Impact of Treatment Time on the Long-Term Outcome of Stroke Patients Treated With Mechanical Thrombectomy

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Objective: To assess the long-term functional outcome of stroke in patients treated with mechanical thrombectomy (MT) performed during work hours (on-hours) versus after-hours, weekends, and official holidays (off-hours). *Methods:* Data on all patients receiving MT at a comprehensive stroke center was collected between December 2014-December 2016. Our primary outcomes were the discharge and 90-day modified Rankin Scale (mRS). We developed propensity scores for off-hours treatment and used inverse probability of treatment weights to address confounding. We estimated logistic regression to assess the relationship between off-hours treatment and favorable patient outcomes. Independent variables include receiving thrombectomy during the off-hours, admission National Institute of Health Stroke Scale (NIHSS), door to groin time in minutes, age, and race. *Results:* During the study period, 80 (41%) patients underwent thrombectomy during on-hours and 116 (59%) during off-hours. Mean age was 69.1 years for the on-hours group and 64.1 years for the off-hours group ($P = .02$). There were no statistically significant differences in median admission NIHSS, rate of alteplase administration, mean time from last known well to thrombectomy, rate of revascularization, and rate of hemorrhagic transformation between the 2 groups. Logistic regression analysis showed the probability of a favorable outcome at discharge (mRS ≤ 2) is 12.6 % lower for off-hours patients ($P = .038$, [95%CI −.25 to −.01]). For patients with a 90-day mRS (n = 117), the probability of a favorable outcome was 18.7% lower for those treated during the off-hours ($P = .029$, [95%CI −.36 to −.02]). *Conclusions:* There is a higher probability of a good functional outcome in acute ischemic stroke patients who receive MT when performed during regular work hours.

Key Words: Ischemic stroke—mechanical thrombectomy—off-hours—functional outcome

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Background

Recent randomized controlled trials on mechanical thrombectomy (MT) provided level 1 evidence supporting the use of MT for patients with anterior circulation large vessel occlusion (LVO) over optimal medical management.[1-7] The American Heart Association/American Stroke Association currently recommends MT as the standard of care for patients presenting with acute ischemic stroke secondary to LVO.[2-8] Data from clinical trials have shown that faster recanalization time leads to better functional outcomes, reflecting the importance of timely revascularization of salvageable brain tissue.[1,2] Efforts have been made to decrease the time to reperfusion, including early prehospitalization detection for signs of LVO as well as using flat detector computed tomography scanner in the angiography suite in an attempt to decrease intrahospital delay in reperfusion.[9,10]

Among the important factors affecting the time to reperfusion is the time of presentation to the hospital. Published data regarding the effect of the time of presentation on the procedural and outcome parameters are scarce and shows conflicting results.[11,12] Saad et al. reported—in a nationwide retrospective study involving about 12,000 patients—that thrombectomy patients who were admitted on the weekends had worse outcomes in the nonteaching hospitals. However, no significant difference in outcomes was noticed when compared to the teaching hospitals.[12] A recent study in Germany has shown that patients who were admitted in the night-time and weekends had longer door to groin (DTG) time and were less likely to have favorable outcomes without reaching significant difference.[11]

In this study, we report the impact of the acute ischemic stroke time of presentation to a comprehensive stroke center on thrombectomy procedural parameters and long-term functional outcome.

Methods

Setting

We retrospectively reviewed the medical records of all patients who received MT between December 2014-December 2016 at 1 comprehensive stroke center located in the Southeastern United States. All patients who received MT had evidence of LVO on cerebral vessel imaging. Thrombectomy was performed using a Direct Aspiration First Pass Technique.[13,14] The following data were collected from the charts: age on presentation, sex, race, National Institute of Health Stroke Scale (NIHSS) on admission, whether patient received intravenous alteplase (tPA) on presentation or not, the location of LVO on cerebral vessel imaging, the time between symptoms onset, and recanalization, finally, DTG time, modified Rankin Scale (mRS) at discharge and at 90-day.

In total, 209 patients received MT during the study time period, of those 13 patients were excluded because of incomplete baseline characteristics or loss of follow-up resulting in a final sample of 196 patients. For the 90-day post discharge mRS, we were unable to contact 79 patients after 3 attempts, leaving 117 patients in the sample for the analysis of this outcome.

Outcome Measures

In this study, our primary outcomes include the mRS, collected upon discharge, and 90-day post discharge. Patients were contacted by a stroke physician or experienced nurse practitioner 90 days post discharge to collect the 90-day mRS. If no contact has been made after 3 attempts, the 90-day mRS is coded as unable to contact. A favorable outcome was defined as mRS 0-2, and poor outcome was defined as mRS greater than 2.[15] If the patient was coded as died (mRS = 6) upon discharge, the patient is also coded as mRS = 6, 90 days post discharge. Our secondary outcome was the rate of hemorrhagic transformation in the first 36 hours of the stroke.[16,17] Successful revascularization was defined as thrombolysis in cerebral infarction score greater than or equal to 2B which corresponds to greater than or equal to 50% reperfusion of the affected vascular territory.[18] Our primary explanatory variable was receipt of thrombectomy during the off-hours. Off-hours include official holidays, weekends, and between 4 pm -7 am on the weekdays. On-hours were defined as the ordinary work hours for the neurointerventional team between 7 am-4 pm in the weekdays. During the off-hours, the stroke service is covered by in-house neurology residents with the help of the stroke fellows and attendings who are available by phone. In addition, the angiography suite team including nursing staff, technician, the interventional fellow as well as the interventional staff are called from home to perform MT during the off-hours. The anesthesia team is available in house, 24 hours/7 days a week and provide continuous in person coverage for MT cases. In the institute where the study was done, the emergency room contains 44 beds and staffing does not usually differ in the off-hours. We also included patient characteristics that could affect the outcome. The patient level covariates include NIHSS score upon admission, age, race (black, white, and other), and time from DTG puncture in minutes.

Propensity Score Estimation

To address potential confounding factors between the patient treatment groups, we utilize doubly robust propensity scores (PS) with inverse probability of treatment weights (IPTW). Standardized differences in means and proportions were used to examine the quality of the PS model. Covariates in the PS model that have a less than .20 standardized difference were considered well-matched. The PS was computed using a multiple logistic

regression with the comparison group (off-hours versus. on-hours) as the dependent variable. PS and outcome models were utilized to account for demographics and clinical characteristics that may have influenced comparison group selection or may have been related to outcome risk. All of these designated covariates were included in the PS model and were tested for inclusion in the outcome analyses models to account for a doubly robust analysis methodology for quasi-experimental studies.[19-21] All final analyses were weighted by using IPTW approaches to create stabilized weights.[22-25] The stabilized weight was the marginal probability of being in the off-hours group given no covariates, divided by the PS (the probability of being in the off-hours group given all covariates). The final model IPTW includes the admission NIHSS, age, receipt of tPA, race, and sex.

After the PS weights were developed, a series of multivariable models were constructed to make formal statistical comparisons testing the hypothesized differences between the off-hours and on-hours groups. Multinomial logistic regression models were used to make these comparisons. The same covariates used in the PS model were tested for inclusion in each outcomes analysis. In this case, classical model fitting was performed where all covariates were included in the full model, and were removed one at a time and the model refit if they were not significant and did not improve model fit until the most parsimonious statistically significant model was found. Statistical significance was set at $\alpha < .05$ level of acceptable Type I error. The IPTW adjusted model estimates the average treatment effects.[23]

Chi-square, Fisher's exact (for categorical variables), and *t* tests (for normally-distributed continuous variables) were used to describe the differences in demographic characteristics across those patient groups who were seen in the off-hours and those who were treated in normal working hours, as appropriate.

The study was approved by the institutional review board. Analysis was completed in Stata 15.1.

Results

The majority of study patients were treated outside of the normal work hours. Of the 196 patients included in the analysis, 116 (59%) patients underwent thrombectomy during off-hours and 80 (41%) in the on-hours. Flowchart of the study is given in Figure 1.

Before the IPTW, the unadjusted mean age of all thrombectomy patients was 66.1 years, with a standard deviation (SD) of 15.2. Mean age for patients who underwent thrombectomy during the off-hours was 64.1 years (SD 1.5) versus 69.1 years for the on-hours patient (SD 1.6) ($P = .0231$). Off-hours patients had a higher percentage of females (72 of 116 patients, 62.1%) compared to the on-hours patients (38 of 80 patients, 47.5 %) ($P = .043$). There was no significant difference between both groups with regards to race ($P = .151$), NIHSS score at admission, or treatment with tPA. Clinical and demographic characteristics of our sample are shown in Table 1. Standardized differences of age, sex, race, and mean NIHSS admission score were all greater than 10% indicating an imbalance by off-hours treatment between the 2 groups. Following propensity scoring and IPTW, all variables standardized differences are below 10% suggesting a balance between the groups.

Thirteen patients (11.2%) in the off-hours group received intravenous tPA versus 9 patients (11.3%) in the on-hours group ($P < .001$). Median DTG time was 51 minutes (interquartile range (IQR) 38.5-72) versus 77.5 minutes (IQR 61-100.5) for the on-hours and off-hours groups respectively ($P < .001$). Median time from symptom-onset to thrombectomy was 290 minutes (IQR 205-668) for the on-hours patients and 360.5 minutes (IQR 235-478.5) for the off-hours patients ($P = .6$). Table 2 summarizes the process measures.

As shown in Table 3, most patients achieved successful recanalization (thrombolysis in cerebral infarction greater than or equal to 2B) in both groups. One hundred and eight (93.1%) patients in the off-hours group and 73 (91.2%) patients in the on-hours group had successful recanalization ($P = .82$). The rate of hemorrhagic transformation was (5 of 116, 4.3%) in the off-hours group and (4 of 80, 5%) in the on-hours group ($P = .918$).

After the IPTW, and controlling for admission NIHSS, age, race, and DTG time, results of the logistic regression

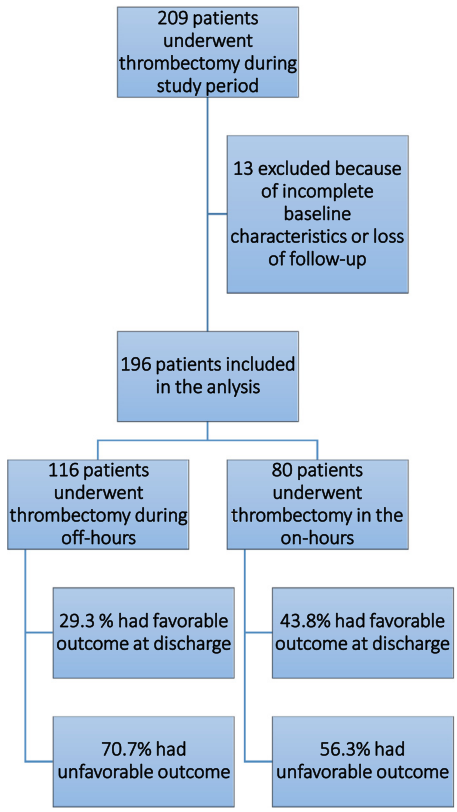

Figure 1. *Flowchart of the study.*

Table 1. *Unadjusted characteristics of patients who received thrombectomy during the study period*

Patient characteristics	On-hours (n = 80)	Off-hours (n = 116)	*P* value	Standardized differences	
				Crude	Weighted
Mean age in years	69.1 (SD 1.6)	64.1 (SD 1.5)	.02	.34	<.001
Sex*					
Female	38 (47.5%)	72 (62.1%)	.04	.3	.02
Male	42 (52.5%)	44 (37.9%)			
Race*			.15	.27	.015
Black	25 (31.3%)	49 (42.2%)			
White	55 (68.8%)	66 (56.9%)			
Other	0 (0.0%)	1 (0.9%)			
Mean NIHSS admission score	14 (SD 0.9)	15.4 (SD 0.7)	.21	.18	<.001
Treatment with tPA*	9 (11.3%)	13 (11.2%)	1	<.001	<.001

n, number; NIHSS, National Institutes of Health stroke scale; SD, standard deviation; tPA, tissue plasminogen activator.
*Values are n (%).

show the probability of a favorable outcome at discharge (mRS ≤ 2) are 12.6% lower for off-hours patients compared to on-hours patients (P = .038, [95% CI −0.25 to −.01]). At 90 days post discharge, patients treated in the off-hours have an estimated 18.7% lower probability (P = .029, [95% CI −.36- to .02] for a favorable outcome. Regression analysis is shown in Tables 4 and 5.

Discussion

In this study, we report the impact of the time of thrombectomy performance on the discharge and long-term outcomes of stroke patients who underwent thrombectomy. Our study shows that patients who had MT in the off-hours had worse functional outcome when compared to patients receiving the procedure during work hours. Our results are consistent with previously national and international published data.[11,12] A recent study by Mpotsaris et al. compared between patients who were admitted during normal business hours to those admitted during night-time and the weekends at one of the university hospitals in Germany. Results of the study indicated that patients who were admitted in the night-time and weekends had longer DTG time and were less likely to have favorable outcomes. However, the difference in the functional outcomes was insignificant, likely because that study was underpowered given that it involved only 98 patients.[11] Another study was done in the United States by Saad et al. involved about 12,000 patients between 2005-2011. Results have shown that thrombectomy patients who were admitted on the weekends had worse outcomes in the non-teaching hospitals, but no significant difference was noticed in the teaching hospitals.[12] However, that study did not provide information about the difference in DTG between weekend versus weekdays admission in both settings (non-teaching and teaching), so it is unclear how much that played a rule in the difference in the outcomes.[12]

The "weekend effect" was noted since before the era of thrombectomy. In a study on a national on the Nationwide Inpatient Sample Database in the United States between 2002-2007, patients who were admitted during the weekends were more likely to receive thrombolysis, and had longer length of stay, but there was no difference in the in-hospital mortality of discharge disposition.[26] Another study in the United States between 1996-2007 showed that stroke patients who were admitted during weekends had a higher risk of 90-day mortality in all hospitals except comprehensive stroke centers.[27] In our study, we found that off-hours patients have a prolonged DTG time compared to on-hours patients and are less likely to achieve functional independence. A possible explanation for the prolonged DTG time in the off-hours patients is that hospitals function with less staff in the off-hours. The reduction in available staff may lead to a delay in the door to imaging time and a delay in imaging to groin puncture time given that the interventional team is called in from home. One possible way to overcome this issue is to make the angiography suite in the main operation room which would provide better staffing. Additionally, rapid imaging interpretation is crucial with regard to treatment decisions regarding thrombectomy candidacy

Table 2. *Process measures*

Treatment times	Off-hours	On-hours	*P* value
Median time from symptom-onset to thrombectomy in min	360.5 (IQR 235-478.5)	290 (IQR 205-668)	.60
Median time from door to groin in min	77.5 (IQR 61-100.5)	51 (IQR 38.5-72)	<.001

IQR, interquartile range

Table 3. *Rate of successful recanalization (TICI score ≥ 2B) and hemorrhagic transformation*

	Off-hours	On-hours	*P* value
Succesful recanalization (TICI score ≥ 2B)*	108 (93.1%)	73 (91.2%)	.82
Hemorrhagic transformation in the first 36 h of the stroke*	5 (4.3%)	4 (5%)	.918

TICI, thrombolysis in cerebral infarction.
*Values are n (%).

Table 4. *Logistic regression analysis for good functional outcome at discharge (mRS ≤ 2) using the inverse probability of treatment weights*

Average treatment effect	Coefficient	Robust standard error	*P* value	95% confidence intervals	
Off-hours	−.126	.06	.038	−.25	−.007
Outcome model for the untreated (on-hours)					
Admission NIHSS	−.11	.03	<.0001	−.18	−.05
Age	−.01	.02	.416	−.04	.02
Race (Black)	−.08	.55	.879	−1.17	1.00
Door to groin	.002	.002	.346	−.002	.01
Outcome model for the treated (off-hours)					
Admission NIHSS	−.14	.04	<.0001	−.22	−.07
Age	−.04	.02	.008	−.73	−.01
Race (Black)	−.46	.46	.318	−1.36	.44
Door to groin	−.001	.001	.131	−.003	.0004

mRS, modified Rankin scale; NIHSS, National Institute of Health stroke scale.

Table 5. *Logistic regression analysis for good functional outcome at 90-day (mRS ≤ 2) using the inverse probability of treatment weights*

Average treatment effect	Coefficient	Robust standard error	*P* value	95% confidence intervals	
Off-hours	−.19	.09	.03	−.36	−.02
Outcome model for the untreated (on-hours)					
Admission NIHSS	−.09	.06	.16	−.22	.03
Age	−.06	.03	.02	−.11	−.01
Race (Black)	.12	.74	.87	−1.33	1.57
Door to groin	.001	.002	.95	−.004	.004
Outcome model for the treated (off-hours)					
Admission NIHSS	−.13	.05	.01	−.24	−.03
Age	−.04	.02	.04	−.08	
Race (Black)	.49	.63	.44	−.74	
Door to groin	−.01	.01	.24	−.02	

mRs, modified Rankin scale; NIHSS, National Institute of Health stroke scale.

for stroke patients, and off-hours are associated with delayed imaging interpretation given that most vascular neurologists and radiologists take calls from home.[8]

Developing solutions to reduce the delay in DTG times in off-hours is vital given that more than 80% of thrombectomy procedures are done in the night-time in one multicenter study that was recently published.[28] Collaboration between different specialties including emergency medicine, radiology, neurology, and neuroendovascular surgery is needed to overcome the logistic challenges and achieve shorter DTG.

Our study has some limitations given that this is a singlecenter study, with a small sample size, and our results might not be generalizable. Moreover, regression analysis showed that patients receiving thrombectomy during the off-hours have worse outcomes independent of the DTG time which indicates the presence of other factors contributing to worse outcomes that we were unable to identify. One of the strengths of this study is that we controlled using IPTW to address potential selection bias.

Conclusion

Our study shows that there is a lower probability of good functional outcome following MT when performed during off-work hours. Strategies to improve DTG time

during off-hours could lead to improvement in the long-term functional outcome of patients receiving MT in the off-hours.

Statement of Compliance with the Guidelines for Human Studies and Animal Welfare Regulations

Authors confirm that the study is observational minimal risk study and no consent is required per the Medical University of South Carolina institute policy. Our study was approved by the institutional review board of the Medical University of South Carolina.

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