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Recanalization Following Various Endovascular Modalities for Treatment of Anterior Circulation Acute Ischemic Strokes

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Abstract

Currently several endovascular modalities and devices are available for use in acute ischemic stroke setting. Limited data exist regarding the relative efficacy of these different options when used individually or in combination. The primary objective of this study was to retrospectively compare the recanalization rates of various endovascular options when used for the treatment of acute ischemic stroke in the anterior cerebral circulation. We retrospectively reviewed 132 consecutive patients treated endovascularly at our center for acute ischemic stroke in the anterior cerebral circulation. Recanalization was defined as mTIMI of ≥ 2 while complete recanalization was defined as mTIMI of 4. Statistical analysis was performed to determine the modality or combination of modalities associated with best recanalization rate. Recanalization was achieved in 74% of patients while complete recanalization was achieved in 39% of patients. No individual endovascular therapy was significantly different from others in achieving recanalization. Where a multimodality approach was used, combination of angioplasty with intra- or extracranial stent placement was significantly ($p=0.05$) associated with recanalization. On regression analysis, combination of intra-arterial tPA with a mechanical modality ($p=0.09$) was significantly associated with recanalization while combination of intravenous tPA with intracranial stent placement ($p=0.06$) was significantly associated with complete recanalization. Combination of pharmacological and mechanical modalities in the setting of multimodal therapy is associated with increased likelihood of successful recanalization in patients with acute ischemic stroke in the anterior cerebral circulation. Stent placement in acute stroke setting is promising and needs further exploration. Further prospective studies are needed.

Introduction

Stroke is the third most common cause of death in the United States [1]. Current treatment options for patients with acute ischemic stroke include intravenous tissue plasminogen activator (iv tPA) administration if presented within 4.5 hrs of symptoms onset [2,3] or endovascular options if presenting beyond this time frame. There has been tremendous evolution of endovascular options over the past decade with several different modalities now available. In general, these modalities can be subdivided into pharmacological modalities such as intra-arterial (IA) tPA [4] or mechanical modalities such as the MERCI device, snare device, balloon angioplasty, stent placement, microcatheter/wire manipulation, and most recently the Penumbra device [5–15]. These endovascular modalities have been shown to be safe and effective in achieving arterial recanalization in acute ischemic stroke in their original reports. However, methodological variations among the original reports such as different inclusion and exclusion criteria, makes it difficult to compare the different modalities. In addition, a multimodality reperfusion approach is now often used where a combination of various modalities is employed to achieve recanalization [8,9,14]. At present, very little is known about the relative efficacy of different endovas-

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cular options in achieving recanalization when used individually or in combination. The main purpose of this study was to retrospectively compare the recanalization rates of various endovascular modalities when used as part of a multimodality approach for the treatment of acute ischemic stroke in the anterior cerebral circulation. The objective was to determine the modality or combination of modalities associated with the best recanalization rate.

Methods

Institutional review board approval was obtained prior to the start of study and data collection. Medical records were retrospectively reviewed to identify patients admitted to the University Hospital of the University of Medicine & Dentistry, New Jersey, with diagnosis of acute ischemic stroke between January 2003 and June 2008. A total of 1256 patients were identified and out of these a total of 196 patients had presented within 8 hrs of symptom onset.

Finally a total of 132 consecutive patients were identified who underwent endovascular treatment during this time period for ischemic stroke in the anterior cerebral circulation. Demographic information, the presence of vascular risk factors, and the National Institutes of Health Stroke Scale (NIHSS) score on presentation were noted.

Angiographic images were retrospectively reviewed to determine the location of the thrombus, determine the endovascular modality/modalities used, and determine the modified Thrombolysis In Myocardial Infarction (mTIMI) grade [8,16]. The location of the thrombus was defined as the proximal-most segment of occlusion. The mTIMI grading was as follows: Grade 0 no flow; Grade 1 some penetration past the site of occlusion but no flow distal to the occlusion; Grade 2 distal perfusion but delayed filling in all vessels; Grade 3 distal perfusion with adequate perfusion in less than half of the distal vessels; Grade 4 distal perfusion with adequate perfusion in more than half of the distal vessels. Recanalization was defined as mTIMI of 2 or greater while complete recanalization was defined as mTIMI of 4. Duration from symptoms onset to recanalization (ORT) was also noted.

Endovascular pharmacological modality comprised of IA tPA (Activase; dose range 2--22 mg, or Reteplase; dose range 0.25--8 mg). Activase was administered in 2-mg aliquots boluses with 5-min intervals between subsequent administrations through the microcatheter distal to, within, and proximal to the thrombus. Reteplase was infused in a similar manner but with lower doses, 0.25-mg aliquots boluses. Mechanical modalities included snare retriever, MERCI device, angioplasty, or stent placement. Balloon angioplasty and stents were undersized to 10% less than the estimated vessel diameter. Coronary angioplasty balloons, coronary stents, balloon-mounted, and selfexpanding stents were used depending on the location of the clot and physician preference. Some patients in whom a self-expanding stent was placed underwent angioplasty before or after stent placement. In general, IA tPA was used as the first modality. Mechanical modalities were used in following situations: failure to achieve recanalization with IA tPA, patient arrived beyond 6 hrs, or patient had contraindication to tPA. The first mechanical modality used was balloon angioplasty, snare, or MERCI device. If these interventions failed, then an attempt was made to place a stent. Patients with extracranial internal carotid occlusions presumably due to underlying severe atherosclerosis were treated directly with stent placement and/or angioplasty. Antiplatelets (Integrillin or Reopro) were used as adjunct if extensive clot burden was noted, a stent was placed, or if there was recurrent occlusion after recanalization.

Repeat NIHSS scale obtained within 24 hrs postendovascular treatment was noted; specific note was made if there were improvement or decline in NIHSS by ≥ 4 points. CT scans obtained within 24 hrs pos-endovascular treatment were reviewed to identify intracranial hemorrhage. An intracranial hemorrhage was considered to be symptomatic if associated with a decline in NIHSS by ≥ 4 points. All other hemorrhages were defined as asymptomatic. Modified Rankin scale (mRS) score on discharge was noted.

SPSS 11.0 was used for statistical analysis. Correlation and the Fisher exact test were used for univariate analysis using a P value ≤ 0.05 for significance. A logistic regression analysis was then performed for analyzing independent predictors of recanalization using a P value ≤ 0.1 for significance.

Results

The patients studied included 61 (46%) males and 71 (54%) females, the mean age was 64±15.8 years, and the mean pretreatment NIHSS score was 16 ± 6. Baseline vascular risk factors were as follows: hypertension 67%, diabetes mellitus 30%, coronary artery disease 24%, atrial fibrillation 22%, previous stroke 16%, hyperlipidemia 15%, and peripheral vascular disease 3%. Internal carotid artery was involved in 20% of cases, middle cer-

Table 1.

Baseline characteristics of patients and site of occlusion in relation to recanalization

Clinical Characteristics	Recanalization mTIMI (2-4) No (n=34) N (%)	Yes (n=98) N (%)	P value
Age ≤ 50	6(18)	21(22)	0.38
Age 51--80	20(59)	63(64)	0.57
Age ≥ 80	8(23)	14(14)	0.20
Admission NIHSS ≤ 10	2(6)	21(22)	**0.03***
Admission NIHSS 11--20	23(68)	56(57)	0.28
Admission NIHSS > 20	9(26)	21(21)	0.35
HTN	21(62)	68(69)	0.37
DM	12(35)	27(28)	0.41
PVD	1(3)	3(3)	0.72
CAD	7(21)	25(26)	0.36
Atrial Fibrillation	10(29)	19(19)	0.17
Hypercholestremia	4(12)	16(16)	0.36
Previous Stroke	10(29)	11(11)	**0.02***
Occlusion Site			
A2 or M3	3(9)	8(8)	0.58
A1 or M2	3(9)	13(13)	0.37
M1	12(35)	61(62)	**0.01***
Carotid	14(41)	11(11)	**0.01***
Carotid + M1	0(0)	1(1)	0.74
Carotid + A1 + M1	1(3)	1(1)	0.45
M1 + A1 or A2	1(3)	2(2)	0.59

[HTN: hypertension; DM: diabetes mellitus; PVD: peripheral vascular disease; CAD: coronary arterial disease; A1: anterior cerebral artery A1 segment; A2: anterior cerebral artery A2 segment; M1: middle cerebral artery M1 segment; M2: middle cerebral artery M2 segment.]

Table 3.

Regression analysis (p values ≤ 0.1 considered significant)

Feature	Significant factor	P value
Recanalization (mTIMI 2-4)	IA tPA combined with a mechanical devise	0.09
Complete Recanalization (mTIMI 4)	IV tPA + Intracranial Stent	0.06
Improvement in NIHSS	Use of mechanical devise	0.05
Improvement in NIHSS	Intracranial or extracranial stent	0.07
mRS 0-3 at discharge	IV tPA	0.08
mRS 0-3 at discharge	Angioplasty	0.05
mRS 0-3 at discharge	Angioplasty + Stenting and MERCI	0.096
Symptomatic ICH	Longer ORT	0.09
Symptomatic ICH	IV tPA + Angioplasty	0.01
Symptomatic ICH	IA rtPA + Angioplasty or Stenting	0.01

[IV tPA: intravenous Alteplase; IA tPA: intra-arterial Activase or Reteplase; NIHSS: National Institute of Health Stroke Scale; MERCI: mechanical embolectomy retrieval device; mRS: modified Rankin scale; ORT: onset-recanalization time; ICH: intracranial hemorrhage.]

ebral artery involved in 74% of cases, and anterior cerebral artery involved in 10% of cases (4% of cases had more than one arteries involved). A total of 52 (39%) patients received intravenous tPA.

The average baseline mTIMI grade was 0.2±0.6 while the postintervention mTIMI was 2.4±1.6. Recanalization (mTIMI 2 or greater) was achieved in 98 (74%) patients while complete recanalization (mTIMI 4) was achieved in 51 (39%) patients. In patients where recanalization was successful, the ORT was 5.9 ± 1.6 hrs.

Average postendovascular treatment NIHSS was 11±7. Improvement of ≥ 4 points on NIHSS occurred in 81 (61%) patients while a decline of ≥ 4 points on NIHSS occurred in 31 (23%) patients. A total of 26 (19.6%) patients were noted to have intracranial hemorrhage on CT scans obtained within 24 hrs of the endovascular treatment; 12 (9%) of these were asymptomatic while 14 (10.6%) were symptomatic. A total of 24 (18%) patients died; this was mostly secondary to the development of cerebral edema and herniation syndrome or medical complications. The average discharge mRS score was 3.67. Discharge mRS of 3 or less was noted for 44% of patients with successful recanalization and 22% of patients with unsuccessful recanalization.

A. Predictors for recanalization

Refer to tables 1–3. Among the baseline clinical characteristics, a low NIHSS was positively associated (p=0.03) with recanalization while a prior history of stroke was negatively associated (p=0.02) with recanalization. In terms of the site of occlusion, an M1 segment occlusion was positively associated (p=0.01) with recanalization while an internal carotid occlusion was negatively associated (p=0.01) with recanalization.

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No individual endovascular therapy was found to be significantly different from others in achieving recanalization, though there was a trend for significance with extracranial internal carotid stenting (p=0.09). In patients where a multimodality approach was used, a combination of angioplasty with intra- or extracranial stent placement was significantly (p=0.05) associated with recanalization.

On regression analysis, the only significant predictor of recanalization was found to be the combination of IA tPA with a mechanical modality (p=0.09). Use of IV tPA (p=0.05) and combination of IV tPA with intracranial stent placement (p=0.06) were significantly associated with complete recanalization.

B. Predictors for improvement in NIHSS

Occlusion at A1 or M2 was positively associated (p=0.04) while occlusion at internal carotid was negatively associated (p=0.002) with improvement in NIHSS by 4 or more on repeat scoring within 24 hrs after recanalization. Analysis of individual modalities showed that the use of extracranial internal carotid stenting was significantly associated (p=0.01) with improvement in NIHSS. Where a multimodality approach was used, combination of iv tPA with extracranial internal carotid stenting (p=0.08) and combination of iv tPA with combination of angioplasty and stenting (p=0.04) were significantly associated with improvement in NIHSS. On regression analysis, use of a mechanical device (p=0.05) or stenting (p=0.07) was significantly associated with improvement in NIHSS.

C. Predictors for discharge modified Rankin scale

Analysis of individual modalities showed that the use of IV tPA (p=0.08) and angioplasty (0.06) was associated with mRS of 0--3 on discharge. Where a multimodality approach was used, a combination of angioplasty, stenting, and MERCI (p=0.096) was significantly associated with mRS of 0--3 on discharge.

D. Predictors for symptomatic ICH

Longer ORT (p=0.09), combination of IV tPA with angioplasty (p=0.01), and combination of IA tPA with angioplasty or stenting (p=0.01) were associated with symptomatic ICH.

Discussion

Multiple studies [e.g., 7–19] in past have underscored the importance of achieving recanalization after acute ischemic stroke as this led to a better clinical outcome as well. Recanalization rates reported for individual endovascular modalities include 66% for IA tPA in the PROACT II study and 57.3% for the MERCI devise in the Multi-MERCI study though methodological variations such as different inclusion criteria make it hard to make a direct comparison between the two studies. Most centers where endovascular treatment for acute ischemic stroke is now offered use a multimodality approach with the thought that this may result in better recanalization rates. There is some evidence available for this such as the Mutli-MERCI trial which exhibited an improvement in recanalization rate from 57.3% for mechanical thrombectomy alone to 69.5% when thrombectomy was combined with IA tPA [7]. Several other single-centre series have reported that a multimodality approach is feasible and safe and potentially more effective. Qureshi et al. [8] reported combination of IA tPA with angioplasty or snare manipulation in 14 patients and found multimodality approach to be safe. Abou-Chebl et al. [9] reported series of 12 patients in which multimodality approach was applied and reported it to be feasible and safe with a symptomatic hemorrhage rate of 8.3%. One of the largest single center series on multimodality approach is by Gupta et al. [14]. In their retrospective analysis of 168 stroke patients, they reported recanalization rates of 50%, 60%, and 71% with the use of single-modality, two-modalities, and multimodality approaches respectively with an overall recanalization rate of 63%. Importantly, there was no significant increase in the rate of symptomatic hemorrhages or other complications with increase in the number of modalities used. On the other hand, improvement in NIHSS was significantly associated with the achievement of recanalization. Recently, Leker et al. [18] in Israel reported a recanalization rate of 56% using multimodality approach and noted an association of recanalization with survival and good outcome. The only multicenter study to date was only very recently published by Gupta et al. [19]. In this retrospective analysis of 1122 patients with anterior cerebral circulations ischemic strokes from 13 centers, a significantly higher recanalization rate (74%) was obtained with multimodality approach when compared with pharmacologic modality alone (61%) or mechanical modality alone (63%). In the present study, we report an overall recanalization rate of 74% using a multimodality approach which is comparable to the abovementioned prior reports.

Other important results of our study are also in line with previous reports. We found mRS on discharge to be 3 or less in 44% of patients where successful recanalization was achieved and only in 22% of patients where recanal-

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ization could not be achieved. Thus, more patients with successful recanalization had a favorable outcome on discharge. Similar results have been reported in multiple large trials for mRS at 90 days including PROACT II and Multi-MERCI studies. Unfortunately due to the retrospective nature of this study and the lack of long-term mRS scores, our study fails to provide long-term correlation of recanalization with favorable clinical outcome. Our results of postintervention hemorrhage are also in line with other studies on multimodality reperfusion therapy. We report an overall rate of 19.6% for postintervention hemorrhagic transformation based on the CT scans obtained within 24 hrs of the procedure. More importantly, the rate of symptomatic ICH (those associated with an increase in NIHSS by 4 or greater) is 10.6% in our study. This rate of symptomatic ICH is similar to the rate of 8.5% reported by Gupta et al. (19) in their large multicentre retrospective study using a multimodality approach. Longer ORT time and use of thrombolytic agents were associated with higher risk of hemorrhagic transformation which again is in line with other previous studies. Significantly, the rate of symptomatic ICH reported in the PROACT II study was 10% and in MERCI I study was 7.8%; this suggests that the rate of symptomatic ICH does not increase with the use of multimodality approach and that the multimodality approach is equally safe in terms of the rates of postintervention symptomatic ICH.

One important issue is to determine the most effective combination of endovascular modalities for obtaining recanalization when a multimodality approach is used. In our study, we found that the only independent predictor of recanalization was multimodality approach with combination of IA tPA with any mechanical devise. Combination of IA tPA with individual mechanical modalities did not reach significance likely secondary to small numbers in each group. These results are in line with the findings of other studies [7,9] where a combination of pharmacological and mechanical modalities resulted in improvement in the recanalization rate. Combination of mechanical manipulation with IA tPA likely improves recanalization as by disrupting the clot through mechanical maneuver the surface area for the thrombolytic agent to act on is increased making it more effective [20].

Some interesting results were noted for stenting. These include a trend toward significance for extracranial internal carotid stenting, significant association with recanalization for the combination of angioplasty and stenting, significant association with complete recanalization for the combination of IV tPA with intracranial stent placement, and significant association with improvement in NIHSS. Of note, stent placement was only performed if other modalities had failed or for extracranial carotid occlusions. There are several reports in the literature for use of intracranial [22,23] as well as extracranial [24] carotid stenting in acute stroke setting and their effectiveness in achieving recanalization and restoring blood flow. Intracranial stenting is mostly reported as rescue intervention after failure of other pharmacological and mechanical modalities. On the other hand, extracranial carotid stenting has mostly been used as a primary intervention. Similar to our results, Gupta et al. [14,19] also reported that stenting is significantly more likely to result in recanalization for both intracranial and extracranial locations. The results of our study further corroborate the potential of stent placement in the acute ischemic strokes of anterior cerebral circulation.

We acknowledge that there are several limitations of this study. First, the data were reviewed retrospectively; however, we feel that the results are clinically relevant especially given the fact that no prospective studies have yet been published. Second, this study includes patients with acute ischemic stroke in the anterior cerebral circulation only; hence, the results of this study cannot be applied to patients with stroke in the posterior cerebral circulation. Third, the number of patients in each group was small which decreased the power of our study in detecting some significant differences among different groups. However this is also a limiting factor in most published reports on the subject. Fourth, the study lacks long-term follow-up, the fact that is related mainly to the retrospective nature of this study; this precludes any correlation of recanalization rates to long-term outcomes. Finally, we did not have patients treated by the latest technique of thromboaspiration with the Penumbra device which has showed the best recanalization rates to date. Thromboaspiration with the Penumbra device is the latest addition to the armamentarium of neurointerventionalists; however, at this point the specific indications for thrombectomy vs. thromboaspiration are yet to be determined.

In summary, the present study indicates that a multimodality approach for the treatment of acute ischemic stroke in the anterior cerebral circulation is feasible, safe, and effective. The combination of pharmacological and mechanical modalities is associated with increased likelihood of recanalization. Similarly stenting by itself or as a part of multimodal approach is safe, feasible, and effective. The limitations of the present and previous studies indicate the need for a large controlled prospec-

Table 2.

Treatment modality in relation to recanalization

Individual Therapy	Recanalization mTIMI (2-4) No (n=34)N (%)	Yes (n=98)N (%)	P value
IV tPA	10(29)	42(43)	0.12
IA rtPA	16(47)	33(34)	0.16
SNARE	7(21)	21(21)	0.57
MERCI	6(18)	19(19)	0.52
Angioplasty	4(12)	18(18)	0.27
Intracranial Stenting	8(24)	29(30)	0.33
Extracranial Stenting	6(18)	31(32)	0.09
Multimodality Approach			
IV tPA& IA rtPA	4(12)	12(12)	0.61
IV tPA & Snare	2(6)	6(6)	0.66
IV tPA & MERCI	2(6)	8(8)	0.50
IV tPA & Angioplasty	1(3)	5(5)	0.51
IV tPA & IC Stenting	3(9)	12(12)	0.43
IV tPA & EC Stenting	1(3)	11(11)	0.13
IA tPA & Snare	2(6)	12(12)	0.25
IA tPA& MERCI	8(24)	28(29)	0.37
IA tPA & Angioplasty	1(3)	7(7)	0.34
IA tPA & IC Stenting	1(3)	5(5	0.51
IA tPA & EC Stenting	1(3)	2(2)	0.59
IA tPA & Any Stenting	2(6)	7(7)	0.58
IA tPA & Angioplasty or Stenting	3(9)	11(11)	0.49
Angioplasty & Stenting	2(6)	19(19)	**0.05***

[IV tPA: Intravenous Alteplase; IA tPA: intra-arterial Activase or Reteplase; MERCI: mechanical embolectomy retrieval device; Snare: snare device; IC: intracranial internal carotid; EC: extracranial internal carotid.]

tive multicentre trial to determine the best multimodality approach for the treatment of patients with acute ischemic stroke. We hope that the present study will add valuable information to the current literature as well as help in the development of future multicentre prospective trials.

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