risk correlates with plaque echogenicity.[12]Additionally, atrial fibrillation, which is the primary cause of cardioembolic stroke, is associated with increased risk for early stroke recurrence.[12]

Understanding the frequency, timing, causes, and angiographic and clinical outcomes associated with rMT may help develop preventive medical strategies and optimize the endovascular approach (ie, use of stent-retriever versus suction thrombectomy versus angioplasty/stenting). In this study, we aimed to describe our cumulative experience with consecutive cases of rMT for rLVO at 6 US medical centers over a period of 4 years.

METHODS

Study Design

Repeated Mechanical Endovascular Thrombectomy for Recurrent Large Vessel Occlusion is a retrospective multicenter cohort study that identified patients who underwent rMT at 6 United States comprehensive stroke centers between March 2016 and March 2020. All data were prospectively collected in endovascular databases maintained by the investigators. The institutional review boards of all 6 institutions approved this study, which included a data-sharing agreement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Clinical Variables

Patients who received an index MT (iMT) in the 6 participating centers were analyzed, and cases in which rMT was performed were identified. All patients received baseline noncontrast computed tomography (NCCT), CT angiography upon presentation, and 24 hours postprocedural NCCT or earlier if clinically indicated. Stroke work-up included in-hospital cardiac rhythm monitoring, and transthoracic or transesophageal echocardiography in all cases. Antiplatelet agents were started either immediately or within 24 hours after thrombectomy unless hemorrhagic infarction was present. Anticoagulation when indicated for atrial fibrillation was started between 3 and 14 days after thrombectomy unless hemorrhage was present.

Demographics, risk factors, clinical, imaging, procedural devices used, number of passes, final TICI score, post-iMT antithrombotic therapy, and outcome at discharge were collected. We defined early reocclusion as occurring during the index hospitalization. Stroke severity was measured with the National Institutes of Health Stroke Scale (NIHSS).[13] Stroke cause was classified based on the TOAST criteria.[14] Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction score of 2b or 3.[15] Postprocedural hemorrhagic complications were defined using the European Cooperative Acute Stroke Study criteria.[16] Neurological outcomes were measured with the modified Rankin Scale (mRS) at the time of hospital discharge. Favorable outcome was defined as mRS score <2 and unfavorable as mRS score 3 to 5, with mortality mRS score 6 counted separately.

Treatment plans were based on each hospital's protocol, including various interventional approaches, for example, aspiration catheters, stent retriever devices, stents, angioplasty balloons, or combinations thereof.

Statistical Analysis

We used proportions, median, and interquartile ranges for descriptive statistics. For comparisons between iMT and rMT, McNemar tests were used for the dichotomized variables, Bowker test for symmetry for the categorical variables, and Wilcoxon signed-rank tests for the continuous variables. For comparisons between patients with reocclusion during hospitalization and reocclusion after discharge, Fisher exact test was used for dichotomized and categorical variables and Wilcoxon 2-sample tests for continuous variables. Significance was set at <0.05, and 2-sided *P* values were reported. Statistical analysis was performed using R Software (version 3.6.1) and SAS (version 9.4).

RESULTS

Of 3059 patients who underwent MT at 6 comprehensive stroke centers between March 2018 and March 2020, 56 patients (1.8%) underwent rMT. Fifty-four patients were analyzed, with 2 patients excluded because of incomplete iMT clinical and procedural data.

Fifty patients (93%) had 1 rMT, 3 (6%) underwent 2 rMT procedures, and 1 (2%) had rMT performed 3 times. Median age was 64 (interquartile range, 54–72) years, and 50% were females (Table 1).

Median time interval between the index LVO (iLVO) and rLVO was 2 days (range, 0.8–17.8 days); in 35 patients (65%), rMT was performed during the index hospitalization (Table 2). There was no statistically significant difference in stroke cause, ASPECTS (Alberta Stroke Program Early CT Score), number of passes during MT, or final modified Thrombolysis in Cerebral Infarction score between those who had reocclusion during hospitalization or reocclusion after discharge (Table 3).

At the time of rMT, 13 patients (24%) were not started on any antithrombotic therapy, 27 patients (50%) received antiplatelet therapy, and 14 patients (26%) were on full anticoagulation (Table 1). Patients with rLVO during hospitalization were less commonly receiving secondary stroke prevention compared with patients with rLVO after discharge (34% versus 5%, $P=0.022$). Both groups had similar discharge mRS (Table 3).

In 30 patients (56%), rLVO occurred in patients with a cardioembolic cause of stroke, with the majority of these (23 of 35, 77%) due to atrial fibrillation. Six patients (11%) had rLVO due to atherosclerotic in situ thrombosis: intracranial atherosclerotic disease in 4 (7%), and extracranial atherosclerosis in 2 (4%). In the remaining 18 patients (33%) rLVO was secondary to other causes (eg, vasculitis) or was cryptogenic (Table 2).

Thirty-two of 54 patients (59%) had rLVO of the same vessel treated during iMT. The most common stroke cause in these patients was cardiac embolism (13/32, 41%), and the left MCA was the most commonly affected vessel in these cases (23/32, 72%) (Table 2). Of the 4 patients who underwent 2 or more rMT procedures, 3 had atrial fibrillation and 1 patient had intracranial stent thrombosis. The single patient who underwent 3 repeat thrombectomies had atrial fibrillation and developed a fixed focal stenosis of the repeatedly treated left MCA that eventually required angioplasty.

Table 1. Demographics of 54 Patients Treated With Repeat Mechanical Thrombectomy

Characteristic	N=54
Age, y	64 (54–72)
Female	27 (50)
LVO recurrence after the index event	
One recurrence	50 (93)
Two recurrences	3 (6)
Three recurrences	1 (12)
Time interval in days between index MT and first rMT, d	2 (0.8–17.8)
Reocclusion during index hospitalization	35 (65)
Reocclusion of same vascular territory	32 (59)

Data are N (%) or median (IQR). LVO indicates large vessel occlusion; MT, mechanical thrombectomy; and rMT, repeat MT.

Median NIHSS at presentation was 14 (range, 9–21) for iLVO and 16 (range, 10–24) for rLVO ($P=0.96$, Table 2). However, post MT NIHSS scores were worse after rMT compared with iMT (median 12 versus 7, $P=0.008$, Table 2) and worse when rMT was performed during the same hospitalization compared with those with reocclusion after discharge (median 7 versus 5, $P=0.028$, Table 3).

Successful revascularization was achieved with 1 pass in 32 of 54 patients (59%) during iMT and in 26 (48%) during rMT. A final recanalization score of modified Thrombolysis in Cerebral Infarction 2b or 3 was achieved in all 54 patients during their iMT (100%) and in 51 of 54 patients (94%) during rMT (Table 2).

Postprocedural intracerebral hemorrhage occurred in 4 of 54 patients (7%) after iMT, 2 of which were symptomatic. After rMT, 7 of 54 patients (13%) had postprocedure intracerebral hemorrhage, 4 of which (7%) were symptomatic, of 2 of which were fatal (Table 2).

Fifty of 54 patients (93%) had a documented discharge mRS after rMT: 15 (30%) had minimal or no disability (mRS score ≤2), 25 (50%) had moderate to severe disability (mRS score 3–5), and 10 (20%) died (Table 2).

DISCUSSION

Large vessel occlusion (LVO) accounts for 30% of ischemic stroke presentations.[17] The 5-year risk of ischemic stroke recurrence due to all stroke etiologies combined is about 30%.[18] To our knowledge, our study represents the largest cohort of patients receiving rMT for rLVO in North America to date. In this cohort, rLVO requiring MT was infrequent, occurring after 1.8% of all MT procedures. Similar and slightly lower rates (0.4%–1.5%) have been previously reported in smaller series.[9,19–22] These infrequent treatment rates likely represent an underestimate of the actual number of rLVO due to: exclusion of patients with rLVO with severe disability, patients presenting with rLVO to different hospitals, and missed rLVO during hospitalization in patients with a subtle worsening of the original NIHSS.

In our cohort, the majority of rLVO occurred early, within a median time to reocclusion of 2 days. Thirty-five patients, 65% developed rLVO during the index hospitalization after successful iMT. A study on very early reocclusion within 48 hours showed that cardio-embolism and atherosclerotic large vessel disease were the first and second most common etiologies associated with reocclusion after successful revascularization.[23] We found similar results, with cardioembolism (51%) and large vessel atherosclerosis (17%) being the most likely stroke mechanisms associated with early rLVO. Other causes that may contribute to early reocclusion

Table 2. Procedural Characteristics Comparing Index Mechanical Thrombectomy and the First Recurrent Thrombectomy

Characteristic	Index MT	First rMT	*P* value
Presenting NIHSS	14 (9–21)	16 (10–24)	0.16*
ASPECTS	9 (8–10)	9 (8–10)	0.96*
Postprocedural NIHSS	7 (3–12)	12 (5–21)	0.008*
Arterial territory			0.45†
MCA	40 (74)	34 (63)	
Basilar artery	6 (11)	9 (17)	
ICA	7 (13)	10 (17)	
PCA	1 (2)	1 (2)	
Endovascular approach			0.018†
Stent retriever	43	41	
Aspiration	13	20	
Intracranial angioplasty	1	3	
Intracranial stenting	0	3	
Extracranial angioplasty	0	0	
Extracranial stenting	0	2	
Number of passes			0.32‡
1 pass	32 (59)	26 (48)	
>1 pass	22 (41)	28 (52)	
mTICI score			0.25‡
2b-3	54 (100)	51 (94)	
1–2a	0 (0)	3 (6)	
Hemorrhage	4 (7)	7 (13)	0.18‡
Symptomatic§	2 (4)	4 (7)	
Fatal	0 (0)	2 (4)	
Stroke cause			0.75†
Cardioembolic	30 (56)	30 (56)	
Intracranial atherosclerotic disease	4 (7)	4 (7)	
Extracranial atherosclerotic disease	4 (7)	4 (7)	
Other causes	16 (30)	18 (33)	
Cryptogenic	11 (20)	11 (20)	
Vasculitis	1 (2)	1 (2)	
Dissection	0 (0)	1 (2)	
Hypercoagulable state	4 (7)	4 (7)	
Stent thrombosis	0 (0)	1 (2)	
Follow-up mRS	N=45	N=50	
Favorable (mRS score ≤2)	17 (38)	15 (30)	
Unfavorable (mRS score 3–5)	28 (62)	25 (50)	
Death (mRS score 6)		10 (20)	

Data are N (%) or median (IQR). ACA indicates anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; ESUS, embolic stroke of undetermined source; ICA, internal carotid artery; ICH, intracerebral hemorrhage; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; and RT, recurrent thrombectomy.

**P* value from signed-rank test.

†*P* value from Bowker test for symmetry.

‡*P* value from McNemar test.

§Symptomatic hemorrhage corresponds to PH2 (hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect) according to the Heidelberg bleeding classification.

Table 3. Comparison Between Reocclusion During Index Hospitalization Versus After Discharge

Characteristic	Reocclusion during index hospitalization, N=35	Reocclusion after discharge, N=19	*P* value
Age, y	62 (53–68)	67 (60.5–80)	0.07*
ASPECTS	9 (8–10)	9 (7.5–9)	0.19*
Postprocedural NIHSS	7 (4–14)	5 (1–7)	0.028*
Time interval, d	1 (0–2)	75 (11–390)	<0.001*
Number of passes		14 (74)	0.15†
1 pass	18 (51)	5 (26)	
>1 pass	17 (49)		
Index stroke cause		12 (63)	0.78
Cardioembolic	18 (51)	2 (11)	
Atherosclerotic	6 (17)	5 (26)	
Other causes	11 (31)		
Reocclusion of same vascular territory	24 (69)	8 (42)	0.08†
Need for stenting, angioplasty, or both		0 (0)	0.043†
Yes	7 (20)	19 (100)	
No	28 (80)		
Medications used following index MER		1 (5)	0.02†
		10 (53)	
None	12 (34)	8 (42)	
Antiplatelets	17 (49)		
Anticoagulation	6 (17)		
Follow-up mRS	N=32	N=18	0.28*
Favorable mRS (≤2)	10 (31)	5 (28)	
		7 (39)	
Unfavorable mRS (3–5)	18 (56)	6 (33)	
Death	4 (13)		
Follow-up mRS, median (IQR)	N=32	N=18	0.39*
	4 (2–4.5)	4 (1–6)	

Data are N (%) or median (IQR). ASPECTS indicates Alberta Stroke Program Early CT Score; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

**P* value from Wilcoxon 22-sample test.

†*P* value from Fisher exact test.

are procedure-related complications like dissection and stent thrombosis.[22] These complications were infrequent in our cohort.

The primary cause for rLVO in our cohort was cardioembolic source, about 56% of the 54 patients, with majority due to atrial fibrillation (77%). This is consistent with prior studies showing that cardioembolic source is the cause of up to 40% of acute ischemic strokes,[24] and 43% to 67% of rLVO.[19–22]

Thirty-two of the 54 patients in our cohort (59%) had reocclusion of the previously treated artery. Recurrent LVO of the same vessel might intuitively seem more likely to occur in patients with intracranial atherosclerotic disease or extracranial atherosclerosis. On the contrary, in our series, cardioembolism was the most common stroke mechanism associated with reocclusion of the pretreated artery (41% of the 32 patients), and the left MCA was more commonly affected than the right. This finding may be explained by hemodynamics, laminar flow patterns, vascular diameter, and aortic arch morphology, all of which play a role in cardioembolic stroke's laterality.[25,26] Elsaid et al[26] studied the relationship between cardioembolic stroke and aortic arch morphology and found that cardioembolic strokes tend to occur more frequently in the anterior circulation, left MCA territory. Another possible explanation is that patients with an underlying stenosis, especially if severe, may have had definitive revascularization (angioplasty or stenting) during the iMT or shortly thereafter or even early carotid endarterectomy, creating a bias in our dataset.

Mosimann et al[27] showed in their study of predictors of early reocclusion after MT that the majority of early reocclusions occurred in patients with residual embolic fragments that were not recognized on the final control run, misinterpreted as focal spasm, or were suboptimally imaged due to overlapping branches.

Other possibility for rLVO in the same location is local vascular endothelial injury caused by the iMT maneuver itself. Previous studies have shown that endothelial injury from the MT can result in a predilection to acute in-situ thrombosis and reocclusion.[28] In preclinical studies, thrombectomy-induced vascular wall damage was found to manifest as endothelial injury, disruption of the internal elastic lamina, and focal edema located in the intimal and medial layers of the vessel.[29] Additionally, more than half of clots retrieved from patients treated with MT contained endothelial cells, suggesting intimal layer damage due to direct mechanical injury from MT.[29] Anecdotaly, one of our patients with cardioembolic stroke with atrial fibrillation developed fixed focal stenosis after the third rMT in the same vascular territory that required angioplasty.

The optimal timing for initiation of antithrombotic therapy in patients presenting with acute cardioembolic LVO is controversial. In the current guidelines, no available prospective data address the appropriate timing for initiation of anticoagulation or antiplatelet agent after MT, especially when intravenous thrombolysis is given. The dilemma is that there is an increased risk of early recurrent stroke for patients with atrial fibrillation, intracardiac thrombi, unstable plaques, or extensive intracranial stenosis. However, there is also a known increased risk of hemorrhagic transformation of the infarcted tissue.[30] A protocol has been proposed to address the timing of anticoagulation timeline in patients with a cardioembolic source based on the index stroke volume.[31] Retrospective studies of early reocclusion after successful MT have found a relationship between atherosclerotic disease, preprocedural platelet counts, and the rate of rLVO, concluding that pretreatment antiplatelet therapy might reduce the rate of recurrence.[32] In our cohort, 24% of patients with rLVO were not on antiplatelet or anticoagulant therapy before the reocclusion. Patients with early rLVO during hospitalization were less frequently started on antithrombotic therapy after iMER than the late rLVO group (34% versus 5%, P=0.022). These data suggest that earlier initiation of antithrombotic therapy may prevent rLVO, but this needs to be balanced against the risk of intracerebral hemorrhage related to early initiation of antithrombotic therapy. More prospective data are needed to study the role of early versus late initiation of antithrombotic therapy after MT.

First pass revascularization was achieved in 32 of the 54 rLVO patients during iMT (59%) and in 26 of the 54 during rMT (48%). All 54 patients with rLVO had initial successful reperfusion on iMT (modified Thrombolysis in Cerebral Infarction 2b/3), and rMT led to successful recanalization in 51 patients (94%), mostly with the combination of stent retrieval and aspiration. Postprocedural neurological deficits were worse after the rMT compared with iMT (median NIHSS 12 versus 7, P=0.008). This finding is expected since the patients undergoing rMT already had deficit from the index stroke. Reassuringly, the rate of intracerebral hemorrhage was not substantially different with rMT compared with the iMT and accepted rates seen in trials of MT.[33]

Data on the safety and long-term outcomes of MT in the setting of high premorbid mRS are limited. The AHA/ASA guidelines state that patients with premorbid mRS score >1 have uncertain benefits and further randomized controlled trials are necessary.[34] Seker et al[35] showed that patients with premorbid mRS score 3 to 4 could return to their premorbid mRS after MT, which can justify MT for those patients. These considerations are relevant to the consideration of performing rMT in patients with rLVO. Thirty-five of the 54 patients had rMT during the index hospitalization due to early reocclusion. Although not strictly within the guidelines, treatment with rMT for these patients may have been reasonable because of the short period since the initial stroke, being already hospitalized and could potentially be treated ultra-early. At discharge time, 30% had minimal or no disability (mRS score ≤2) after rMT, 50% had moderate to severe disability (mRS score 3–5). Based on this study's results, these patients' outcomes seem to be acceptable with a favorable discharge mRS of 30%, which would be expected to rise at 3 months. Furthermore, patients with rLVO may be sicker and may have a worse functional baseline from their previous stroke, which may negatively affect functional recovery after rMT.

Again, we have no doubt that judicious patient selection played a role in selecting patients with rLVO for rMT, contributing to some of the good outcomes that we observed.

Overall mortality in our cohort was 20%, comparable to other recurrent large vessel occlusion studies (18%–20%).[9,20–23] However, this was slightly higher than the mortality figures (10%–15%) reported in the randomized thrombectomy trials.[36]

Our study has limitations, mainly its retrospective nature. Also, the low rate of rLVO requiring rMT hampered our ability to do multivariable regression analysis. We have missing outcomes data for 4 patients treated with MT. However, our cohort's rate of favorable functional outcomes is comparable to other rMT studies and is only slightly less than the landmark randomized trials. Our data clearly underestimate the absolute rate of rLVO since we only captured patients who qualified for rMT. Since we only had outcome data at hospital discharge, our data may underestimate the good neurological outcome rate with rMT, which is better assessed at 90 to 180 days. Finally, the study centers are comprehensive stroke centers in the United States; practices and patient selection for rMT may be different in other health care systems worldwide.

CONCLUSIONS

To our knowledge, this is the largest multicenter study in North America of rLVO requiring rMT. Almost 2% of patients treated with MT experience rLVO, usually of a previously treated artery during the same hospitalization. Repeat MT seems to be safe and effective for attaining vessel recanalization, and good outcome can be expected in 30% of patients. Inadequate anticoagulation or antiplatelet therapy and a cardioembolic source may be risk factors for early rLVO. Further research is needed to better understand the true rate or rLVO after MT, and to identify optimal treatment strategies to minimize this risk.

ARTICLE INFORMATION

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