Mechanical thrombectomy for acute stroke: early vs. late time window outcomes

Chantal Bhan[1,2] , Tracy J. Koehler[3], Lee Elisevich[4] , Justin Singer[2,5], Paul Mazaris[2,4], Elysia James[1,2], Joseph Zachariah[1,2], Jordan Combs[1,2], Michelle Dejesus[1,2], Tricia Tubergen[6], Laurel Packard[1], Jiangyong Min[1,2], Nabil Wees[1,2], Nadeem Khan[1,2], Todd Mulderink[7,8,9], Muhib Khan[1,2]

[1]Neuroscience Institute, Division of Neurology, Spectrum Health;[2]Michgan State University; [3]Scholarly Activity Solution, LLC; [4]University of Michigan;[5]Neuroscience Institute, Division of Neurosurgery, Spectrum Health; [6]Nursing Administration, Spectrum Health; [7]Department of Radiology, Spectrum Health; [8]Division of Radiology, Michigan State University; [9]Advanced Radiology Services, PC

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Corresponding Author: Muhib Khan, MD

Department of Clinical Neuroscience, Spectrum Health

College of Human Medicine, Michigan State University

Tel: 616.267.7900 Fax: 616.267.7901

E-mail: muhib.khan@spectrumhealth.org

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## Abstract

Background and Purpose: Recent trials have shown benefit of thrombectomy in patients selected by penumbral imaging in the late (>6 hours) window. However, the role penumbral imaging is not clear in the early (0-6 hours) window. We sought to evaluate if time to treatment modifies the effect of endovascular reperfusion in stroke patients with evidence of salvageable tissue on CT perfusion (CTP).

Methods: We retrospectively analyzed consecutive patients who underwent thrombectomy in a single center. Demographics, comorbidities, National Institute of Health Stroke Scale (NIHSS), rtPA administration, ASPECTS, core infarct volume, onset to skin puncture time, recanalization (mTICI IIb/III), final infarct volume were compared between patients with good and poor 90-day outcomes (mRS 0-2 vs. 3-6). Multivariable logistic regression analyses were used to identify independent predictors of a good (mRS 0-2) 90-day outcome.

Results: 235 patients were studied of which 52.3% were female. Univariate analysis showed that the groups (early vs. late) were balanced for age (p=0.23), NIHSS (p=0.63), vessel occlusion location (p=0.78), initial core infarct volume (p=0.15) and recanalization (mTICI IIb/III) rates (p=0.22). Favorable outcome (mRS 0-2) at 90 days (p=0.30) were similar. There was a significant difference in final infarct volume (p=0.04). Shift analysis did not reveal any significant difference in 90 day outcome (p=0.14). After adjustment; age (p<0.001), NIHSS (p=0.01), recanalization (p=0.008) and final infarct volume (p<0.001) were predictive of favorable outcome.

Conclusion: Penumbral imaging based selection of patients for thrombectomy is effective regardless of onset time and yields similar functional outcomes in early and late window patients.

Introduction:

Recent clinical trials have confirmed the efficacy of endovascular treatment in restoring blood flow for proximal intracranial arterial occlusion within 6 hours of symptoms onset.[1] This treatment window was extended to 24 hours utilizing computed tomography perfusion (CTP) and magnetic resonance imaging (MRI) to select patients for thrombectomy based on the results of DAWN and DEFUSE III.[2-4] Patients were selected for endovascular treatment in this extended window after assessment of infarct core and salvageable penumbra. In recent years, penumbral imaging has become widely available providing physiologic information. However, the role of advanced imaging in selecting patients for mechanical thrombectomy (MT) during the early (0-6 hours) window is unclear.[5]

Studies have suggested that assessment of infarct core and salvageable penumbra constitutes valuable information independent of onset time.[6] Conventional imaging paradigm of CT and CT angiography (CTA) might not provide a good assessment of tissue status for decisions regarding MT. Despite widespread use, utility of advanced imaging in selecting patients across the time continuum of early (0-6 hours) and late (6-24 hour) window for thrombectomy has not been assessed. Therefore, in this study we evaluated the impact of advanced neuroimaging based selection for thrombectomy on functional outcomes across the time continuum. We hypothesized that patients will have similar outcomes after MT in early and late windows if selected by advanced imaging.

Methods:

The retrospective cohort study was approved by our Institutional Review Board, and Health Insurance Portability and Accountability Act waiver of informed consent was granted. We adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[7]

*Study population:*

Consecutive stroke patients who received a multi-parametric CT brain imaging (non-contrast CT+CTP+CT angiography) on presentation and underwent MT within 24 hours from last known normal between January 2016 and June 2018 at our comprehensive stroke center (CSC; Spectrum Health) were included. Patient demographics, comorbidities, pre-stroke modified Rankin scale (mRS) and stroke etiology (using the Trial of Org 10172 in Acute Stroke Treatment classification) after completion of diagnostic evaluation and National Institute of Health Stroke Scale (NIHSS) scores were assessed.

*Imaging protocol and analysis:*

The Alberta Stroke Program Early CT Score (ASPECTS) was calculated on non-contrast CT scan (NCCT).[8] CTP was performed on a Discovery General Electric (GE, Waukesha, WI) CT750 HD 64 row detector scanner. Volumetric assessments of the ischemic core and critically hypoperfused territory were performed using the RAPID software (iSchemaView, Menlo Park, CA).[9] Infarct core was defined as relative decrease in cerebral blood flow (CBF) to <30% of normal. Critically hypoperfused tissue likely to infarct in absence of reperfusion was defined as time-to-maximum of residue function over 6 seconds (Tmax >6s). The target mismatch was defined as an absolute difference of 15 mL or more between the Tmax >6s volume and the infarct core volume. Patient were selected for thrombectomy based on the published criteria of EXTEND-IA and DEFUSE III.[6] Endovascular procedures were performed by experienced interventionalists using commercially available stent retrievers and aspiration catheters. Recanalization was defined as modified Thrombolysis In Cerebral Infarction (mTICI) IIb/III. The final infarct volume was measured on the follow-up 24–48 hour NCCT and Diffusion weighted Imaging (DWI) by ABC/2. This method produces reliable results when compared to planimetry and has good inter-rater and intra-rater reliability.[10]

*Statistical analysis:*

The primary and secondary outcomes were good modified Rankin Scale (mRS 0-2) score at 90 days and final infarct volume, respectively. Descriptive statistics were used to summarize baseline characteristics and outcome measures and were stratified by LKN to skin puncture time. Summary statistics were calculated for the data. Continuous variables were analyzed using a two-tailed t-test. Normally distributed continuous variables are shown as mean ±SD standard deviation. Non-normally distributed continuous variables were transformed using either the log or inverse hyperbolic sine procedure prior to analysis and are shown as median (min-max). Categorical variables were analyzed using the chi-square or Fisher's Exact test and are shown as percentages (% frequency). Baseline characteristics were stratified by mRS (0-2 vs. 3-6) in a univariate analysis. To maintain validity of regression for our study sample size; our model was limited to 8 variables for the regression analysis. Variables with a $p<0.01$ on univariate analysis as well as LKN to skin puncture (variable of interest) were used as independent variables in multivariable logistic regression. Multivariable logistic regression model was used to determine if LKN to skin puncture was independently associated with good outcome (mRS 0-2) at 90 days. Secondary analysis for independent predictors of excellent outcome (mRS 0-1) at 90 days was also evaluated with multivariable logistic regression. The distribution on mRS scores at 3 months among patients was also compared between the groups using the a ridit score (shift) analysis.[11] Significance was assessed at $p<0.05$. All statistical analyses were generated performed using IBM SPSS Statistics, v 23 (Armonk, NY: IBM Corp).

Results:

A total of 245 patients underwent thrombectomy between January 2016 to June 2018 at our CSC. Patients who had recanalization after rtPA (tissue plasminogen activator) and prior to thrombectomy were excluded from the analysis. A total of 235 patients were included in the final analysis. Demographics and clinical characteristics of the study participants stratified by LKN to skin puncture time in early (0-6 hours) and late (6-24 hours) windows are summarized in Table 1. On presentation to the CSC, both groups were similar with regards to age, NIHSS, hypertension, diabetes and atrial fibrillation. However, late window patients were predominantly female (61% vs 47%). There was no significant difference between the groups for pre-stroke mRS. The etiology of stroke was mainly cardioembolic and did not differ between the groups. ASPECTS, core infarct core volume, vessel occlusion location and rates of recanalization (TICI IIb/III) were similar as well (Table 1). Patients in the early window received intravenous thrombolysis significantly more often than the late window patients. Univariate analysis stratified by functional outcome (mRS 0-2 vs. 3-6) at 90 days are summarized in Table 2. Age, NIHSS, Female sex, Diabetes, Atrial fibrillation, ASPECTS, Core infarct Volume, mL (CT-P), rtPA administration, Recanalization (mTICI IIb/III), Final Infarct Volume were significant variables ($p<0.05$). Onset to Skin Puncture was not different between the two groups (Table 2). In unadjusted analyses, good outcome (mRS 0-2) at 90 days was similar between the early and late window groups (Table 3). However, final infarct volume was significantly higher in the late window group (Table 3).

Results of the multivariable logistic regression are shown in Table 4. Predictors of a good outcome at 90 days included age, (OR: 0.95; 95% confidence interval [CI]: 0.92-0.97), NIHSS (OR: 0.94; 95% CI: 0.89-0.99), recanalization (OR: 7.63; 95% CI: 1.69-34.6) and final infarct volume (OR: 0.38; 95% CI: 0.27-0.54). Accordingly, if all other factors were held constant, patients who underwent recanalization were 7.6 times more likely to achieve a good outcome (mRS 0-2) and every 10% increase in final infarct volume led to 8.8% reduction in likelihood of achieving good outcome (mRS 0-2). LKN to skin puncture was not an independent predictor of good outcome. Predictors of excellent outcome (mRS 0-1) at 90 days included age, (OR: 0.95; 95% confidence interval [CI]: 0.93-0.98), NIHSS (OR: 0.92; 95% CI: 0.87-0.97), recanalization (OR: 6.24; 95% CI: 1.12-35.16) and final infarct volume (OR: 0.94; 95% CI: 0.92-0.97). (Table 5). LKN to skin puncture was not an independent predictor of excellent outcome. Shift analysis of 90 day mRS categories did not show any significant difference between the groups. (Figure 1; p=0.14).

Discussion:

Our study found that good functional outcome is not time dependent if the patients are selected through advanced imaging. Age, stroke severity (NIHSS), successful recanalization (TICI IIb/III) and final infarct volume predicted good functional outcome. LKN to skin puncture was not predictive of outcome. Our findings are consistent with recent studies emphasizing that collateral status and salvageable penumbra are major predictors of tissue fate and functional outcome.[12-14]

We selected patients for thrombectomy based on CTP profile regardless of onset time. This raises the concern about the utility of advanced neuroimaging in the early (0-6 hour) time window and might lead to exclusion of otherwise suitable patients for MT.[14] The American Heart Association (AHA) guidelines 2019 do not recommend perfusion imaging in the early (0-6 hours) window.[15] However, recent studies have suggested that advanced neuroimaging based selection for thrombectomy nearly doubles the probability of good functional outcomes as compared to minimalistic approach of CT/CTA based selection.[16-18] All the patients in EXTEND-IA and 80% of the patients in SWIFT PRIME, were enrolled based on the target mismatch profile on perfusion imaging.[6] Both the tPA and thrombectomy groups had twice as large good outcome as compared to MR CLEAN.[6] The treatment effect of thrombectomy for good outcome was also about twice as large. However, it is important to note that selecting patients for thrombectomy based on target mismatch profile in the early window can potentially lead to exclusion of patients who would benefit from thrombectomy despite unfavorable imaging.

Time-based eligibility is based on the concept of progression from ischemia to infarction. However, time since last seen normal is a poor proxy for such determination. It has been noted that a significant number of patients with large vessel occlusion (LVO) are "fast progressors" whose infarct growth is very sensitive to time and collaterals fail early within the 6 hour.[6] On the other hand, "slow progressors" maintain a small ischemic core and significant salvageable tissue beyond 6 hours despite a persistent LVO by maintaining robust collaterals. The pathophysiology of collateral blood flow regulation during LVO in unclear. Moreover, strategies to slow down the progression of infarct core are not well established.[19] Therefore, it is important to assess the infarct core and salvageable brain-tissue prior to thrombectomy as they are important prognostic factors independent of LKN-to skin puncture time.

Infarct core and penumbra can be assessed through multiple modalities. Early ischemic changes can be assessed on CT scan by the ASPECTS.[20] However, inter-rater reliability, infarct core assessment and prediction of good outcome utilizing CT-ASPECTS are moderate.[21] Salvageable penumbra due to collaterals has been shown to predict outcome in patients undergoing MT.[22] Collaterals can be assessed in multiple ways. CTA is commonly used to assess collateral status. However, CTA can underestimate collateral status and caution is advised in excluding patients with poor collaterals on CTA for MT.[23] Multi-phase CTA can be used to visualize this delayed collateral flow.[24] Multi-phase CTA was used for patient selection in the ESCAPE trial. However, a recent analysis showed that about 10% of these patients were misclassified based on multi-phase CTA and probably should have been excluded.[25] CT perfusion provides objective assessment of temporal and spatial collaterals by capturing the entire transit of contrast bolus. It provides estimation of ischemic core based on reduced cerebral blood flow or cerebral blood volume. CTP has been shown to provide accurate infarct core assessment using MRI-DWI as reference standard.[26] False overestimation of infarct core is rare.[27] Recent studies have shown that penumbral profile on CTP is a better predictor of outcome as compared to ischemic changes on non-contrast CT and collaterals on CTA even within the early (0-6 hours) treatment window and is a better modality for patient selection.[25-28] Recent studies have suggested superiority of MRI in assessing ischemic core as compared to CTP.[29-31] However, subgroup analyses from SWIFT-PRIME (early window) and DEFUSE III (late window) studies did not show a difference in outcome for CTP vs. MRI selected patients.[32-34] Therefore, even though MRI is a superior modality; CTP is a reliable alternative to diffusion-weighted imaging for assessing penumbra without significant contraindications and superior accessibility.[5]

Time is still important and delays in treatment should be avoided. A significant number of patients presenting in the extended window do not have favorable imaging profile.[35] Moreover, those with favorable profile (slow progressors), become ineligible for treatment if not recanalized immediately after onset and develop extensive infarction leading to poor outcomes.[36, 37] Patient presenting with favorable penumbral pattern on imaging should receive thrombectomy expeditiously with careful monitoring of imaging to skin puncture and imaging to recanalization time metrics. Recent studies have highlighted the need for improved work flow for prompt vascular access as well as superior procedural skills in achieving recanalization in an expedited manner.[38-40]

Our study has few limitations, which include the retrospective single center nature, lack of data on patients excluded due to unfavorable penumbral pattern and exclusion of patients with recanalization with thrombolysis prior to thrombectomy. Final infarct volume was predictive of outcome and patients in the late window (6-24 hours) had larger final infarct volumes in this study. However, the overall outcome for both good and excellent outcomes did not defer between the two groups (early vs. late). This paradox could be explained by the infarct volume calculation method used in our study which despite being a valid approach; is still subject to errors. This paradox will need further studies. These limitations can potentially introduce physician practice and selection bias. Our large sample size, robust neuroimaging analysis, long term outcome and multivariate analysis mitigate these limitations. Moreover, our cohort reflects contemporary clinical practice.[41]

Tissue based approach with penumbral imaging to select patients for thrombectomy was effective regardless of onset time in our study and yields similar functional outcomes in early and late window patients. Advanced neuroimaging should be considered for selection of thrombectomy candidates instead of time from symptom onset. Further studies are needed to validate our findings.

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Table 1. Baseline Characteristics of the Studied Patient Population

| Characteristics | All patients (n=235) | EARLY WINDOW Onset to Skin Puncture 0-6 hours (n=147) | LATE WINDOW Onset to Skin Puncture 6-24 hours* (n=88) | P value |
|---|---|---|---|---|
| Onset to Skin puncture† | 271 (70-1700) | 191 (70-360) | 668 (365-1700) | - |
| Age, years* | 69.7±15.9 | 70.7±15.6 | 68.1±16.4 | 0.23 |
| NIHSS* | 17.3±8.8 | 17.5±8.6 | 16.9±9.2 | 0.63 |
| Female sex | 52.3% (123/235) | 46.9% (69/147) | 61.4% (54/88) | 0.03 |
| Hypertension | 66.0% (155/235) | 67.3% (99/147) | 63.6% (56/88) | 0.56 |
| Diabetes | 32.8% (77/235) | 33.3% (49/147) | 31.8% (28/88) | 0.81 |
| Atrial fibrillation | 33.6% (79/235) | 33.3% (49/147) | 34.1% (30/88) | 0.93 |
| Pre-stroke mRS | | | | 0.19 |
| 0 | 67.2% (158/235) | 61.9% (91/147) | 76.1% (67/88) | |
| 1 | 15.7% (37/235) | 19.0% (28/147) | 10.2% (9/88) | |
| 2 | 10.2% (24/235) | 11.6% (17/147) | 8.0% (7/88) | |
| 3 | 6.0% (14/235) | 6.1% (9/147) | 5.7% (5/88) | |
| 4 | 0.9% (2/235) | 1.4% (2/147) | 0% (0/88) | |
| TOAST classification | | | | 0.99 |
| Cardioembolic | 47.7% (112/235) | 48.3% (71/147) | 46.6% (41/88) | |
| Large artery | 7.7% (18/235) | 7.5% (11/147) | 8.0% (7/88) | |
| Atherosclerosis | 40.4% (95/235) | 40.1% (59/147) | 40.9% (36/88) | |

| | | | | |
|---|---|---|---|---|
| Cryptogenic | 4.3% (10/235) | 4.1% (6/147) | 4.5% (4/88) | |
| ASPECTS | 8.9±1.2 | 9.0±1.1 | 8.8±1.2 | 0.18 |
| Core infarct Volume, mL (CT-P)[†] | 5.9 (0-256) | 8.9 (0-256) | 1.5 (0-119) | 0.15 |
| Symptomatic Vessel | | | | 0.78 |
| ICA | 8.9% (21/235) | 8.2% (12/147) | 10.2% (9/88) | |
| MCA | 77.0% (181/235) | 76.2% (112/147) | 78.4% (69/88) | |
| Basilar | 5.1% (12/235) | 5.4% (8/147) | 4.5% (4/88) | |
| Other | 8.9% (21/235) | 10.2% (15/147) | 6.8% (6/88) | |
| rtPA administration | 39.1% (92/235) | 55.1% (81/147) | 12.5% (11/88) | <0.001 |
| Recanalization (mTICI IIb/III) | 81.7% (192/235) | 84.4% (124/147) | 77.3% (68/88) | 0.22 |

NIHSS= National Institute of Health Stroke Scale; mRS=modified Rankin scale; TOAST=Trial of Org 10172 in Acute Stroke Treatment; ASPECTS=Alberta Stroke Program Early CT Score; CT-P= Computed tomography perfusion; ICA=Internal Carotid Artery; MCA= Middle Cerebral Artery; rtPA=recombinant tissue plasminogen activator; mTICI= modified Thrombolysis In Cerebral Infarction; ml=milliliters

*Mean ± standard deviation

†Median (min-max)

Table 2. Univariate analysis of 90 day outcomes (Modified Rankin Scale (mRS) 0-2 vs. Modified Rankin Scale (mRS) 3-6)

| Characteristics | All patients (n=235) | mRS 0-2 (n=82) | mRS 3-6 (n=153) | P value |
|---|---|---|---|---|
| Age, years* | 69.7±15.9 | 64.0±15.7 | 72.8±15.2 | <0.001 |
| NIHSS* | 17.3±8.8 | 13.1±6.9 | 19.5±8.9 | <0.001 |
| Female sex | 52.3% (123) | 40.2% (33) | 58.8% (90) | 0.007 |
| Hypertension | 66.0% (155) | 59.8% (49) | 69.3% (106) | 0.142 |
| Diabetes | 32.8% (77) | 22.0% (18) | 38.6% (59) | 0.010 |
| Atrial fibrillation | 33.6% (79) | 23.2% (19) | 39.2% (60) | 0.013 |
| ASPECTS* | 8.9±1.2 | 9.2±1.0 | 8.8±1.2 | 0.002 |
| Core infarct Volume, mL (CT-P)* | 17.5±28.7 | 8.1±13.5 | 22.8±33.2 | <0.001 |
| rtPA administration | 39.1% (92) | 50.0% (41) | 33.3% (51) | 0.013 |
| Onset to Skin Puncture* | 381.6±288.9 | 384.6±303.4 | 380.1±281.8 | 0.91 |
| Recanalization (mTICI IIb/III) | 81.7% (192) | 95.1% (78) | 74.5% (114) | <0.001 |
| Final Infarct Volume, mL* | 55.0±81.7 | 14.9±27.8 | 76.9±92.6 | <0.001 |

mRS= Modified Rankin Scale; n= Number of patients; NIHSS=National Institute of Health Stroke Scale; ASPECT=Alberta Stroke Program Early CT Score; CT-P= Computed tomography perfusion; rtPA=recombinant tissue plasminogen activator; mTICI= modified Thrombolysis In Cerebral Infarction; ml=milliliters.

*Mean ± standard deviation

Table 3. Comparison of Outcomes

| Outcome | All patients | EARLY WINDOW Onset to Skin Puncture 0-6 hours | LATE WINDOW Onset to Skin Puncture 6-24 hours | P value |
|---|---|---|---|---|
| 90 day mRS (0-2) | 34.9% (82) | 37.4% (55) | 30.7% (27) | 0.30 |
| Final Infarct Volume, mL | 21.6 (0-531) | 20.5 (0-531) | 35 (0.4 – 450) | 0.04 |

mRS=modified Rankin scale; ml=milliliters; Data are shown as the median (min-max)

Table 4. Logistic Regression Analysis for factors associated with Good Outcome (90 mRS 0-2)

| Independent Variable | OR | 95% CI |
|---|---|---|
| Age[†] | 0.95 | (0.92 – 0.97) |
| Sex | 0.66 | (0.32 – 1.38) |
| Onset to Skin Puncture | 0.91 | (0.42 – 2.00) |
| NIHSS[†] | 0.94 | (0.89 – 0.99) |
| ASPECTS | 1.24 | (0.88 – 1.74) |
| Core Infarct Volume (CT-P) | 1.16 | (0.91 – 1.48) |
| Recanalization (mTICI IIb/III) [†] | 7.46 | (1.64 – 33.86) |
| Final Infarct Volume[†] | 0.39 | (0.27 – 0.55) |

mRS= Modified Rankin Scale; NIHSS= National Institute of Health Stroke Scale; ASPECTS=Alberta Stroke Program Early CT Score; CT-P= Computed tomography perfusion; mTICI= modified Thrombolysis In Cerebral Infarction; OR=Odds Ratio; CI=Confidence Interval

[†]$p<0.05$

Table 5. Logistic Regression Analysis for factors associated with Excellent Outcome (90 mRS 0-1)

| Independent Variable | OR | 95% CI |
|---|---|---|
| Age[†] | 0.95 | 0.93 - 0.98 |
| NIHSS[†] | 0.92 | 0.87 – 0.97 |
| ASPECTS | 1.11 | 0.77 – 1.62 |
| Core Infarct Volume (CT-P) | 1.03 | 1.00 – 1.06 |
| Recanalization (mTICI IIb/III)[†] | 6.24 | 1.12 – 35.16 |
| Final Infarct Volume[†] | 0.94 | 0.92 – 0.97 |

mRS= Modified Rankin Scale; NIHSS= National Institute of Health Stroke Scale; ASPECT=Alberta Stroke Program Early CT Score; CT-P= Computed tomography perfusion; mTICI= mTICI= modified Thrombolysis In Cerebral Infarction; OR=Odds Ratio; CI=Confidence Interval

[†]$p<0.05$

Figure Legend

Figure 1. Modified Rankin Scale (mRS) at 90 days Ridit score (shift) analysis