Treatment Outcomes of Tissue Plasminogen Activator Infusion for Branch Atheromatous Disease

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Background: The objective of this study was to evaluate treatment outcomes of tissue plasminogen activator (t-PA) infusion for hyperacute branch atheromatous disease (BAD) within 3 hours after onset. *Methods:* A total of 152 BAD patients with lenticulostriate artery (LSA) or paramedian pontine artery (PPA) territory infarcts (LSA 114; PPA 38) were hospitalized between April 2007 and June 2012. Of these, 21 BAD patients (LSA 19; PPA 2) arrived at the hospital within 3 hours after onset, and, among these, 8 patients who received t-PA infusion (.6 mg/kg) were included in this study. All BAD patients who received t-PA infusion had LSA territory infarcts. *Results:* Six of 8 patients (75%) had improvement of neurologic findings within 60 minutes after t-PA infusion, but neurologic findings deteriorated within 24 hours in 4 of these patients (67%). In all patients with deterioration, diffusion-weighted imaging after 24 hours revealed infarct expansion. One patient (13%) had symptomatic intracranial hemorrhage. After 3 months, the modified Rankin Scale (mRS) score was 0 to 2 in 6 patients (75%) and 3 to 6 in 2 patients (25%). *Conclusions:* With t-PA infusion for BAD, symptoms transiently improved, but the rate of symptom deterioration was high. The outcome after 3 months was relatively good. **Key Words:** Branch atheromatous disease—tissue plasminogen activator.

Branch atheromatous disease (BAD), a pathologic concept proposed by Caplan,[1] refers to perforating artery infarction with infarction of an entire perforating artery territory caused by occlusion by microatheroma proximal to or at the orifice of a perforating artery. In BAD, the symptoms become progressively worse because of treatment resistance in many cases, and controversy exists regarding both pathophysiology and treatment strategy. Currently, there is no established treatment, and the effectiveness of tissue plasminogen activator (t-PA) infusion in BAD has seldom been investigated.[2-8] In this study, in patients who arrived at the hospital within 3 hours after onset and received t-PA infusion for BAD, the National Institutes of Health Stroke Scale (NIHSS) score, changes in infarct size, acute phase treatment, and functional outcome after 3 months (modified Rankin Scale [mRS]) were retrospectively examined.

Methods

Among 1665 patients with cerebral infarction who were hospitalized between April 2007 and June 2012, there were 152 patients with BAD who had lenticulostriate artery (LSA) territory or paramedian pontine artery (PPA) territory infarctions meeting the definition of BAD (LSA 114; PPA 38). Of these, 21 BAD patients (LSA 19; PPA 2) arrived at the hospital within 3 hours after onset, and this study included 8 of these patients who received t-PA infusion (.6 mg/kg) (5 men and 3 women;

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Table 1. *Clinical characteristics of patients with branch atheromatous disease who received tissue plasminogen activator infusion*

Age, y (mean ± SD)	70 ± 7.8
Male, n (%)	5 (63)
Blood pressure on arrival, mm Hg (mean ± SD)	
Systolic	184 ± 28
Diastolic	99 ± 13
Coexisting disease, n (%)	
Hypertension	3 (38)
Diabetes	2 (25)
Dyslipidemia	4 (50)
History of stroke, n (%)	0 (0)
Smoking, n (%)	2 (25)
Antithrombotic therapy, n (%)	0 (0)
NIHSS score on arrival, median (range)	7 (6-11)
Time to t-PA infusion, min (mean ± SD)	145 ± 22

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; t-PA, tissue plasminogen activator.

mean age [±SD] 70 ± 7.8 years; Table 1). Reasons that 13 patients did not receive t-PA infusion included: mild symptoms (5 patients), rapid improvement (4 patients), gastrointestinal or urinary tract bleeding (2 patients), and t-PA infusion not possible within the time window (2 patients). All 8 patients who received t-PA infusion had LSA territory BAD. BAD was defined (Table 2), based on diffusion-weighted imaging (DWI) at the time of arrival, as infarction involving ≥3 horizontal slices in the LSA territory or characteristic infarction extending to the basilar pons in the PPA territory, and on magnetic resonance angiography (MRA) as no stenosis (≥50%) or occlusion of a major artery of the branch artery and no cardioembolic source (e.g., atrial fibrillation).[2,4] As for the perforating arteries involved in BAD, Caplan[1] also mentioned the thalamogeniculate, anterior choroidal, Heubner's, and thalamoperforating arteries, but this study targeted BAD clearly defined as only involving the LSA and PPA territories. The survey items included the NIHSS score, infarct size (maximum diameter and number of slices on DWI axial images), changes in infarction on magnetic resonance imaging (MRI), details of acute phase treatment, and clinical outcome (mRS score after 3 months) were retrospectively examined. Symptom improvement was defined as NIHSS score improvement ≥1, and symptom progression was defined as NIHSS score worsening ≥1. MRI/DWI imaging was performed on arrival and 24 hours after t-PA infusion (5 days after t-PA infusion in 1 patient).

This study was approved by the Ethics Committee at Saitama Medical University International Medical Center.

The MRI devices used were a 1.5-T Achieva Nova Dual (Philips; Amsterdam, The Netherlands) and a 1.5-T Magnetom Avanto (Siemens; Berlin, Germany).

DWI conditions were as follows: Achieva using the spin-echo echo-planar imaging (SE-EPI) method: repetition time (TR) 3829 ms; echo time (TE) 65 ms; b = 1000; slice thickness 5 mm; intersection gap 1.5 mm; field of view (FOV) 230 mm × 207 mm; matrix 144 × 100.8; Avanto using the SE-EPI method: TR 4200 ms; TE 81 ms; b = 1000; slice thickness 5 mm; intersection gap 1.5 mm; FOV 230 mm × 230 mm; matrix 128 × 102.

MRA was performed from the branching point of the internal carotid artery to the inside of the cranium according to the following conditions: Achieva using the 3-dimensional time of flight (3D-TOF) method: TR 20 ms; TE 6.0 ms; flip angle 16°; FOV 200 mm × 200 mm; slice thickness .65 mm; Avanto using the 3D-TOF method: TR 22 ms; TE 7.0 ms; flip angle 18°; FOV 220 mm × 220 mm; slice thickness .7 mm.

Results

Table 3 shows the treatment outcomes with t-PA infusion for BAD. With regard to infusion/oral therapy, all patients received edaravone before or simultaneously with t-PA infusion; at 24 hours after t-PA infusion, 5 patients (63%) received argatroban, 6 (75%) received clopidogrel/aspirin, and 4 (50%) received cilostazol. In 6 of 8 patients (75%), combination therapy with ≥3 drugs was administered. The median NIHSS scores before, 60 minutes after, 24 hours after, and 1 week after t-PA infusion were 7, 3.5, 7.5, and 3.5, respectively. In 6 of 8 patients (75%), neurologic findings improved within 60 minutes of t-PA infusion, but in 4 of the 6 patients (67%), there was deterioration of the neurologic findings. In all patients with deterioration, DWI at 24 hours after t-PA infusion revealed infarct expansion, but in the 2 patients without deterioration, infarct size was reduced. Representative cases of deterioration after t-PA infusion are shown in Fig 1. Symptomatic ICH occurred in 1 patient (13%; Fig 2). After 3 months, the mRS scores were: 0 in 1 patient (12.5%), 1 in 3 patients (37.5%), 2 in 2 patients (25%), 3 in 1 patient (12.5%), and 5 in 1 patient (12.5%).

Discussion

Because BAD often has a progressive and labile course, the time of onset is imprecise, and patients themselves delay coming to the hospital. In addition, t-PA is sometimes

Table 2. *Diagnostic criteria for branch atheromatous disease*

Paramedian pontine artery territory infarct: Infarct extending to the basal surface of the pons
Lenticulostriate artery territory infarct: Infarct involving >3 consecutive horizontal slices on magnetic resonance imaging scan
Neither evidence of large artery disease (>50% stenosis or occlusion) nor of a cardioembolic source