Preliminary Experience with Air Transfer of Patients for Rescue Endovascular Therapy after Failure of Intravenous Tissue Plasminogen Activator

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Abstract

The present report describes our experience with air transfer of patients with acute ischemic stroke in whom intravenous tissue plasminogen activator (IV t-PA) failed for rescue endovascular therapy (EVT). Twenty-three consecutive patients in whom IV t-PA failed were transferred to our hospital for rescue EVT between February 2011 and April 2013. The amount of time required for transfer, distance, clinical outcomes, and complications were compared between patients transferred by ground (TG group; n = 17) and by air (TA group; n = 6). Computed tomography imaging on arrival revealed hemorrhagic transformation in 1 (5.9%) patient in the TG group, whereas none of the patients in the TA group developed any type of complication. The remaining 22 patients received rescue EVT. The elapsed time from the request call to arrival at our hospital did not significantly differ between the TG and TA groups (45.8 ± 4.9 min vs. 41.6 ± 2.3 min). However, the distance from the primary hospital to our institution was significantly longer for the TA group than for the TG group (38.8 ± 10.4 km vs. 13.5 ± 1.2 km, p = 0.001). The frequency of favorable outcomes (modified Rankin Scale 0–1 at 90 days after onset) in the TG and TA groups were 25.0% and 50.0%, respectively (p = 0.267). Air transfer for patients after IV t-PA failure allowed for more rapid delivery of patients over longer distances than ground transfer.

Key words: acute ischemic stroke, rescue endovascular therapy, tissue plasminogen activator, air transfer, helicopter

Introduction

The results of a recent randomized controlled trial have shown that intravenous tissue plasminogen activator (IV t-PA) is the first-line treatment for patients with acute ischemic stroke within 4.5 hours of onset.1–3 However, the clinical outcomes of IV t-PA for treating intracranial large vessel occlusion (LVO) remain poor.4,5 On the other hand, the favorable effects of early recanalization by endovascular therapy (EVT) are reported.6–12

The effectiveness of EVT depends on the interval between symptom onset and reperfusion.13 However, EVT is not available at all stroke centers, which means that patients for whom rescue EVT is indicated must be transferred to another comprehensive stroke center where EVT is available.14,15

The initiation of IV t-PA in a primary hospital with subsequent transfer to another stroke center is called the “drip-ship” approach. We apply this approach particularly for patients in whom IV t-PA has failed and rescue EVT is necessary.

Air transfer is one way to minimize the interval between onset and reperfusion therapy, and it has become a safe and useful transport modality for patients with acute stroke.16,17 However, these studies focused on the effectiveness of patient care after IV t-PA treatment at a stroke center. On the other hand, we selectively transfer patients with LVO for rescue EVT after IV t-PA has failed. Therefore, the indication for transfer in the present study differs from those of the previous reports.
Here, we describe our preliminary experience with air transfer of patients with LVO for rescue after IV t-PA has failed.

**Materials and Methods**

All consecutive patients with LVO in whom IV t-PA failed and who were transferred to our hospital for rescue EVT between February 2011 and April 2013 were assessed. The inclusion criteria comprised acute ischemic stroke due to intracranial LVO confirmed by magnetic resonance imaging (MRI) and MR angiography, IV t-PA therapy (approved dose in Japan: 0.6 mg/kg with 10% of the dose given as an initial bolus and the remainder infused over 1 h) administered at the primary hospital within 3 hours (between February 2011 and July 2012) or within 4.5 hours (between August 2012 and April 2013) of onset, no significant improvement after therapy defined as National Institutes of Health Stroke Scale (NIHSS) scores ≥ 4, and rescue EVT judged effective by a primary physician.

Air transfer is available during the daytime and during clear weather in our region, and the type of transfer is influenced by time, weather, and distance. If air transfer is considered faster than ground, physician who treats at the first hospital requests flight doctors in our hospital to transfer the patient. Transfer time is defined as the interval between the request call and arrival at our hospital.

I. Computed tomography (CT)

Transferred patients were assessed by CT just before EVT and then Alberta Stroke Program Early Computed Tomography (ASPECT) scores were evaluated.

II. EVT

EVT is defined as intra-arterial (IA) catheter procedures such as clot removal/aspiration, balloon angioplasty, stenting, and IA thrombolysis using a microcatheter. EVT was started within 8 hours of stroke onset when NIHSS scores were ≥ 8. However, EVT was also applied to patients with NIHSS scores < 8 if they had unstable ischemic symptoms or were considered at high risk for deterioration due to poor collateral circulation.

III. Evaluation of clinical outcome

Patient outcomes were evaluated using the modified Rankin scale (mRS) at 90 (± 10) days after onset. We defined favorable outcomes as mRS scores of 0–1.

IV. Statistical analysis

Values are shown as mean ± standard deviation (SD). Categorical variables were analyzed using the Chi-squared or Fisher’s exact test, as appropriate. Continuous variables with normal and non-normal distribution were analyzed using Student’s t test and the Mann-Whitney U test, respectively. P < 0.05 was considered a significant difference. Data were statistically analyzed using SPSS software version 18 (SPSS Japan Inc., Tokyo).

**Results**

Among 23 consecutive patients who were transferred to our hospital for rescue EVT during the study period after IV t-PA failed, 17 and 6 were transferred by ground (TG group) and air (TA group), respectively. Rescue EVT was administered to 22 of the 23 patients because CT identified hemorrhagic transformation in 1 (5.9%) patient in the TG group.

Table 1 shows the baseline characteristics of the patients who received rescue EVT. Age, sex, vascular risk factors, initial NIHSS scores, and ASPECT scores did not significantly differ between the TG and TA groups.

The interval between the request and arrival at our hospital did not significantly differ between the TG and TA groups.

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<tr>
<th>Table 1 Baseline characteristics of patients who were transferred by air and ground for treatment with rescue endovascular therapy</th>
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<td>Ground transfer (n = 16)</td>
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<td>Age (y)</td>
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<td>No. of males, n (%)</td>
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<td>Risk factors, n (%)</td>
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<td>Distance between hospitals (km)</td>
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<td>Interval between request call and arrival (min)</td>
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<td>Onset to IV t-PA (min)</td>
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<td>IV t-PA to arrival (min)</td>
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<td>Onset to EVT (min)</td>
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<td>Termination of IV t-PA, n (%)</td>
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<td>After arrival</td>
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<td>Favorable outcome (mRS 0-1) at 90 days, n (%)</td>
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</table>

ASPECT: Alberta Stroke Program Early Computed Tomography, EVT: endovascular therapy, IV t-PA: intravenous tissue plasminogen activator, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale.
TA groups (45.8 ± 4.9 min vs. 41.6 ± 2.3 min). However, the distance from the primary hospital to our institution was significantly longer for the TA group than the TG group (38.8 ± 10.4 km vs. 13.5 ± 1.2 km; p = 0.001). The relationship between the termination of IV t-PA and arrival, and the mean intervals between stroke onset and IV t-PA and between stroke onset and EVT did not significantly differ. The frequency of favorable outcomes in the TG and TA groups was 25.0% and 50.0%, respectively (p = 0.267).

Discussion

Recent randomized, controlled trials have not found that

Case Report

A 73-year-old right-handed male with acute onset of right hemiparesis and aphasia was transferred to a primary hospital located 23 km from our institution. The NIHSS score at that time was 8. Assessment by MRI revealed a new infarction in the left middle cerebral artery (MCA) territory (Fig. 1a), and MR angiography showed left internal carotid artery (ICA) occlusion (Fig. 1b). The patient received IV t-PA 135 min after onset, but significant improvement was not evident after 15 min from IV t-PA. The primary physician requested air transfer, and the patient arrived at our hospital 210 min after stroke onset. The patient got repeated CT, and it did not reveal any hemorrhage. The patient was moved to the angiography suite 260 min after onset. The patient could not keep rest, we induced general anesthesia with endotracheal intubation. Digital subtraction angiography (DSA) revealed persistent left ICA occlusion (Fig. 2a). Aspirin (200 mg) and clopidogrel (300 mg) were administered because atherothrombotic occlusion was suspected. A total of 5,000 IU heparin was intravenously administered, and initial carotid artery stenting proceeded under proximal balloon protection (Fig. 2b). Thereafter, the ICA was dilated (Fig. 2c), but the left MCA occlusion persisted (Fig. 2d). Recanalization was not achieved despite an IA infusion of urokinase (120,000 IU). The MCA was dilated with a balloon catheter (Fig. 2e), which resulted in complete recanalization (Fig. 2f).

The NIHSS score at 24 hours after onset improved to 4. Assessment by MRI at 7 days after onset showed limited infarction in the frontal lobe (Fig. 3a) and MR angiography showed a patent left MCA (Fig. 3b). The patient remained free of neurologic deficits at 2 months after stroke onset.

Fig. 1 Diffusion-weighted magnetic resonance imaging (MRI) and MR angiography of a 73-year-old male with acute onset of right hemiparesis and aphasia. a: Small acute infarction in the left middle cerebral artery territory revealed by MRI. b: MR angiography shows occluded left cervical internal carotid artery.

Fig. 2 Angiography findings. Common carotid angiography confirmed occluded cervical portion of internal carotid artery (a). Carotid stenting under proximal balloon protection (b) resulted in recanalization (c). Left internal carotid angiography shows persistently occluded middle cerebral artery (d). Balloon angioplasty (e) resulted in reperfusion (f).

Fig. 3 Imaging findings 1 day later. a: Enlargement of infarction is not evident on MRI and b: MR angiography shows patent left internal carotid and middle cerebral arteries. MRI: magnetic resonance imaging.
Air Transfer for EVT after Failure of IV t-PA

EVT is effective against acute stroke.\textsuperscript{19–21} For example, the Interventional Management of Stroke III trial that aimed to determine whether IV t-PA combined with EVT is more effective than IV t-PA alone did not identify any benefits in terms of rates of favorable outcomes (mRS of ≤ 2) compared with IV t-PA alone.\textsuperscript{19} The interval between starting IV t-PA and groin puncture was 86 min in that trial. This delay before starting EVT might explain why EVT was ineffective. Therefore, minimizing the interval before starting EVT should be a critical issue. If IV t-PA fails and patients are indicated for rescue EVT but admitted to a hospital where EVT is not available, then they will require transfer to a stroke center where EVT is available. When a stroke center is located far from a primary hospital, air transfer will help to reduce transfer time to EVT.

Although the TA group travelled farther, transfer time did not significantly differ between the TG and the TA groups. Thus, air transfer seemed useful to transfer patients after IV t-PA failure to stroke centers where EVT is available.

On the other hand, some concerns have been voiced about the risk of neurological deterioration due to the complications of IV t-PA therapy, such as hemorrhage during transfer. However, hemorrhagic complications did not arise in the TA group in the present study. Pfefferkorn et al. reported that 24 of 52 patients treated using the "drip, and ship" approach were transferred by air, and complications associated with transfer did not occur.\textsuperscript{22} Medical doctors in Japan usually accompany patients during helicopter transfer, which might have helped to reduce the risk of complications in the present study.

Finally, the indication for air transfer was influenced by time and weather in the present study. Air transfer is usually not proscribed after sunset and during bad weather, because helicopters should operate according to visual flight rules in Japan. Another concern is that patient status, weather, amount of time, and distance complicate decisions regarding how to transfer patients. Guidelines are needed to transfer patients for rescue EVT after IV t-PA failure in each area, because the required time is supposed to be different due to the difference of emergency system and traffic conditions.

This preliminary retrospective study included a small patient cohort. Therefore, more patients need to be studied to improve the understanding of air and ground transfer.

**Conclusion**

Air transfer for patients after IV t-PA failure allowed for more rapid delivery of patients over longer distances than ground transfer. This finding require confirmation with more patients.

**Conflicts of Interest Disclosure**

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

**References**


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