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The Clinical and Radiographic Importance of Distinguishing Partial from Near-Complete Reperfusion Following Intra-Arterial Stroke Therapy

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ABSTRACT

BACKGROUND AND PURPOSE: Reperfusion following intra-arterial stroke therapy is associated with improved clinical outcomes. However, the degree of reperfusion needed to achieve successful outcomes is unknown. The purpose of this analysis was to determine whether the degree of reperfusion has an impact on final infarct volumes and clinical outcomes.

MATERIALS AND METHODS: A retrospective analysis identified 88 consecutive patients who underwent intra-arterial therapy for acute anterior circulation stroke. Reperfusion was graded by using the TICl scale into none (TICl 0 or 1), partial (TICl 2a), or near-complete (TICl 2b/3). Baseline characteristics were compared. For each of these groups, we compared discharge disposition and final infarct volumes.

RESULTS: Near-complete, partial, and no reperfusion occurred in 44.3%, 26.1%, and 29.6% of patients, respectively. Baseline characteristics were similar across all 3 groups. The median NIHSS score was 15. Significant differences in discharge disposition were seen, with 41.0% of the TICl 2b/3 group discharged home versus 17.4% of TICl 2a and 7.7% of TICl 0/1. In-hospital mortality was 12.8% for TICl 2b/3 compared with 39.1% for TICl 2a and 34.6% for TICl 0/1. Patients with near-complete reperfusion were significantly more likely to have infarct volumes ≤ 70 mL (OR = 12.1; 95% CI, 2.7–54.2), compared with patients with partial reperfusion (OR = 2.2; 95% CI, 0.5–9.6).

CONCLUSIONS: Significant differences exist in outcomes and infarct volumes between partial (TICl 2a) and near-complete (TICl 2b/3) reperfusion following intra-arterial stroke therapy. Further trials should separately report these groups to facilitate comparison among treatment paradigms.

ABBREVIATIONS: CI = confidence interval; IAT = intra-arterial thrombolysis; IMS = Interventional Management of Stroke; OR = odds ratio; TICl = Thrombolysis in Cerebral Ischemia; TIMI = Thrombolysis in Myocardial Ischemia

Intra-arterial therapy, including thrombolytic infusion and mechanical thrombectomy, has emerged during the past decade as a potential treatment option for patients with acute ischemic stroke from large-vessel occlusion who are ineligible for or fail to improve following intravenous tPA.^{1–5} While there is a strong association between any reperfusion and favorable clinical outcome, there is not a universal benefit to reperfusion. For example, analysis of the Mechanical Embolus Removal in Cerebral Ischemia and Multi MERCI trials showed that 48% of patients in whom reperfusion was achieved had a favorable clinical outcome, compared with 6% of nonreperused patients.⁶

The angiographic efficacy of either IAT or mechanical thrombectomy can be described by using a variety of grading systems. The most commonly reported means is the TICl score, derived from the TIMI schema. The definition and classification have been previously described.⁷ Many stroke trials have considered TICl 2/3 to be “successful” reperfusion and TICl 0/1 to be “failed reperfusion.” The TICl 2 class is further subdivided into either TICl 2a or 2b, depending on whether the residually occluded territory involves more or less than two-thirds of the vascular distribution of the initial occlusion, respectively (On-line Table 1).

While several previous studies have shown improved clinical outcomes with reperused (defined as TICl 2/3 flow) compared with nonreperused patients (TICl 0/1), few studies have specifically examined the relationship between TICl 2a and 2b/3 reperfusion. The purpose of our study was to determine whether differences in clinical outcomes exist between patients in whom partial reperfusion (which we defined as TICl 2a) is achieved versus those with near-complete reperfusion (which we defined as TICl 2b/3). We also sought to examine the relationship between reperfusion class, final infarct volume, and clinical outcome.

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Table 1: Baseline demographics and clinical characteristics

	All Patients	By Final TIC1 Class			P Value
		TIC1 0/1	TIC1 2a	TIC1 2b/3	
No. (%)	88	26 (29.6)	23 (26.1)	39 (44.3)	
Age (mean)	68.2	68.9	68.1	67.9	.81
Sex (% female)	50%	57.70%	47.80%	46.10%	.68
History of hypertension	72.70%	65.40%	73.90%	76.90%	.62
Diabetes mellitus	28.40%	26.90%	21.70%	33.30%	.63
Coronary artery disease	25%	30.80%	30.40%	17.90%	.36
Atrial fibrillation	31.80%	23.10%	34.80%	35.90%	.58
Prior ischemic stroke	19.30%	15.40%	26.10%	17.90%	.63
Cigarette smoking within past 12 months	22.70%	23.10%	17.40%	25.60%	.77
Peripheral artery disease	9.10%	3.90%	8.70%	12.80%	.58
Mean admission NIHSS score	14.9	15.2	15.5	14.3	.83
Median admission NIHSS score	15	14.5	16	15	.83
Admission systolic BP (mm Hg, mean)	144.60	143.50	146.00	144.50	.87
Admission blood glucose (mg/dL, mean)	131.10	122.60	130.80	137.10	.51
Proximal occlusion (ICA or proximal M1 segment of MCA with lenticulostriate involvement)	51.10%	57.7%	65.2%	38.5%	.09
Time from symptom onset to angiography (min, mean)	288.80	302.3	299.6	272.7	.51

Note:—BP indicates blood pressure.

MATERIALS AND METHODS

Institutional review board approval was obtained for the study. The stroke center data bases at 2 teaching hospitals were reviewed for patients 18 years of age or older who underwent intra-arterial therapy (either alone or in conjunction with intravenous tPA) for acute anterior circulation ischemic stroke between January 1, 2005, and December 31, 2010. Such patients typically had admission NIHSS scores of ≥ 8 or moderate-to-severe aphasia, initial CT findings of less than one-third MCA territory involvement with acute infarct signs such as hypoattenuation with sulcal effacement and angiographically documented occlusion (TIC1 0/1) of the ICA, M1, or proximal M2 segment. Additional imaging studies (eg, CTA, diffusion MR imaging) were performed in some patients. General anesthesia was not routinely used for angiography unless the patient's clinical status necessitated airway protection. Patients were excluded if the stroke was in the posterior circulation, the event was a complication of another angiographic procedure, or angiography showed no proximal arterial occlusion (defined as TIC1 0/1).

For all patients, the following demographics were recorded from a retrospective review of the medical records: age, sex, history of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, prior stroke, cigarette smoking in the past year, peripheral artery disease, NIHSS score at admission, admission systolic blood pressure, and admission blood glucose. In some cases when a documented NIHSS score at admission could not be found in the medical record, it was extrapolated on the basis of the documented neurologic examination.⁸ Angiographic/treatment parameters recorded were the following: site of occlusion, time from symptom onset (or last seen well) to the start of angiography, administration of intravenous tPA, intra-arterial therapy performed (mechanical thrombectomy and/or IAT), location of arterial occlusion, and TIC1 status pre- and posttreatment.

TIC1 scoring was performed by retrospective review of angiographic images on a PACS workstation by a single interventional neuroradiologist (M.V.J.) blinded to the clinical outcome of the patient. We used the TIC1 score as presented in the previously published reporting standards document,⁷ in which TIC1 2a

would imply patent flow through the site of the initial occlusion but distal filling of less than two-thirds of the affected territory. We defined TIC1 0/1 as "failed reperfusion," TIC1 2a as "partial reperfusion," and TIC1 2b or 3 as "near-complete reperfusion." In the TIC1 classification that we used (On-line Table 1), TIC1 2a reperfusion implies not just recanalization of the proximal arterial branches but also washout of contrast during the angiographic run in a timely fashion, suggestive of end tissue reperfusion. For this reason, we will use the term "reperfusion" in the remainder of this article. For patients with ICA or M1 occlusion, infarct volumes on posttreatment images obtained between 24 and 48 hours after treatment were calculated by determining volumes on each axial section and multiplying by the section thickness. The presence of any hemorrhage on posttreatment imaging was recorded, and hemorrhage was classified according to the European Cooperative Acute Stroke Study definition.⁹⁻¹¹ Outcomes were categorized on the basis of hospital discharge status into 3 categories: home (with or without services), rehabilitation (short- or long-term), or death (including discharge to hospice care).

Statistical Analysis

All statistical analysis was performed by using R software (<http://www.R-project.org>). We used the Fisher exact test for significance testing for differences between groups for categorical variables; for ordinal variables, we used the Mann-Whitney *U* test for medians. Odds ratios were calculated for likelihood of final infarct volume (≤ 70 mL) for each of TIC1 2b/3, TIC1 2/3 (including 2a and 2b), and TIC1 2a alone compared with TIC1 0/1. Odds ratios for discharge home and in-hospital mortality were also similarly calculated. Odds ratios were calculated by using <http://www.hutchon.net/ConfidOR.htm>. *P* values $< .05$ were considered significant.

RESULTS

Eighty-eight patients met the defined inclusion criteria. The mean age was 68.2 years, 50% of patients were female, and the median NIHSS score at admission was 15 (range, 2–29). The baseline characteristics of all patients and by TIC1 grouping are recorded

Table 2: Treatment details of intra-arterial therapy

Angiographic Parameters	No.	%
IV tPA given prior to IA therapy	14	15.9
Intubated at any point during angiography	3	3.4
Site of occlusion		
ICA	22	25.0
M1, proximal (involves lenticulostrlates)	23	26.1
M1, distal (spares lenticulostrlates)	16	18.2
M2	25	28.4
M3	2	2.3
Concomitant cervical segment ICA stenosis (>70%) or occlusion	16	18.2
Treatment		
Thrombolytic infusion alone	65	73.9
Mechanical thrombectomy alone	4	4.5
Both MT and IAT	19	21.6
Intracranial stent placement	4	4.5

Note:—IA indicates intra-arterial; MT, mechanical thrombectomy.

Table 3: Discharge disposition by TICl class and infarct volume

	Home	Rehab	Death/Hospice	P Value
All Patients	25%	48.9%	26.1%	
By TICl class				
TICl 0/1	7.7%	57.7%	34.6%	.0084
TICl 2a	17.4%	43.5%	39.1%	
TICl 2b/3	41.0%	46.2%	12.8%	
By infarct volume				
Infarct volume ≤70 mL	36%	50%	14%	
Infarct volume >70 mL	0%	38%	63%	

Note:—Rehab indicates rehabilitation.

in Table 1. No significant differences were noted. Sixty-five patients (73.9%) had IAT alone, 19 (21.6%) had both IAT and mechanical thrombectomy, and 4 (4.5%) had mechanical thrombectomy alone (Table 2). Intracranial stents were placed in 4 patients (4.5%) for presumed underlying stenosis. Final thrombolysis scores were TICl 0/1 (failed reperfusion) for 29.6%, TICl 2a (partial reperfusion) for 26.1%, and TICl 2b/3 (near-complete reperfusion) for 44.3%.

Table 3 summarizes the relationship between TICl score and outcome. Significantly more patients had better outcomes with TICl scores of 2b/3 compared with 2a. Home discharges increased from 7.7% for TICl 0/1 to 17.4% for TICl 2a to 41% for TICl 2b/3 ($P = .0084$). Mortality was significantly lower in the TICl 2b/3 group compared with TICl 2a (12.8% versus 39.1%) ($P = .0084$).

Posttreatment imaging was unavailable for 1 patient who died within 24 hours of the procedure, and 27 patients had an M2 or M3 occlusion, leaving 60 patients for the imaging analysis. Mean infarct volumes based on reperfusion class were 33.7 ± 46.3 mL for TICl 2b/3, 84.8 ± 88.3 for TICl 2b, and 147.9 ± 103.2 for TICl 0/1. Based on discharge disposition, mean final infarct volumes were 12.5 ± 19.9 mL, 46.5 ± 43.8 mL, and 161.8 ± 165 mL for home, rehabilitation, and death/hospice respectively. Mortality was 63% in patients with a final infarct volume >70 mL compared with 14% in those with ≤70 mL (Table 3).

The odds ratios for smaller final infarct for different reperfusion classes are summarized in Table 4. Patients were more likely to have infarct volumes ≤70 mL with TICl 2b/3 versus TICl 2a reperfusion (Table 4). When TICl 2a and 2b/3 are all grouped together, there remains a significant likelihood that patients with

Table 4: Odds ratios for final infarct volume <70 mL by final reperfusion class, compared with TICl 0/1 reperfusion

	OR Compared with TICl 0/1 for Final Infarct Volume <70 mL (95% CI)
TICl 2b/3 reperfusion	12.1 (2.7–54.2)
TICl 2a or 2b/3 reperfusion (any reperfusion)	6.79 (1.8–25.2)
TICl 2a reperfusion	2.2 (0.5–9.6)

Table 5: Odds ratios for discharge home and in-hospital mortality comparing various reperfusion groups versus TICl 0/1, for all patients and those with ICA and M1 occlusions only

	All Patients (n = 88)		ICA, M1 Only (n = 61)	
	OR	95% CI	OR	95% CI
OR for discharge home				
TICl 2a vs 0/1	2.52	(0.41–15.2)	N/A ^a	
TICl 2b/3 vs 2a	3.30	(0.94–11.56)	5.18	(0.99–27.07)
TICl 2b/3 vs 0–2a	4.99 ^b	(1.72–14.48) ^b	10.03	(1.99–50.51) ^b
OR for in-hospital mortality				
TICl 2a vs 0/1	1.21	(0.38–3.88)	0.88	(0.22–3.45)
TICl 2b/3 vs 2a	0.23 ^b	(0.07–0.81) ^b	0.17	(0.04–0.68) ^b
TICl 2b/3 vs 0–2a	0.25 ^b	(0.08–0.76) ^b	0.16	(0.04–0.55) ^b

^a N/A indicates that no patients with ICA or M1 occlusion with TICl 0/1 reperfusion were discharged home in this series.

^b Comparisons in which the 95% confidence interval does not cross 1.0 are considered significant.

any reperfusion will have smaller infarcts compared with those with no reperfusion, but the effect is smaller.

We also considered the possibility that patients with M2 occlusions might have a more benign clinical course than those with ICA or M1 occlusion. We compared the odds ratios for discharge home and in-hospital mortality in our entire sample and in those with ICA or M1 occlusions only; the data are summarized in Table 5. As would be expected, the difference between partial and near-complete reperfusion appears to be greater when M2 occlusions are eliminated from the analysis. When occlusions of M2 and beyond are removed from the analysis, the OR for discharge home with TICl 2b/3 versus TICl 2a reperfusion almost reaches statistical significance (lower limit of 95% confidence interval, 0.99) and may do so with a larger sample size.

Rates of all hemorrhage on imaging were similar between the TICl 0/2a and TICl 2b/3 groups (38.8% and 41.0%, respectively). Rates of parenchymal hematoma type 2 (European Cooperative Acute Stroke Study definition) were higher with TICl 0/2a versus TICl 2b/3 (10.2% versus 2.6%), but this difference was not statistically significant.

DISCUSSION

In this retrospective analysis, we show that for patients presenting with acute anterior circulation stroke, complete or near-complete angiographic reperfusion (TICl 2B/3) appears to result in significant improvement in discharge outcomes versus partial reperfusion (TICl 2a). Our patients with TICl 2b/3 reperfusion had higher rates of discharge to home (41.0% versus 17.4%), lower rates of in-hospital mortality (12.8% versus 39.1%), and a higher percentage with ≤70-mL final infarct volume (81% versus 56%). While other series have shown a benefit to reperfu-

sion overall (defined as TICI 2/3), to our knowledge, this is the first study showing a significant improvement in outcomes between TICI 2a and 2b/3 reperfusion. This would suggest that the threshold for success in intra-arterial stroke therapy for proximal large-artery occlusion is best defined as TICI 2b flow or better.

An analysis of the IMS I and II trials of combined intravenous and intra-arterial therapy showed a trend toward better outcomes with TICI 2a versus 2b/3, but this did not reach statistical significance ($P = .08$).¹² That analysis did show, however, that the relationship between angiographic reperfusion and good outcome was stronger for TICI 2b/3 reperfusion than for TICI 2/3. Differences in outcomes between partial and complete revascularization were also presented for the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial,⁵ but not by using the same TICI scale. Our threshold for near-complete was 66% of affected territory, compared with 50% for IMS I/II. It would seem intuitive that a higher degree of reperfusion would be more predictive of good clinical outcome.

There are several schema available for classifying angiographic results, including the Mori scale,⁵ TIMI, the arterial occlusive lesion score from IMS, and the original TICI and the modified TICI, with 2a and 2b defined separately. The relationship between these schema and outcomes, including comparison of TIMI and Mori schemes and comparison of outcomes based on TIMI, has also been done,¹³ with both of those series suggesting a benefit to partial reperfusion. However, the definition of partial reperfusion is key, with TIMI 2 (encompassing both 2a and 2b) considered partial reperfusion in both of those series. Our data would suggest that the distinction between partial and near-complete reperfusion should be made at the TICI 2a/2b level.

In a recently published analysis of the MERCI and Multi MERCI trials, Fields et al¹⁴ showed increases in favorable clinical outcomes and decreases in mortality with increasing rates of TIMI recanalization. In our series, we combined TICI 0/1 grades as “no reperfusion,” as has been done in almost all previous trials of intra-arterial therapy. Another important issue is whether further revascularization attempts should be pursued when TICI 2a reperfusion has been achieved. It is conceivable that further attempts, especially with mechanical devices, to reperfuse distal branches once TICI 2a reperfusion has been achieved may be deleterious to the patient.

Our results evaluating the relationship of final infarct volume with reperfusion class and outcomes are concordant with recent data showing a relationship between volume of infarct core at arrival to the hospital and clinical outcomes. Yoo et al¹⁵ showed that for patients undergoing intra-arterial therapy, a baseline diffusion-weighted infarct volume of 70 mL predicted poor outcome, irrespective of reperfusion. Similar data have also been shown for the Echoplanar Imaging Thrombolysis Evaluation Trial, by using extended-time-window treatment with IV tPA, with a cutoff of 65 mL, beyond which intravenous tPA appeared to be harmful, with the greatest benefit seen for patients with DWI lesions <25 mL.¹⁶ Another extended-time-window trial, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution trial, also showed that patients with an admission DWI lesion of >100 mL did poorly even with reperfusion.¹⁷

It appears from our data that clinical outcomes in patients with final infarct volumes >70 mL are poor, with a 63% in-hospital mortality. Our results would suggest that in patients with proximal large-artery occlusion (ICA, M1), most of the territory would need to be salvaged to minimize final infarct volume and thus offer the greatest possible clinical benefit.

Despite some increases in reperfusion rates from intra-arterial prourokinase administration to mechanical thrombectomy, patient outcomes have not improved at the same rate. Many trials of IAT have not separately reported TICI 2a versus 2b reperfusion, and this omission may partially explain the lack of improved clinical outcomes, despite increasing published rates of reperfusion. In On-line Table 2, we summarize major multicenter studies of IAT. Most of these studies do not separate reperfusion into partial (TICI 2a) versus complete (TICI 2b/3).

This study has limitations. First, it is a retrospective single-center study. Second, patient selection and treatment protocols were not precisely defined as they are for prospective trials. Nevertheless, baseline demographics in this study are similar to those in other trials, and reperfusion results were similar to those in several multicenter trials (On-line Table 2). Third, 90-day outcomes were not available for most patients, and outcome status was based on discharge location. Discharge disposition has been used as an outcome marker in previously published studies of intra-arterial therapy for stroke.¹⁸ In addition, our study included patients with an NIHSS <10, and patient outcomes (regardless of treatment) are generally better with lower admission NIHSS scores.

Future studies of intra-arterial therapy should separate angiographic results into none, partial (TICI 2a), and near-complete (TICI 2b/3). Clinical outcomes should be reported separately for these groups. Both our results and those from IMS I and II have shown that the greatest benefit appears to be for the near-complete reperfusion group, though different thresholds were used (66% for near-complete in this study and 50% for near-complete in IMS I/II). While the optimal degree of reperfusion necessary to be considered successful may not yet be determined, it seems that including patients with low degrees of reperfusion (<50%) in the “success” group may overstate the angiographic results of intra-arterial therapy. If indeed the outcome of therapy needs to be dichotomized, perhaps angiographic success from intra-arterial therapy should be defined as TICI 2b/3 reperfusion. It may also be beneficial for all multicenter trials to have angiographic core lab evaluation because local angiographers can overgrade their outcomes.¹⁹ Analysis of ongoing and future multicenter trials may allow us to further refine the TICI 2 subcategories and help determine the optimal threshold to be considered successful. We hope that newer therapies will allow rapid achievement of complete reperfusion in a greater percentage of patients, with the expectation that complete reperfusion translates into better outcomes for our patients.

CONCLUSIONS

Significant differences exist in clinical outcomes between partial (TICI 2a) and near-complete (TICI 2b/3) reperfusion following intra-arterial stroke therapy for acute anterior circulation stroke.

Further trials should separately report these groups to facilitate comparison among treatment paradigms.

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