Not All “Successful” Angiographic Reperfusion Patients Are an Equal Validation of a Modified TICI Scoring System

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Summary

Rapid reperfusion of the entire territory distal to vascular occlusions is the aim of stroke interventions. Recent studies defined successful reperfusion as establishing some perfusion with distal branch filling of <50% of territory visualized (Thrombolysis In Cerebral Infarction “TICI” 2a) or more. We investigate the importance of the quality of final reperfusion and whether a revision of the successful reperfusion definition is warranted.

We retrospectively evaluated a prospective database of anterior circulation strokes treated using stentrievors to assess the quality of final reperfusion using two scores: the traditional TICI score and a modified TICI score. The modified TICI score includes an additional category (TICI 2c): near complete perfusion except for slow flow or distal emboli in a few distal cortical vessels. We compared different cut-off definitions of reperfusion (TICI 2a – 3 vs. TICI-2b-3 vs. TICI 2c-3) using the area under the curve to identify their correlation with a favorable 90-day outcome (mRS≤2). In our cohort of 110 patients, 90% achieved TICI 2a-3 reperfusion with 80% achieving TICI 2b-3 and 55.5% achieving TICI 2c-3. The proportion of patients with a favorable 90-day outcome was higher in the TICI 2c (62.5%)

compared to TICI 2b (44.4%) or TICI 2a (45.5%) but similar to the TICI 3 group (75.9%). A TICI 2c-3 reperfusion had a better predictive value than TICI 2b-3 for 90-day mRS 0-1.

Defining successful reperfusion as TICI 2c/3 has merits. In this cohort, there was evidence toward faster recovery and better outcomes in patients with the TICI 2c vs. the traditional TICI 2b grade.

Introduction

Mechanical stroke therapy gained momentum with the advent of endovascular stentrievors, which achieve high reperfusion rates in short procedural times¹⁻³. Still, many trials describe dissociation between high rates of successful reperfusion and relatively low rates of independent functional outcome⁴⁻⁶. One potential explanation for such dissociation is the heterogeneity in defining the procedural success of mechanical stroke therapy.

Ideally, angiographic success should entail restoring both the patency of the target occlusion (full recanalization) and blood flow in the downstream vascular territory (complete reperfusion)⁷⁻⁹. The scoring systems used to measure the success of recanalization are the Arterial

Occlusive Lesion (AOL) and the Thrombolysis in Myocardial Infarction (TIMI) recanalization scales¹⁰. However, interest started to shift toward global reperfusion rather than local recanalization with the increasing use of mechanical devices that achieve a relatively high recanalization compared to intravenous or local chemical thrombolytics¹¹. These factors prompted the use of the TIMI reperfusion scale¹⁰ which was derived for use in the coronary circulation. This scale proved to have many shortcomings when applied to the more complex cerebral circulation¹². Therefore, the Thrombolysis In Cerebral Infarction (TICI) grading system was devised to be the standard for reporting the angiographic results of mechanical stroke therapies¹³. Using the existing TICI score, successful reperfusion has been defined as perfusion of at least half of the territory visualized with the presence of some distal occlusions.

The TICI score has a number of limitations that are either inherent in the score itself or in the way it is applied. The definition of successful reperfusion used in major endovascular trials including IMS-II,¹⁴ IMS-III,¹⁵ and the Trevo trial has been criticized¹⁶. Considering TICI-2a as the minimum reperfusion required to define successful reperfusion has been questioned given the high rate of reperfusion with use of stentriever. Reperfusion of less than half of the MCA territory is expected to result in a sizable infarct that would make independent recovery less likely. In addition, the discrepant TICI scoring between trial core labs and the trial sites described in some intra-arterial randomized trials raises concerns about the interrater reliability of the score. Some of this discrepancy might have occurred when the presence of one or few distal occlusions was scored as TICI 2b by the core labs when the reperfusion was considered near complete by the site. To account for these situations, a TICI 2c grade was proposed as an addition to the current TICI score to incorporate subjects with near complete perfusion. This additional grade is particularly relevant when considering the high rates of near complete reperfusion achieved using the stentriever². A consensus statement encouraged exploring the use of different TICI thresholds as TICI 2c with careful assessment of its impact on outcome¹⁹.

This report investigates the importance of the final reperfusion quality in deciding patients' outcomes and whether patients with the

proposed TICI 2c score are different in their baseline characteristics and outcomes from the TICI 2a, 2b or 3. In addition, we explore the need for a modification of the existing definition of successful reperfusion using three different TICI score cut-offs.

Methods

Design and population

This is a retrospective analysis of the prospectively-populated, Alberta Comprehensive Outcomes Research in Neurosciences (ACORN) database. The study cohort includes all anterior circulation acute stroke patients who underwent mechanical stroke therapy using stentriever from January 2011 to December 2012 at the Foothills Medical Center in Calgary, Alberta, Canada. Data collection for this database has been approved by the University of Calgary Conjoint Health Research Ethics Board.

Clinical and imaging characteristics

Patients' demographics, presenting history and baseline NIHSS scores were obtained independently by the treating stroke team members. All patients underwent unenhanced CT scan of the head followed by CT angiography prior to treatment. Once the decision to proceed with endovascular therapy was made by a stroke neurologist, patients were rushed to the angiography suite.

The Alberta Stroke Program Early CT Score (ASPECTS) for baseline and 24-hour CT scans was determined by consensus of two stroke neurologists blinded to the patients' clinical and angiographic outcomes. All patients underwent 24-hour clinical and radiographic assessments. Repeat 24-hour CT scan was scored for the extent of ischemic changes using the ASPECTS score as well as the presence of intracranial hemorrhage as classified using the SITS-MOST criteria²⁰.

Angiographic data

Angiograms were reviewed and scored independently by two interventionalists: one used the traditional TICI score²¹ while the other used the modified TICI score (Table 1). For the purpose of angiographic data interpretation,

Table 1 **The proposed modified TICI score**

Score	Revised Thrombolysis in Cerebral Infarction Scale
0	No perfusion or anterograde flow beyond site of occlusion
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared to non-involved territories
2A	Some perfusion with distal branch filling of <50% of territory visualized
2B	Substantial perfusion with distal branch filling of $\geq$ 50% of territory visualized
2C	Near complete perfusion except for slow flow in a few distal cortical vessels, or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches

successful reperfusion was defined as a score of TICI 2a or more. The reperfusion time was defined as the time of the first angiographic run showing successful reperfusion after the stentriever was removed. The imaging to reperfusion time is the time interval from the last non-contrast CT head image acquisition to the time of successful angiographic reperfusion. The onset of reperfusion time was defined as the time interval from the witnessed symptoms onset or last seen normal to the time of successful angiographic reperfusion.

Outcomes

The proportion of patients with significant clinical improvement was defined as a drop of 75% or more of the 24-hour NIHSS score compared to the baseline NIHSS. Functional outcomes were determined using the 90-day modified Rankin Scale (mRS) with favorable functional recovery defined as a score of 2 or less.

Statistical analysis

Variables are summarized as medians or proportions as appropriate. Continuous variables were compared using the Mann Whitney U test and proportions were compared by Fischer's exact test. The baseline and treatment variables were compared among the groups.

The primary objective of this study was to compare the predictive values of variable definitions of successful reperfusion on the 90-day outcome. To explore the optimal definition of successful reperfusion, three proposed successful reperfusion definitions were used: TICI 2a-3 vs. TICI 2b - 3 vs. TICI 2c-3. We compared the

ability of each of these reperfusion definitions to predict a favorable 90-day outcome by comparing the area under the curve (AUC) of models using each of the above definitions of successful reperfusion as exposure and pre-defined 90-day clinical outcomes. Other clinical outcomes such as 24-hour NIHSS score, and the proportion of patients with significant clinical improvement (defined as a 24-hour NIHSS score of 0 or 1) were also compared among the three definition groups. All testing was two-tailed and was done at the 0.05 level of significance. Analyses were performed using Stata 11 software (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics

This cohort included 110 patients with a median age of 68 years (inter quartile range "IQR" 19) and a median presenting NIHSS score of 17 (IQR 9). The cohort included 53 females (48.2 %). The median ASPECTS score on baseline CT was 8 (IQR 2). Final reperfusion score of TICI 2a was achieved in 11 patients (10%), TICI 2b in 27 (24.5%), TICI 2c in 32 (29.1%) and TICI 3 in 29 (26.4%). Among the 32 patients with the TICI 2c score, 17 were originally scored as a TICI 3 while 15 were scored as TICI 2b using the traditional TICI score. The baseline characteristics of patients classified by their TICI scoring are shown in Table 2. There was no significant difference between the three groups in the baseline NIHSS scores or extent of early ischemic changes on baseline CT as as-

sessed by the ASPECTS score. Patients in the TICI 2a group were relatively older than those in the other groups.

Treatment details

More patients were treated with IV tPA in the TICI 2c and 3 groups compared to the other groups (Table 2; Fisher exact p 0.8). There was a significant trend toward shorter imaging to reperfusion time across the TICI 2a to 3 groups (Wilcoxon rank-sum trend test p 0.003). There was a non-significant trend toward shorter onset to reperfusion times across these groups (p 0.08).

Clinical outcomes

Clinical improvement at 24 hours from intervention was observed in all groups (Table 2). A significantly higher proportion of patients with clinical improvement (NIHSS 75% drop over 24 hours) were seen in TICI-2c group compared to the traditional TICI-2b (56.3 vs 32.4%, p 0.04) or the modified TICI-2b (56.3 vs 25.9%, p 0.019). The distribution of the 90-day mRS scores across the TICI 2a to 3 groups is shown in Figure 1. Independent functional recovery (mRS $\leq$ 2) at 90 days was highest in the TICI 3 group (Table 3). A higher number of patients in the TICI 2c achieved a 90-day mRS $\leq$ 2 compared to the

Table 2 **Clinical outcomes**

	TICI 2a	TICI 2b	TICI 2c	TICI 3
Number	11	27	32	29
Mean age (SD)	71.7 (10)	66.1 (15)	63.6 (15)	68.2 (13)
Median baseline NIHSS (iqr)	17 (13)	19 (9)	17 (6)	17 (10)
Median baseline ASPECTS (iqr)	8 (4)	8 (3)	8 (2)	8 (2)
Median puncture to reperfusion (iqr)	102 (60)	60 (44)	44 (35)	33 (20)
Median imaging to reperfusion (minutes, iqr)	169 (155)	127.5 (67)	103 (40)	92 (55)
Median onset to reperfusion (minutes, iqr)	305 (44)	308 (209)	233 (198)	204.5 (151)
Number treated with IV tPA (%)	5 (45.5%)	14 (51.9%)	19 (59%)	17 (58.6%)
Median 24-hour NIHSS (iqr)	11 (9)	11 (11)	5 (10)	3 (8)
Number with clinical improvement * (%)	3 (27.3%)	7 (25.9%)	18 (56.3)	16 (55.2)
Median 24-hour ASPECTS (iqr)	6 (5)	5 (3)	7 (3)	7 (3)
Proportion with 24-hour sICH (%)	1 (9.1%)	3 (11.1%)	2 (7.7%)	1 (3.6%)

sICH: symptomatic intracranial hemorrhage as per SITS-MOST definition.
 * Significant clinical improvement: a drop of 75% or more of the 24-hour NIHSS score compared to the baseline NIHSS.

Table 3 **90-day outcomes stratified by traditional and modified TICI scoring**

90-day Functional outcome	Traditional TICI scoring (N 94)*			Modified TICI scoring (N 99)			
	2a (n 11)	2b (n 37)	3 (n 46)	2a (n 11)	2b (n 27)	2c (n 32)	3 (n 29)
Median mRS (iqr)	2 (5)	3 (3)	1 (2)	2 (5)	3 (3)	2 (3)	1 (2)
Number with mRS 0-2 (%)	5 (45.5%)	17 (47%)	34 (73.9%)	5 (45.5%)	12 (44.4%)	20 (62.5%)	22 (75.9%)
Number with mRS 0-1 (%)	2 (18.2%)	10 (27.8%)	25 (54.4%)	2 (18.2%)	6 (22.2%)	15 (46.9%)	15 (51.7%)
Mortality (%)	4 (36.4%)	6 (16.7%)	6 (13.6%)	4 (36.4%)	6 (22.2%)	3 (9.4%)	3 (10.7%)

* Five patients scored as TICI 1 in the traditional scoring cohort were scored as TICI-2a in the modified scoring cohort.

Figure 1 The distribution of 90-day mRS by TICI group.

Figure 2 Comparison of the area under the curve (AUCs) for various definitions of successful reperfusion using mRS 0-2 (A) and mRS 0-1 (B) as outcomes.

TICI 2b group (62.5% vs. 44.4%) although this difference was not statistically significant. However, a significant proportion of patients in the TICI 2c achieved a 90-day mRS of 0 or 1 compared to the TICI 2b group (46.9 % vs. 22.2%, p 0.04). When patients in the traditional vs. modified TICI 2b groups are compared, their 90-day outcomes were essentially the same.

Comparisons of successful reperfusion definitions

Three different definitions of successful reperfusion were compared using the AUC approach: TICI 2a to 3 vs. TICI 2b to 3 vs. TICI 2c to 3. The three definitions had comparable ability to predict mRS score ≤ 2 at 90 days (AUC of 0.56, 0.57, and 0.62 for TICI 2a to 3, TICI 2b to 3, and TICI 2c to 3 respectively; p value for all two way comparisons >0.05) (Figure 2A). However, when the 90-day mRS of 0-1 was considered, the TICI 2c to 3 definitions had a

better predictive value compared to TICI 2a to 3 (AUC 0.65 vs. 0.55 respectively; p 0.02) and TICI 2b to 3 (AUC 0.65 vs. 0.57 respectively; p 0.04) (Figure 2B). There was no statistically significant difference in AUC between TICI 2b to 3 and TICI 2a to 3. (AUC 0.57 vs. 0.55, $p=0.8$).

Discussion

We describe the clinical characteristics and functional outcomes of intra-arterial reperfusion groups using a modification of the TICI scoring system. In our cohort, the proposed TICI 2c group appeared to have similar characteristics to the complete reperfusion group (TICI 3) in ability to determine clinical outcome. In comparison to the TICI 2b group, the TICI 2c patients achieved better clinical improvement in the 24-hour NIHSS scores and had a significantly better functional outcome with mRS 0 or 1 at 90 days. However, the proportion of patients

with 90-day mRS 0 to 2 did not differ between the TICI 2b vs. 2c groups. There is an increasing need to modify the existing angiographic scoring systems to capture the full spectrum of successful mechanical reperfusion. This is especially relevant with the increasingly reported high rates of successful reperfusion. However, reperfusion is considered complete only in a minority of patients. The TREVO 2 trial reported a TICI-3 score in only 14% of patients compared to 54% in the TICI-2b¹⁶. The presence of patients with only one or few residual distal occlusion (i.e. meeting our proposed TICI-2c score) could explain the reported discrepancy between local sites and core lab angiographic scores in a number of trials. Therefore, defining a TICI 2c group could improve the inter-rater reliability of the TICI scoring system in addition to its potential to define a group with a more favorable outcome than the TICI 2b group. Prior evidence has reinforced the importance of the quality of reperfusion²²⁻²⁴. The quality of reperfusion was described to be a better predictor of infarct size than recanalization²⁵. Therefore, the smaller the areas of perfusion defect on the final angiographic images, the smaller the size of the final infarct. The small infarct expected with the small areas of perfusion defect may account for the higher rate of recovery seen in the TICI 2c group compared to TICI 2b. Another potential explanation is the improved antegrade flow into the few occluded branches in the TICI 2c group which may enhance IV tPA effect and promote thrombi washout and subsequent spontaneous reperfusion²⁶. It is our observation, along with those of other interventionalists, that at least some of these distal perfusion defects spontaneously reperfuse on subsequent angiographic runs repeated a few minutes later.

It could be argued that a modification of the existing TICI scoring system may further complicate the literature and would only add to the existing heterogeneity. We demonstrated a better predictive value of a TICI 2c to 3 when compared to a TICI 2b to 3 definition of successful reperfusion when the outcome modeled was mRS 0 to 1 but not 0 to 2. This shows that patients who achieve a more complete reperfusion (TICI 3, or TICI 2c and 3 using the modified scoring system) are likely to achieve a more complete recovery. These observations emphasize prior observations that in carefully selected patients (small infarct core with proximal occlusion), fast and complete reperfusion lead to a higher likelihood of disability-free recovery.

The current definitions of successful reperfusion have failed to explain the low rates of favorable outcome. The traditional TICI 2b grade appears to dilute the beneficial effect of the interventional arm (Table 3) and may neutralize any beneficial effect of endovascular therapy in the ongoing trials. Patients with near complete reperfusion (TICI 2c) have a higher likelihood of achieving a very good clinical outcome (mRS 0-1) as our data show. Patients with near complete reperfusion (TICI 2c) should therefore be distinguished from those with a lower grade of reperfusion meeting the current TICI 2b definition. In order to avoid adding further complexity to the grading system, one solution would be to modify the definition of TICI 3 to include the proposed TICI 2c grade as truly successful reperfusion in comparison to the TICI 2b group. Therefore, TICI 3 reperfusion definition would become: complete or near complete perfusion.

Our study has limitations. This is a single center experience where patients are carefully selected for mechanical therapy. The observed differences in outcome between the TICI 2b vs. TICI 2c groups may be attributed to a number of factors other than the reperfusion quality. The TICI 2b group patients had a relatively longer onset to reperfusion and imaging to reperfusion times. These delays might have resulted from difficulties in achieving reperfusion due to tortuous anatomy or tough thrombus composition. In addition, this group had a higher proportion of sICH on the 24-hour CT which impacted their recovery. Nonetheless, this still supports the hypothesis that patients in the TICI 2b group have a worse outcome whether it results from a large final infarct volume or a high rate of sICH that could relate to delayed reperfusion of a relatively large infarct. We did not evaluate the inter- or intra-observer variability for the new grading system. Finally, we had a limited number of patients in the TICI 2a group which may affect the generalizability of our results to this patient group.

Conclusions

We describe a modification to the existing TICI angiographic scoring system. A new category of TICI2c is introduced to capture patients with near complete reperfusion after mechanical revascularization to differentiate them from patients with TICI2b reperfusion. TICI2c grade reperfusion patients as defined in this study closely resemble patients with complete reper-

fusion achieving better functional outcomes (mRS0-1) than do patients with TICI2b reper-

fusion. The modified scoring system needs further validation in larger cohorts.

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