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Clinical Study

Intravenous tissue plasminogen activator in acute branch atheromatous disease: Does it prevent early neurological deterioration?

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ABSTRACT

Early neurological deterioration (END) and poor outcome frequently occur in lenticulostriate artery (LSA) infarction due to branch atheromatous disease (BAD). We evaluate whether the tissue plasminogen activator (tPA) can prevent END and improve the outcome by comparing with anti-platelet treatment in LSA infarction due to BAD. We enrolled the patients with LSA infarction due to BAD who arrived at the hospital within 24 h from onset, and divided those into two groups by whether tPA was given or not. END and good outcome (modified Rankin score: 0–1) at 3 months were examined between two groups. Consecutive 35 patients of LSA infarction due to BAD enrolled in this study. Nine patients were given tPA (tPA group) and 26 patients antiplatelets only (non-tPA group). Patients in tPA group showed no symptomatic hemorrhage. END occurred in 68.6% (24/35) of all patients, 66.7% (6/9) of tPA group and 69.2% (18/26) of non-tPA group ($p = 0.886$). The proportion of good outcome at 3 months were 25.7% in all patients, 22.2% (2/9) in tPA group and 26.9% (7/26) in non-tPA ($p = 0.781$). tPA did not adequately prevent END, and did not show better outcome in LSA infarction due to BAD compared with antiplatelet therapy only. More effective treatment strategies are needed for prevention of END and favourable outcome in BAD.

1. Introduction

Branch atheromatous disease (BAD) is a unique stroke etiology caused by atheromatous occlusion at the orifice of large caliber penetrating arteries [1]. Recent studies have shown that BAD is strongly associated with progressive motor deficits and worse outcome compared to small artery disease [2–5]. It has been suggested that antiplatelet would be an important therapeutic strategy in BAD [1]. However, despite antiplatelet therapy, early neurological deterioration (END) is still troublesome and associated with poor outcome and permanent neurological deficit in patients with BAD [4,6].

Tissue-plasminogen activator (tPA) have been used in acute cerebral ischemia within 4.5 h after symptom onset and its efficacy for outcome have been proved in numerous studies so far. However, tPA still has some unresolved problems: first, END is not unusual with tPA-treated patients [7–9]; Second, antiplatelet is prohibited for 24 h after intravenous tPA [10]. Therefore, it is not unusual to have a doubt whether tPA would show the positive effect on preventing END and improving the outcome in BAD [7]. In this study, to identify the effectiveness of tPA for BAD, we compared END and outcome in BAD patients whether receiving tPA or antiplatelet only.

2. Methods

2.1. Patients

We retrospectively reviewed data of stroke patients admitted to the stroke center at our institute between January 2011 and July 2014. Patients were enrolled if they have met all of the following inclusion criteria: (1) lenticulostriate artery (LSA) infarction confirmed by diffusion-weighted imaging (DWI); (2) meeting the definition of BAD; (3) within 24 h from stroke onset. The BAD was defined as follows [1,3,11]: (1) infarction involving ⩾3 horizontal slices on DWI in the LSA territory; (2) no evidences of large artery disease (>50% stenosis of relevant artery) and cardioembolism according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [12].

The routine laboratory tests were performed in all of the patients: complete blood count, chemistry, serology, high-sensitivity C-reactive protein, urinalysis, chest X-rays, electrocardiography (ECG), transthoracic and/or transesophageal echocardiography.

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The Holter monitoring for 24 h was performed in the selective patients: (1) those with history of cardiac diseases, irregular rhythm on pulse palpation, or abnormal rhythm on ECG; (2) those without abnormality of relevant artery stenosis or atherosclerotic risk factors.

We divided the enrolled BAD patients into two groups according to initial treatment: tPA group and non-tPA group. Patients in tPA group were treated with the standard dose (0.9 mg/kg) of intravenous tPA within 4.5 h after stroke onset. All patients had follow-up brain CT scan in 24 h after treatment with tPA. After confirming the absence of intracranial hemorrhage on the brain CT, 75 mg of clopidogrel once daily was started without loading dose. In non-tPA group, 300 mg of clopidogrel was started as a loading dose, followed by the standard dose of 75 mg or standard dose only. Our Institutional Review Board approved this study; however, informed consent was not required because this study was retrospective.

2.2. Clinical assessments

Clinical data were obtained from medical records and stroke registry of our institute. All patients were monitored stroke unit for at least 3 days. Patients with neurological deterioration were observed in the stroke unit until they are neurologically stable. Initial stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). The NIHSS assessment was performed daily in all of an enrolled patients by our team members of stroke center (faculties, fellows, residents or stroke unit nurses). In patients receiving tPA, more frequent NIHSS assessment was performed in the initial 24 h after tPA administration according to the guidelines. When neurological deterioration was detected, the NIHSS was reassessed. END was defined as an increase of $\geqslant 1$ point in motor power (0 = no drift, 1 = drift but sustained antigravity, 2 = some effort vs gravity, 3 = no effort vs gravity, 4 = no movement) or an increase of $\geqslant 2$ points in the total NIHSS score within 7 days. A modified Rankin Scale (mRS) score was obtained at 3 months after stroke onset. Scores of 0 or 1 on the mRS were considered as an indication for good neurologic outcome.

2.3. Statical analysis

The Pearson's chi-squared test was used to determine whether there is a statistically significant difference in END and outcomes between the tPA and non-tPA groups. The clinical characteristics of the two groups were compared using the Pearson's chi-squared, Fisher's exact, and student *t*-tests. Mann–Whitney test was used to compare variables between patients with good and poor neurological outcomes. Chi-squared test was used for evaluating categorical variables between patients with good and poor outcomes. Variables ($p < 0.20$) associated with outcome at 3 months in the univariate analysis were selected to be evaluated in the multivariate logistic regression analyses. We analyzed the data using Statistical Package for Social Sciences software for windows (Version 21; IBM, Armonk, New York). Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Baseline characteristics

Thirty-five patients with BAD (42.3% were men; mean age was 63.0 ± 12.9 years) were finally enrolled in the study: nine patients in tPA group and 26 in non-tPA group. Clinical characteristics and demographic features of included patients are summarized in Table 1. The median initial NIHSS score was 5 (range 1–11). There was no significant difference in initial NIHSS score between the tPA and the non-tPA group ($p = 0.631$). The mean time from onset to tPA administration was 144.3 min (median 155 min, range 60–196 min) in tPA group. The mean time to arrival from symptom onset was 12.1 h (median 11.9, range 4.4–22.8 h) in non-tPA group. In non-tPA group, there was no patient who did not receive tPA because of mild symptoms despite of early arrival to hospital. All patients of tPA group showed no symptomatic intracranial hemorrhage on the follow-up brain CT scan 24 h after tPA administration. In 69.2% (18/26) patients of non-tPA group, clopidogrel was started with loading dose, followed by the standard dose.

Table 1
Baseline characteristics of the enrolled patients

Characteristics	tPA group (n = 9)	Non-tPA group (n = 26)	*P* Value
Male, n (%)	7 (77.8)	14 (53.8)	0.042
Age, mean ± SD, year	55.3 ± 8.9	65.7 ± 13.2	0.021
Arriving time, mean ± SD	91.7 ± 48.8 min	13.5 ± 6.2 h	<0.001
Time from onset to tPA, mean ± SD	144.3 ± 45.9 min		
Hypertension, n (%)	5 (55.6)	20 (76.9)	0.221
Diabetes, n (%)	2 (22.2)	3 (11.5)	0.430
Hyperlipidemia, n (%)	2 (22.2)	2 (18.2)	0.639
Smoking, n (%)	5 (55.6)	5 (19.2)	0.081
Initial NIHSS score, median, IQR	8 (5–11)	5 (1–10)	0.631
Early neurological deterioration, n (%)	6 (66.7)	18 (69.2)	0.886
1st day	0	1 (5.6%)	
2nd day	4 (66.7%)	12 (66.7%)	
3rd day	1 (16.7%)	3 (16.7%)	
4th day	1 (16.7%)	4 (22.2%)	
mRS at 3 months			
0	1	2	
1	1	6	
2	2	6	
3	3	7	
4	2	4	
5	0	1	
mRS $\leqslant 1$ at 3 months, n (%)	2 (20%)	7 (29.6%)	0.781

IQR = interquartile range, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation, tPA = tissue plasminogen activator.

3.2. Early neurological deterioration and outcome

END occurred in 66.7% (six of nine patients) of tPA group and 69.2% (18 of 26 patients) of non-tPA group ($p = 0.886$) (Fig. 1). In both groups, most END occurred on the second day (Table 1). In tPA group, 77.8% (seven of nine patients) showed initial improvement (within 24 h) after tPA administration, but 57.1% (four of seven patients) of them deteriorated again following the improvement. The median mRS at 3 months was 2 (range 0–5). The good neurological outcomes 3 months after stroke was not different between tPA group and non-tPA group: 22.2% (two of nine patients) in tPA group and 26.9% (seven of 26 patients) in non-tPA ($p = 0.781$) (Fig. 2).

Univariate analysis showed that hypertension and END were associated with outcome (Table 2). Multivariate testing was performed to test further for variables ($p < 0.20$) that may be independently associated with outcome. END remained an significant factor in the final regression analysis after adjusting for initial NIHSS score and hypertension (Table 2).

4. Discussion

Our study shows that tPA does not prevent END and improved outcome in patients with LSA infarction due to BAD. Based on the NINDS clinical trial showing that tPA has similar positive effect on