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Correlation of AOL Recanalization, TIMI Reperfusion and TICl Reperfusion with Infarct Growth and Clinical Outcome

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Abstract

Objective—To understand how three commonly utilized measures of endovascular therapy correlate with clinical outcome and infarct growth.

Methods—Prospectively enrolled patients underwent baseline MRI and started endovascular therapy within 12 hours of stroke onset. The final angio was given a recanalization score of the primary arterial occlusive lesion- AOL (0-3), a Thrombolysis in Myocardial Infarct (TIMI) Score (0-3) and a Thrombolysis in Cerebral Infarction (TICI) Score (0-3). Scores were dichotomized into poor revascularization (AOL 0-2, TIMI 0-1 and TICI 0-2a) versus good (AOL 3, TIMI 2-3, TICI 2b-3). Patients were classified as Target Mismatch (TMM) or no TMM. Good outcome was a 90 day mRS of 0-2.

Results—100 patients had attempted endovascular treatment. TICI 2B-3 patients had 57% good outcome compared to 24% of TICI 0-2A patients ($p=0.001$). TIMI 2-3 patients and AOL 3 patients had lower rates of good outcome (44% and 47% respectively) which were not significantly better than TIMI 0-1 or AOL 0-2. In the TMM patients these rates of good outcome improved with all scoring systems and were significantly better for TIMI and TICI scores. TICI 2A patients had rates of GFO and lesion growth which were not different then TICI 0-1 patients but significantly worse than TICI 2B-3 patients.

Conclusion—TIMI 2-3 and TICI 2B-3 reperfusion scores demonstrated improved outcome in mismatch patients with small infarct core and a larger hypoperfused region. AOL scores did not. TICI 2A patients had poorer outcome and more lesion growth than TICI 2B-3 patients.

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Introduction

Trials evaluating success for endovascular therapy have relied on a variety of angiographic grading scales to measure how well an ischemic vascular bed responds to treatment. Some of these scales use recanalization of the affected artery and some use reperfusion of the ischemic territory supplied by the artery in question.¹⁻⁷ The use of multiple scales has resulted in some controversy because of the variability in measurements are not easily translated from one study to another.⁸⁻¹¹ In addition, studies may define the grades of the same scale in different ways.^{8,11} Ultimately, standardizing the system for reporting results would help to allow more direct comparison between studies and endovascular treatment methods. Understanding how these scales may affect outcome measures would be important to this process.

The DEFUSE 2 study was a prospective study of acute ischemic stroke patients treated within 12 hours of symptom onset with endovascular therapy. The primary clinical results of the study were recently published.¹² In order to be included in the study patients had an MRI within 90 minutes of the start of endovascular treatment and using predefined MRI parameters it was hypothesized that patients with a favorable MR pattern would benefit from endovascular therapy. This post-hoc analysis of the angiographic data was designed to evaluate how three scales used to measure success of endovascular treatment correlate with clinical outcome and observed infarct growth following treatment. These three scales which have been previously described are the TICI score, the primary Arterial Occlusive Lesion (AOL) Recanalization score, the Thrombolysis in Myocardial Infarct (TIMI) Score.

Methods

DEFUSE 2 enrolled patients with acute anterior circulation strokes treated with endovascular therapy which was initiated within 12 hours of symptom onset. At the outset patients underwent MRI imaging and were eligible for enrollment if they had a large vessel occlusion. Multi-center enrollment occurred from July 2008 to September 2011¹². Approval for the study enrollment was provided at each center's IRB.

Imaging

Head MR imaging was performed on 1.5 or 3.0 T MR systems using a previously described imaging protocol. Image reconstruction was done off line using a computer system which generated quantitative DWI and PWI lesion maps (RAPID).¹³ Following endovascular therapy an early follow up scan with the same sequences used in the baseline study was obtained within 12 hours of the procedure. An additional MRI study was obtained at discharge or on day 5 and included a fluid-attenuated inversion recovery (FLAIR) sequence which was used to determine infarct volume.

The automated maps generated by the RAPID system included a measure of the ischemic core volume. This volume measured regions of apparent diffusion coefficient (ADC) thresholds of $< 600 \times 10^{-6} \text{mm}^2/\text{sec}$. A PWI volume map was used to determine the amount of hypoperfused tissue based on the time to maximum of the tissue residue function (Tmax) threshold of > 6 seconds. Target mismatch (TMM) was pre-defined by a ratio between the

hypoperfused tissue and ischemic core of 1.8, with an absolute difference of 15ml. In addition, patients with a TMM profile also had to have an ischemic core volumes < 70 ml and the volume of tissue with more severe hypoperfusion ($T_{max} > 10$ seconds) had to be < 100 ml.

Endovascular Treatment

Intervention was started within 12 hours of the onset of ictus and 90 minutes of completion of the baseline MRI study. Local sites were encouraged to use FDA approved devices for thrombectomy which included the Concentric Merci Retriever and the Penumbra Suction Thrombectomy catheter, however no device or technique was mandated. In addition sites were encouraged to minimize IA- tPA use. If no prior tPA had been used centers were encouraged to use less than 25 mg of tPA maximum intra- arterially. If patients had received prior IV-tPA centers were encouraged to use 5 mg intra-arterially.

Imaging Evaluation

All MRI and cerebral angiography studies were evaluated by a core imaging laboratory blinded to clinical data. Infarct growth was defined as the difference between the 5 day FLAIR infarct volume and the baseline DWI lesion volume. A single reader (MPM) evaluated the baseline angiogram prior to treatment to identify the primary arterial occlusive lesion (AOL) and also assigned a TICI score pre-treatment. The final post- treatment angiogram was evaluated by the same reader for reperfusion and recanalization scores using previously described measures for thrombectomy in myocardial infarction (TIMI) scores,¹⁴ thrombolysis in cerebral infarction (TICI) scores¹⁵ and Arterial Occlusive Lesion (AOL) Recanalization score scores.¹ The TICI score was modified from the original definition in that 2A was partial reperfusion 50% of the vascular territory of the occluded artery and 2B was partial reperfusion of > 50% of the occluded artery.⁵ These scores are summarized in Tables 1–3. Post-treatment TICI scores and Arterial Occlusive Lesion (AOL) Recanalization scores were evaluated at the same time and a subsequent blinded evaluation was performed to assign post-treatment TIMI scores.

A dichotomous analysis was performed comparing poor revascularization scores (AOL 0-2, TIMI 0-1, TICI 0-2A) with good revascularization scores (AOL 3, TIMI 2-3, TICI 2B-3). TICI 2B-3 reperfusion was chosen as a pre-specified endpoint to indicate that there had been successful early reperfusion as it correlated with the MR definition of early reperfusion.¹²

Statistics

We compared rates of good outcome between groups using Fisher's exact test. We used the Cochran-Armitage test to evaluate trends in the rates of good outcome with increasing recanalization or reperfusion scores. Lesion growth between dichotomized groups was analyzed with the Mann-Whitney U test. All tests were two-tailed and considered significant at $\alpha < 0.05$ level. Statistical analysis was done using SAS 9.3 (SAS Institute Inc., CARY, NC).

Results

One-Hundred patients went to the cath lab for endovascular therapy and had attempted treatment. There were 49 men and 51 women treated with a mean age of 65 ± 16 years. Median time from symptom onset to femoral puncture was 5.8 hours (IQR 4.5–7.8).

Ten additional patients went to the cath lab but had no attempted treatment because the interventionalist decided it was not necessary after performing a diagnostic angiogram. There was either no angiographic lesion (4 patients) or a more distal lesion was seen (M2, M3 or M4 branches- 6 patients) and it was decided no treatment should be given. Two patients have been included in the group of patients with attempted treatment because the interventionalist intended to treat them but decided after starting the angiogram that they could not proceed. One patient had a difficult femoral artery access with bleeding and the interventionalist decided they could not safely proceed. The second patient had a carotid occlusion just distal to the aortic arch which the interventionalist felt could not be opened safely.

Table 4 shows the distributions of primary arterial occlusive lesions and endovascular therapies employed in the 100 patients with attempted treatment. The mismatch profiles were available in 94 patients (in 6 patients the baseline PWI was technically inadequate) with 75 showing a TMM profile and 19 not having TMM. Eighty-seven of the patients had a five day follow-up MRI to calculate lesion growth.

The pre-treatment angiogram demonstrated TICI 0, 1 flow of the primary occlusive lesion in 87 patients (87%), and TICI 2A,B flow in 13 (13%). Following treatment or attempted treatment 23% remained TICI 0-1, 31% were TICI 2A, 28% TICI 2B and 18% were TICI 3. The distributions of the TIMI scores post-treatment were: 22% TIMI 0-1, 58% TIMI 2 and 20% TIMI 3. The Arterial Occlusive Lesion (AOL) Recanalization scores post-treatment were: 24% AOL 0-1, 17% AOL 2 and 59% AOL 3. The patient with femoral access complications and the patient with very proximal carotid occlusion were scored as TICI 0-1, TIMI 0-1 and AOL 0-1 and the scoring for these two patients relied on MRA studies performed shortly after the attempted procedure.

Figure 1 shows the 90 day modified Rankin Scores 0-2 for the individual recanalization and reperfusion scores in the entire group of 100 patients with the number of patients in each group. There was a strong trend for higher rates of good outcome with increase of AOL score, $p=0.052$. The rate of good outcome was found to increase along with better TIMI score ($p=0.023$) and TICI score ($p=0.008$). Of note those patients with TICI 2A reperfusion had outcomes that were similar to the TICI 0-1 patients.

Figure 2 demonstrates the rates of good outcome for patients using a dichotomous analysis for the different scoring systems. It compares the Arterial Occlusive Lesion Recanalization scores (AOL) 0-2 with AOL 3, TIMI 0-1 with TIMI 2-3 and TICI 0-2A with TICI 2B-3 scores for the entire group of patients and the patients stratified by TMM and no TMM profiles. There was a trend to higher rates of good outcome for AOL 3 scores compared to AOL 0-2 scores in the entire group ($p=0.06$). In the TMM patients, more AOL 3 patients had good outcome compared to the AOL 0-2 group but these differences were not significant

($p=0.096$). The differences were not significant between the TIMI 2-3 patients and TIMI 0-1 patients for the entire group ($p=0.088$) but in the TMM group TIMI 2-3 patients had better outcome ($p=0.025$). The TICI 2B-3 patients did better than the TICI 0-2A patients in the entire group ($p=0.001$) and in the TMM group ($p=0.003$).

Table 5 demonstrates the infarct growth seen in the patients as it correlated with the scoring systems. All the scoring systems demonstrated higher scores had lower rates of infarct growth, with significant differences seen in the dichotomous analysis of the AOL and TIMI and TICI scores. A separate analysis comparing lesion growth for TICI 0-1 (74 ml, 47–127; median, IQR) and TICI 2A (89 ml, 21–178) showed no difference [$p=0.7$], while there was a difference between TICI 2A and TICI 2B-3 growth (23 ml, 6–69) [$p=0.003$].

Discussion

This study evaluated three commonly used measures of revascularization following endovascular therapy for acute ischemic stroke. When the Arterial Occlusive Lesion (AOL) Recanalization scores were analyzed in a dichotomous fashion we also saw a difference between good (AOL 3) and poor (AOL 0-2) recanalization ($p=0.06$). However in the TMM patients the AOL 3 scores were not significantly different compared to the AOL 0-2 scores. The dichotomous analysis showed that outcomes were not better for TIMI 2-3 scores in the entire group ($p=0.088$), but when the TMM patients were evaluated, TIMI 2-3 outcomes were improved ($p=0.025$). We saw improved 90 day outcome rates with TICI 2B-3 scores in the entire study group ($p=0.001$) and the TMM patients with TICI 2B-3 reperfusion also did better at 90 days ($p=0.003$).

These findings show that higher degrees of reperfusion appear to correlate with a greater likelihood of having a good outcome. Using the modified TICI score system we found that TICI 2A flow good outcome rates (26%) were similar to TICI 1 rates (25%) and that TICI 2B good outcome rates (61%) showed a real improvement in good outcome. This suggests that there is possibly a threshold for reperfusion that translates to a higher rate of good functional outcome. The TIMI scoring system does not distinguish these degrees of partial reperfusion, lumping partial reperfusion into a single grade.

The Arterial Occlusive Lesion (AOL) Recanalization score is a measure of recanalization and is likely correlated to some degree with the reperfusion scores because recanalization of the primary arterial occlusive lesion is usually a prerequisite to establishing reperfusion. However recanalization of the primary arterial lesion does not guarantee that there will be full reperfusion of the downstream vascular bed because there may be additional downstream occlusion that is not accounted for in the recanalization score.⁸ This may explain our finding that the recanalization score did not definitely correlate with good functional outcome, particularly in the TMM patients.

Our results for good outcome are similar to the recently reported IMS 3 trial.¹⁶ In the patients treated with endovascular therapy there was a correlation with TICI scores and good outcome ($p<0.001$). In the IMS 3 trial 27.6% of TICI 1 patients, 34.3% of TICI 2A patients, 47.9% of TICI 2B patients, and 71.4% of TICI 3 patients had a good outcome. Another

recently reported randomized trial which did not show a benefit for endovascular therapy, MR RESCUE, used TICI 2A-3 reperfusion as a measure of successful reperfusion.¹⁷ 67% of patients in this study had “successful” reperfusion with at least TICI 2A scores. However, only 27% showed TICI 2B-3 reperfusion, although it should be noted that the definition of TICI 2B used in this trial was greater than 2/3s of the territory in question.

There was a wide variation and certainly overlap in the amount of infarct growth seen with the AOL, TIMI and TICI scoring systems. However, the amount of infarct growth was significantly different between the groups using a dichotomous analysis for all the scores. We also saw that infarct growth was not significantly different with TICI 0-1 and TICI 2A reperfusion, but was lower comparing TICI 2B-3 with TICI 2A reperfusion. This decrease in infarct growth with better reperfusion also suggests that there may be a threshold of reperfusion needed to see improvement in clinical outcome.

The initial description of TICI score system used greater than 2/3s of the territory being reperfused for a TICI 2B definition.¹⁵ A modification of this score was suggested for TICI 2B where the reperfusion was greater than half, which was utilized in this study.⁵ We utilized this modified definition for our evaluation because it most closely matched our pre-specified endpoint for reperfusion measured by the follow-up MR perfusion studies where the follow-up perfusion deficit volume decreased by >50%.¹² A recent review of how the TICI score has been defined in various studies points out that there is tremendous variability in the definitions used for the various categories of the TICI score.¹⁸ A recent single center retrospective comparison of endovascular therapy patients showed that use of TICI 2B >50% rather than >66% included about 20% more patients in the TICI 2B category.¹⁹ In addition the study found that using >50% for TICI 2B reperfusion (as opposed to >66%) was more likely to identify patients in the TICI 2B-3 category with good outcome. A recently reported analysis of 308 patients undergoing endovascular therapy also found that TICI 2B-3 reperfusion, where > 50% reperfusion was used for the definition of TICI 2B flow, had the greatest sensitivity for predicting good outcome at 90 days.²⁰ These types of results have prompted investigators to call for the use of this threshold for defining adequate reperfusion.^{21, 22}

In conclusion, we found that TMM patients with TIMI 2-3 and TICI 2B-3 reperfusion had significantly higher rates of good functional outcome compared to TIMI 0-1 and TICI 0-2A reperfusion respectively. However, TICI 2A reperfusion was similar to TICI 0-1 in the rates of good functional outcome. Outcome was not significantly improved in TMM patients with AOL 3 recanalization compared to those with AOL 0-2 recanalization. Median lesion growth was also found to be less in the patients with good reperfusion or recanalization scores.

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Figure 1.

Rates of Good Functional Outcome for individual Recanalization and Reperfusion scores

Figure 2.
Rates of Good Functional Outcome in Dichotomous analysis of Recanalization and Reperfusion scores

Table 1

Thrombolysis in Myocardial Ischemia (TIMI) Scale

TIMI Grade	Definition
Grade 0	Absence of any antegrade flow beyond the target occlusion (no perfusion)
Grade 1	Antegrade flow beyond the target occlusion, without distal branch filling (penetration without perfusion).
Grade 2	Delayed antegrade flow with some filling of the distal branches (partial perfusion).
Grade 3	Normal flow which fills all distal branches (complete perfusion).

Table 2

Treatment in Cerebral Ischemia Scale (TICI)

TICI Grade	Definition
Grade 0	No perfusion
Grade 1	Antegrade perfusion beyond the occlusion, but limited distal branch filling with slow distal perfusion
Grade 2a	Antegrade perfusion of less than half of the occluded artery ischemic territory
Grade 2b	Antegrade perfusion of more than half of the target artery ischemic territory
Grade 3	antegrade perfusion of the occluded target artery ischemic territory

Table 3

Arterial Occlusive Lesion (AOL) Scale

AOL Grade	Definition
Grade 0	Complete occlusion of the primary occlusive lesion
Grade 1	Incomplete or partial recanalization of the primary occlusive lesion with no distal flow
Grade 2	Incomplete or partial recanalization of the primary occlusive lesion with any distal flow
Grade 3	Complete recanalization of the primary occlusive lesion with any distal flow

Table 4

Vessel Occlusion and Therapy

Vessel occlusion on angiogram – no. (%)	
Internal carotid artery, proximal	17 (17)
Internal carotid artery, distal	13 (13)
Middle cerebral artery, proximal (M1)	58 (58)
Middle cerebral artery, distal (M2,3)	20(20)
Endovascular therapy employed – no. (%)	
Merci device	48 (48)
Penumbra system	42 (42)
Intra-arterial tPA	42 (42)
Other	31 (31)

Table 5

Lesion Growth

	AOL Score		TIMI Score		TICI Score	
	0 - 2	3	0-1	2-3	0-2A	2B-3
Number	36	51	23	64	44	43
Median * (IQR)	74 (34-165)	39 (7-85)	68 (46-127)	41 (18-93)	83 (39-159)	23 (6-69)
	P = 0.002		P = 0.019		P < 0.001	

* median lesion growth in ml