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ORIGINAL RESEARCH

Is early mobilization associated with functional improvement in acute middle cerebral artery ischemic stroke treated with recombinant tissue plasminogen activator? A proof of concept and retrospective single-center study

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Abstract

Background: The benefit of commencing early mobilization for patients after ischemic stroke (IS) is well established. However, the timing and benefits of early mobilization in recombinant tissue plasminogen activator (rtPA)-treated patients remain mostly undefined.

Methods: In this retrospective observational cohort study, we analyzed rtPA-treated patients after a first-episode middle cerebral artery (MCA)-IS, that were admitted in a Stroke Center, using electronic medical records during the period of January 1, 2015 through December 31, 2017. These patients who received a standard early rehabilitation during the stay in the Stroke Center served as the control group. We examined the association between early mobilization via early rehabilitation within 24-72 hours and activities of daily living and postural control improvements, as indicated by the Barthel Index (BI) effectiveness and the Postural Assessment Scale for Stroke (PASS) effectiveness, respectively.

Results: Total 60 patients with a first MCA-IS treated after rtPA were analyzed. Multiple linear regression analysis indicated that BI and PASS effectiveness were positively correlated with not only age and the stroke severity at 24 hours after rtPA treatment but commencing early mobilization within 24-72 hours after stroke in patients with a first MCA-IS treated after rtPA.

Conclusions: This study concludes that early mobilization may be associated with an acceleration of functional improvement in patients with a first MCA-IS treated with rtPA within four weeks after the onset.

Keywords

Acute stroke; Early mobilization; Thrombolytic therapy; Functional outcome; rtPA

1. Introduction

Even though the treatments for stroke have evolved rapidly in recent years, the stroke remains a major global cause of mortality and disability. The middle cerebral artery (MCA) was found to be involved in more than two-thirds of all cases of brain infarcts included in a number of stroke registries. Systemic treatment with intravenous thrombolysis (IVT) of recombinant tissue plasminogen activator (rtPA) is the key factor for the prognosis of acute MCA ischemia [1] and achieve recanalization pharmacologically [2]. However, rtPA bears the potential for adverse effects, such as cerebral hemorrhage, and its protocols even include a recommendation for 24-48 hours of bed rest after treatment [3]. The optimal timing of early mobilization (EM) in rtPA-treated patients remains largely undefined.

EM after ischemic stroke (IS) might prevent immobility-related complications [4–6], promote brain recovery [7] and contributed to an improved functional outcome [8, 9]. Preclinical studies also provided evidence that intervention within the first 72 hours of stroke event decreases inflammatory cytokines [10, 11], tightens the blood-brain barrier [12], suppresses apoptosis [13, 14], increases brain-derived neurotrophic factor (BDNF) levels [15], and promote neurogenesis [14, 16]. While some clinicians may have concerns that EM (i.e., involving upright activity) might inhibit the reperfusion of salvageable penumbral tissue [17], no significant differences were found in cerebral blood flow velocity between patients assessed at 6 to 16 hours after stroke and controls tested in 70°, 45°, 0°, and -15° positions [18]. Thus, commencement of EM soon after an IS may not be harm.

However, there is limited information on the specific timing of starting early mobilization after intravenous rtPA treatment that would potentially optimize the recovery during the acute period [19–21]. Although, one large retrospective study of

subjects treated with intravenous rtPA in Japan showed an association between starting early rehabilitation within three days of admission and functional independence at hospital discharge [19], the data were taken from the diagnosis procedure combination database [22]. Therefore, that study did not provide detailed information about the used rehabilitation programs, the exact timing of admission, rtPA dose, the precise lesion locations, or stroke severity upon admission [19]. In addition, the inclusion criteria in AVERT (A Very Early Rehabilitation Trial) were included IS patients treated after rtPA [21], but the protocol was characterized by high-frequency early mobilization within the first 24 hours and by the lack of the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours post-rtPA [20, 21]. Besides, very EM protocol within 24 hours of stroke onset may also be associated with a worse outcome at the three-months post-stroke time point [7, 8]. Therefore, it is needed to establish the impact of the EM within 24-72 hours after stroke onset that treated with rtPA on the functional outcomes, compared to the standard early rehabilitation in which the mobilization starts after ICU discharge.

Therefore, the aim of the study was to assess whether beginning the early mobilization within 24-72 hours after stroke in MCA-IS patients was associated with improved functional gain after IVT with rtPA treatment by using daily medical records and daily assessment reports of rehabilitation built into the electronic medical records (EMR) of National Taiwan University Hospital (NTUH).

2. Methods

2.1 Study population

This retrospective cohort study covering the period from January 1, 2015, through December 31, 2017 was conducted in the 12-bed stroke center of NTUH. The criteria for admission to the stroke center included being an IS patient receiving thrombolytic therapy, which was approved at a standard dose of 0.9 mg/kg or a modified dose of 0.6 mg/kg within three hours of stroke onset. The study was approved by the Institutional Review Board (IRB) of NTUH (ID number: 201801125RINA).

The inclusion criteria for participants in the study were: patient experienced a first MCA-ischemic stroke that was diagnosed using conventional MRI or perfusion CT scan; patient was treated IVT with rtPA within 3 hours of onset without intra-arterial rescue therapy; patient was fully activities of daily living (ADL) independent before the stroke; a NIHSS score of < 25 at admission; rehabilitation programs started within 3 days of the stroke; and patient had related complete prognosis records within 30 days of onset. The exclusion criteria were as follows: patients admitted for recurrent ischemic stroke, brain tumor, and other previous central nervous system dysfunction (for example, Parkinson's disease, dementia, etc.); and patient found to have an infarction located outside the area of the MCA during the same admission.

2.2 Exposure of interest

According to the content of rehabilitation programs recorded in EMR during the stroke center stay, the participants were divided into (1) the standard early rehabilitation (SER) group and (2) the early mobilization group.

For the SER group, a standard program started within 3 days of the stroke, but out-of-bed activities were started after ICU discharge. SER programs included positioning, range of motion exercises, in-bed mobilization, facilitation exercises, and caregiver education. However, since the effectiveness of EM for stroke have been confirmed [23], the rehabilitation team in stroke center started to commence EM within 24-72 hours after ischemic stroke since June 2016 (based on stable vital signs including SBP < 180 mmHg in resting; resting HR < 130 bpm; no hydrocephalus before intervention and no early deterioration within 24 hours after stroke). Therefore, we identified the stroke patients who received treatment involving task-specific activities, such as sitting unsupported out of bed, and standing, within 24-72 hours of the stroke onset, and recorded the programs in EMR as the EM group [8, 9]. Both groups received routine rehabilitation treatment performed by trained physical therapists based on the hospital policy, generally lasting about 30 minutes a day, for five days or until discharged.

2.3 Data source and covariates

In the NTUH Stroke Center, the patients received intensive medical, nursing, and early rehabilitative care. Before early rehabilitation, the patients received full functional and postural evaluations [24, 25], which were usually performed by a physical therapist. The rehabilitation program and the prognosis were recorded every day in the EMR. Besides, the BI total scores were recorded after every fifth intervention session in progress reports. Subsequently, if a patient was not transferred to the rehabilitation ward and was discharged from the neurological ward, the patient was typically scheduled to come back to the clinic for an evaluation at one month after the stroke onset.

In the study, age, sex, body height and weight, diagnosis, treatment methods, and the NIHSS score at admission and at 24 hours post-rtPA for each enrolled patient were collected. Using the parameters quantified were length of stay in stroke center, history of vascular risk factors, in-hospital post-thrombolysis complications, malignant stroke, and uncontrolled atrial fibrillation [26, 27]. The comorbidities were identified using the codes for each patient [22]. The Charlson comorbidity index (CCI) was used to evaluate the accumulation of comorbidities [19, 28]. The total scores of the BI and PASS at the initial intervention after admission was recorded and calculated.

2.4 Outcome measures

The variables recorded included BI [25] and PASS [24] total scores at four weeks after the stroke. A total BI score to measure basic ADL ranges from 0 to 100 , including feeding, bathing, grooming, dressing, bowel movements, bladder control, toilet use, transfers, mobility, and stair usage [25]. The PASS contains 12 four-level items of varying difficulty with a maximum score of 36 and is used to assess a patient's ability to maintain or change a given lying, sitting, or standing posture. The primary outcome measure of this study was the BI effectiveness, expressed as a percentage, reflecting the

TABLE 1. Characteristics of patients with middle cerebral artery ischemic stroke after rtPA treatment

Characteristic	Standard early rehabilitation (N = 30)	Early mobilization (N = 30)
Sex (Male)	12 (40%)	16 (53.3%)
Age upon admission, mean ± SD	70.5 ± 11.7	63.7 ± 15.3
Lesion site (Left)	15 (50.0%)	19 (63.3%)
Body mass index (kg/m^2), mean ± SD	24.7 ± 4.4	25.1 ± 6.7
rtPA dose (Standard), n (%)	19 (63.3%)	10 (33.3%)
Charlson Comorbidity Index, n (%)		
0	10 (33.3%)	19 (63.3%)
1	11 (36.67%)	7 (23.3%)
2	6 (20.0%)	3 (10.0%)
3	2 (6.7%)	0 (0%)
≥ 4	1 (3.3%)	1 (3.3%)
The length of hospital stay (day), mean ± SD	35.7 ± 18.3	17.5 ± 12.9
The length of ICU stay (day), mean ± SD	7 ± 2.2	4.1 ± 2.2
NIHSS score upon admission, mean ± SD	14.3 ± 6.5	11.6 ± 5.4
NIHSS score at 24 hours after rtPA treatment, mean ± SD	13.9 ± 7.7	6.6 ± 3.8
Complications during hospitalization, n (%)		
Symptomatic intracerebral hemorrhage	4 (13.3%)	0 (0%)
Myocardial infarction	0 (0%)	0 (0%)
Early seizure	0 (0%)	0 (0%)
Infection	14 (46.7%)	1 (3.3%)
Uncontrolled atrial fibrillation	0 (0)	0 (0)
BI upon admission (score), mean ± SD	2.8 ± 6.3	9.1 ± 5.4
PASS upon admission (score), mean ± SD	2.9 ± 1.7	7.2 ± 6.3
BI effectiveness, mean ± SD	0.5 ± 0.4	0.9 ± 0.2
PASS effectiveness, mean ± SD	0.6 ± 0.3	0.9 ± 0.1
Initial out-of-bed mobilization after stroke (day), mean ± SD	9.4 ± 3.9	2.7 ± 0.6

SD: standard deviation
NIHSS: National Institute of Health Stroke Scale
rtPA: recombinant tissue plasminogen activator
BI: Barthel Index
PASS: Postural Assessment Scale for Stroke

proportion of potential improvement vs. actually achieved improvement and was calculated using the following equation: ([BI at four weeks after the stroke onset - admission BI] / [maximum BI - admission BI]) [29]. Similarly, the second outcome measure of this study, the PASS effectiveness ([PASS at four weeks after the stroke onset - admission PASS] / [maximum PASS - admission PASS]).

2.5 Statistical analysis

All data were analyzed using the IBM SPSS software for Windows (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the means ± standard deviations if they were normally distributed. The chi-square or Fisher's exact tests for categorical variables was used and unpaired *t*-tests was used for continuous variables. *P*-values less than 0.05 were considered significant.

Several univariate regression analyses determined the best predictors for better BI or PASS effectiveness after four weeks of stroke onset, as well as to investigate the additional effects of time of mobilization commencement on the outcomes. Potential variables mentioned in previous studies, listed in Table 1. All univariate potential predictors with a *P*-value < 0.1 were entered into the multivariate model. Collinearity among potential variables was evaluated; variables with moderate to high intercorrelations ($r \geq 0.5$ or $r \leq -0.5$) were regarded as collinear, and only one was entered into the regression model. Next, multiple linear regression analyses were used to assess the effects of early mobilization on BI or PASS effectiveness adjusted for selected variables. In the multiple linear regression models, a stepwise strategy was used to select the variables remaining in the final model.

TABLE 2. Univariate regression analysis results for Barthel Index effectiveness

	Coefficient (β)	95% CI	P-value (< 0.1*)
Rehabilitation type			
Early standard rehabilitation	Reference		
Early mobilization	0.39	(0.25,0.54)	< 0.001*
Age	-0.01	(-0.02,0.00)	0.001*
Sex			
Male	Reference		
Female	-0.12	(-0.30,0.06)	0.18
Lesion site			
Left	Reference		
Right	-0.10	(-0.28,0.07)	0.26
Body mass index	0.01	(-0.01,0.02)	0.45
Duration of ICU stay	-0.07	(-0.10,-0.04)	< 0.001*
NIHSS score upon admission	-0.01	(-0.03,0.00)	0.11
NIHSS score at 24 hours after rtPA treatment	-0.03	(-0.04,-0.02)	< 0.001*
rtPA dose			
Standard dose	Reference		
Modified dose	0.26	(0.09,0.42)	0.003*
Charlson Comorbidity Index (as a continuous variable)	-0.09	(-0.18,-0.01)	0.038*

NIHSS: National Institute of Health Stroke Scale; rtPA: recombinant tissue plasminogen activator

3. Results

3.1 Cohort characteristics

During the study period, 171 of a total of 557 new admissions collated during a manual review of the EMRs were first-episode MCA ischemic patients. Ultimately, 72 met the inclusion criteria and were included in this study. The reasons for 12 further exclusions in the final analysis were death (n = 1) and incomplete data sets (n = 11). As a result, the analyzed 60 first-episode MCA-IS patients treated with rtPA, of whom 30 were included in the early mobilization group.

3.2 Outcome data

Table 1 shows the clinical characteristics of the MCA-IS with rtPA treatment. The average interval from stroke onset to the commencement of out-of-bed mobilization in the EM group (30 patients) was 2.70 $\pm$ 0.6 days, while that for the SER group (30 patients) was 9.43 $\pm$ 3.9 days ($P < 0.001$). Compared to the SER group, the mean BI and PASS scores as well as BI and PASS effectiveness, upon admission, were significantly higher, the mean NIHSS score at 24 hours after rtPA treatment was significantly lower, and the percentage using the standard rtPA dose was significantly lower in the EM group. There was no significant difference in age or mean NIHSS score upon admission between the two groups. Otherwise, infections were significantly less frequent in the EM group.

The results of univariate analyses are shown in Table 2 and Table 3, respectively. Two sociodemographic variables (age and CCI) and several clinical stroke-related variables were significantly associated with the BI effectiveness and with PASS effectiveness. The potential predictors listed in Table 2 and Table 3 were put into the multiple regression analysis. The multiple linear regression analysis identified the role of early mobilization therapy as a significant positive factor affecting BI effectiveness (coefficient, 0.23; 95% confidence interval (CI), 0.08~0.39; $P = 0.004$; Table 4). In addition, age and the NIHSS score at 24 hours after rtPA treatment were also significant positive factors for BI effectiveness (Table 4). Together, these three variables accounted for 49% of the total variance.

Similarly, early mobilization therapy as a significant positive factor affecting PASS effectiveness (coefficient, 0.17; 95% confidence interval (CI), 0.03~0.32; $P = 0.019$, Table 4). In addition, age and the NIHSS score at 24 hours after rtPA treatment were also significant positive factors affecting PASS effectiveness. Together, these three variables accounted for 39% of the total variance.

4. Discussion

In this proof-of-concept study, the results demonstrated that beginning timely mobilization via early rehabilitation for patients with a first MCA-IS treated with rtPA in a stroke center was associated with better functional progress. A prompt

TABLE 3. Univariate regression analysis results for Postural Assessment Scale for Stroke effectiveness

	Coefficient (β)	95% CI	*P*-value (< 0.1*)
Rehabilitation type			
Early standard rehabilitation	Reference		
Early mobilization	0.29	(0.16,0.42)	< 0.001*
Age	-0.01	(-0.01,0.00)	0.001*
Sex			
Male	Reference		
Female	-0.11	(-0.26,0.04)	0.14
Lesion site			
Left	Reference		
Right	-0.09	(-0.24,0.06)	0.26
Body mass index	0.01	(-0.01,0.02)	0.44
Duration of ICU stay	-0.05	(-0.08,-0.03)	< 0.001*
NIHSS score upon admission	-0.01	(-0.02,0.00)	0.076*
NIHSS score at 24 hours after rtPA treatment	-0.02	(-0.03,-0.01)	< 0.001*
rtPA dose			
Standard dose	Reference		
Modified dose	0.20	(0.05,0.34)	0.007*
Charlson Comorbidity Index (as a continuous variable)	-0.06	(-0.14,0.01)	0.084*

NIHSS: National Institute of Health Stroke Scale; rtPA: recombinant tissue plasminogen activator

TABLE 4. Multiple linear regression analysis results of factors potentially impacting outcome in patients suffering middle cerebral artery ischemic stroke after rtPA treatment

Outcome	BI effectiveness			PASS effectiveness		
	Coefficient (β)	95% CI	*P*-Value	Coefficient (β)	95% CI	*P*-value
Age	-0.01	(-0.01,0.00)	0.045	-0.01	(-0.01,0.00)	0.031
Rehabilitation type, Early mobilization	0.23	(0.08,0.39)	0.004	0.17	(0.03,0.32)	0.019
NIHSS score at 24 hours after rtPA treatment	-0.02	(-0.03,0.00)	0.006	-0.01	(-0.02,0.00)	0.043

NIHSS: National Institute of Health Stroke Scale;
rtPA: recombinant tissue plasminogen activator
BI: Barthel Index
PASS: Postural Assessment Scale for Stroke

commencement of EM as well as age and NIHSS score at 24 hours post-rtPA may be associated with better functional improvement and postural control.

A previous study using a nationwide database showed that very early rehabilitation was associated with a significant increase functional independence in patients after treatment with rtPA [19]. However, in that study, the very early rehabilitation group included those who received any type or intensity of rehabilitation, including physical and occupational therapy and no detailed rehabilitation programs. In addition, patients treated with rtPA included in AVERT demonstrated a modest change in NIHSS score 24 hours post-rtPA [30]. Conversely, we could identify the exact timing of admission, the rtPA dosage and the starting date of out-of-bed activities by the EMR in our study. Moreover, the definition of "early" differed from that in our study: our mean time to a first mobilization in the EM group was 2.7 days, which was longer than the 22.4 hours for the usual care group in AVERT [21].

The results showed that starting out-of-bed mobilization within 24-72 hours of onset after rtPA treatment rather than later after ICU discharge resulting in facilitating functional recovery; however, our findings still need to be confirmed by future studies using a randomized controlled trial. These results are in agreement with findings of other studies that suggest that out-of-bed activities should commence early after stroke after receiving the rtPA treatment for better functional

outcomes [19, 31]. Functional or motor recovery from a stroke event occurs through a combination of spontaneous and experience-dependent processes [32]. The effects of early mobilization may be rooted in the extreme sensitivity of the sensorimotor experiences due to the use of a limited time window during the acute stage of stroke [33, 34]. Enhancing motor experiences or providing greater vertical stimulation through active out-of-bed sitting and standing constituted early mobilization is thought to play an important role in functional recovery after stroke [34].

In addition, age and the NIHSS score at 24 hours after rtPA treatment were predictive of functional improvement in our study. The functional outcomes after acute stroke survivors are mainly influenced by the patients' age due to the lower functional reserve and the more advanced comorbidities [35, 36]. Moreover, stroke severity based on the NIHSS score at admission is as an independent predictor of post-stroke outcome, but patients showed a significant early improvement of 0.5-4 or more points in terms of NIHSS scores after rtPA treatment [37]. Early neurological recovery has been identified as a significant predictor of long-term outcome in thrombolysis studies [38, 39]. Therefore, in our study, it was also found that the NIHSS score at 24 hours post-rtPA, compared to the NIHSS score upon admission, is predictive of better functional improvement. A prompt neurological improvement has shown to be more accurate as the baseline NIHSS score increases [38]. The result indicate that future related prospective studies might need to consider including the 24-hour post-rtPA NIHSS score as a predictive factor for the functional outcome improvement after the stroke.

5. Limitations

First, this study was a retrospective correlation study, therefore we could not make a definitive causal claim about the impact of early mobilization. Second, the subjects were recruited from a single center, and there were no long-term follow-up examinations. However, a homogeneous group of patients was analyzed. Third, the actual length of each rehabilitation time was not obtained in this study. Finally, the small sample size of the study and the associated medical records confined the determination of all possible potential confounding effects [40, 41]. Besides, the study population was heterogeneous in their nutrition status and cognitive status after stroke, which may have influenced the functional outcomes.

6. Conclusions

Early mobilization commencement within 24-72 hours after MCA-IS treated with rtPA might predispose to better functional outcomes during the acute phase. Future studies will need to examine the early mobilization intervention for such an approach and to estimate its effectiveness within IS treated with rtPA.

AUTHOR CONTRIBUTIONS

Yen H-C takes responsibility for the content of the manuscript, including the data and analysis. Yen H-C and Chuang W-Y had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. Yen H-C, Jeng J-S and Chen W-S contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board (IRB) of NTUH (ID number: 201801125RINA).

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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