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Efficacy of the Drip and Ship Method in 24-h Helicopter Transportation and Teleradiology for Isolated Islands

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Abstract

Our hospital, located on the mainland, serves as a hub center for nine hospitals on the remote islands of Nagasaki Prefecture, Japan. There are no stroke specialists on these islands. We can transfer emergency patients from these islands to our hospital at any time, using a teleradiology system and three types of helicopter transport. We examined the efficacy of the drip and ship (DS) method for treating patients with acute ischemic stroke (AIS) on these islands, in comparison with patients on the mainland. From 2010 to 2017, we reviewed 98 consecutive patients with AIS who received intravenous recombinant tissue plasminogen activator (IV rt-PA) in our hospital or were transported to our hospital after IV rt-PA. Patients were divided into the Islands group (received IV rt-PA on the islands, DS; 31 cases) and the Mainland group (67 cases). The median transport distance from the islands was 112 km. The rate of patients achieving favorable outcomes was 54.8% in the Islands group and 64.2% in the Mainland group, with no significant differences. Multivariate analysis revealed that patients living on isolated islands did not have increased risks of unfavorable outcomes. Endovascular therapy (EVT), as part of the drip, ship, and retrieve method, was performed in 22.6% of patients in the Islands group and EVT in 38.8% of those in the Mainland group. The DS method seems feasible and safe for patients living on isolated islands with the use of 24-h helicopter transportation and teleradiology.

Key words: drip and ship, drip and ship and retrieve, isolated islands, helicopter transportation, teleradiology

Introduction

Intravenous recombinant tissue plasminogen activator (IV rt-PA) is the standard treatment for patients with acute ischemic stroke (AIS) within 4.5 h of stroke onset. The effectiveness of endovascular therapy (EVT) for AIS has been shown in recent randomized controlled trials.[1,2] The time from symptom onset to recanalization of occluded arteries could affect the prognosis of patients.[3]

Nagasaki Prefecture has 51 inhabited islands, the highest number in Japan. There are approximately 120,000 people living on these islands, making up 9% of the population of Nagasaki Prefecture. However, there are no stroke specialists on the islands. Our hospital, located in the mainland, serves as the main hub for these remote islands using two systems: a 24-h helicopter transportation system and a teleradiology system. Most patients with stroke on remote islands who need emergency medical care are transported to our hospital.

We use three types of helicopter: helicopter emergency medical services (HEMS), a Maritime Self-Defense Force (MSDF) helicopter, and a firefighting disaster

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prevention (FDP) helicopter.[4] Use of a helicopter transport system has been reported to be a very safe and beneficial transport method for patients.[5,6] Initiation of IV rt-PA at a regional hospital with subsequent transfer to a specialized stroke center is referred to as the drip and ship (DS) approach. Several reports have demonstrated the safety and feasibility of this strategy in patients with AIS.[7,8] However, there are no published studies in English showing the effectiveness of DS on remote islands.

The purpose of this study was to clarify whether the DS method is effective in patients with stroke on remote islands, where general physicians initially treat these patients in the absence of stroke specialists. The present study is important in that we investigated the efficacy and safety of treating patients with AIS on remote islands using the DS method, in comparison with patients on the mainland.

Materials and Methods

Study population

From 2010 to 2017, we reviewed the data of 98 consecutive patients with AIS who received IV rt-PA in our hospital or were transported to our hospital after IV rt-PA therapy. Patients were divided into two groups: the "Islands" group (those who received rt-PA on the islands of Nagasaki) and the "Mainland" group (those who received rt-PA at our hospital or other hospitals on the mainland). These islands are located in Nagasaki Prefecture and consists of three main island groups: Goto, Iki, and Tsushima (Table 1). A total of 31 patients with AIS were transferred to our hospital from Nagasaki's remote islands via the DS method. In addition, we included 67 patients who received IV rt-PA on the mainland. Patient demographic and baseline characteristics including age, sex, severity of neurological deficit using the National Institutes of Health Stroke Scale (NIHSS) score, and stroke subtype [according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification][9] were compared between the two groups. Occlusion of the M1 and M2 segments of the middle cerebral artery, internal cerebral artery, and basilar artery was defined as large vessel occlusion. Other variables included the recanalization rate based on the modified Thrombolysis in Cerebral Infarction (mTICI) grade,[10] modified Rankin Scale (mRS) score at 90 days post-treatment, and adverse event incidence.

Table 1 Basic data of the main remote islands of Nagasaki Prefecture (2015)

Islands	Numbers of inhabited islands	Population	Distance from islands to Nagasaki medical center (km)
Tsushima	6	31,468	165
Iki	5	27,106	97
Goto	18	57,053	88–112

Helicopter system

Helicopter emergency medical services are generally used for patient transport in the daytime. An FDP helicopter is used in the daytime when HEMS are unavailable, and an MSDF helicopter is usually used at night, in bad weather, or in the daytime when other helicopters are unavailable. In this study, the FDP and MSDF helicopters were used only for patients on the isolated islands.

Teleradiology system

Our hospital is a hub center for nine hospitals on the remote islands of Nagasaki. The Fujifilm Synapse teleradiology system connects our hospital and the nine hospitals on the islands via Ajisai net. We performed consultation using this teleradiology system for all 31 patients with AIS on the remote islands who were transferred to our hospital using the DS method.

DS protocol

Initial emergency assessment and administration of IV rt-PA in patients with stroke at hospitals located on isolated islands or on the mainland and subsequent transfer to our stroke center is referred to as the DS approach, as mentioned above. In selected cases using the DS approach, EVT was performed, as part of the drip, ship, and retrieve (DSR) method.

Evaluation of clinical outcomes

Patients' outcomes were evaluated using the mRS score at 90 days after stroke onset. Favorable outcomes were defined as mRS scores of 0–2, unfavorable outcomes as mRS scores of 3–6.

Statistical analysis

The Mann–Whitney U and Chi-squared tests were used to examine the differences among continuous and categorical variables. A *P*-value of 0.05 was considered statistically significant. Data analysis was performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and JMP 14.2 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics and characteristics

The median patient age was 75.0 years in the Islands group and 74.0 years in the Mainland group

(Table 2). Among the 98 patients, there were no differences between the two groups regarding the initial NIHSS score, symptom onset-to-needle time, percentage of large vessel occlusion, and distribution of stroke subtype. All patients in the Islands group were transported via the DS method. Among 67 patients who received IV rt-PA on the mainland, DS was used in six patients and 61 patients were delivered to our hospital directly. Three types of helicopter were used in the Islands group: HEMS (16 patients), an MSDF helicopter (13 patients), and an FDP helicopter (two patients). Helicopter transport was used for 10 patients in the Mainland group, and all these patients were transported using HEMS. The distance of transport from the islands to our hospital was 112 ± 5 km (median ± standard error), and the transport distance by HEMS in the Mainland group was 29 ± 2 km.

Results of rt-PA treatment

In the Islands group, the time from symptom onset to arrival at our hospital was within 6 h in 21 cases (67.7%), and within 6–24 h in 10 cases (33.3%). Symptomatic intracranial hemorrhage (ICH) was not observed in the Islands group but was present in 6.0% of patients in the Mainland group (Table 2).

Table 2 Baseline characteristics and results of patients treated with intravenous recombinant tissue plasminogen activator in the Islands and Mainland groups

	Total	Islands	Mainland	*P*-value
Number of cases	98	31	67	
Sex				0.539
Male, *n* (%)	56 (57.1)	18 (58.1)	38 (56.7)	
Female, *n* (%)	42 (42.9)	13 (41.9)	29 (43.3)	
Age (years), median (IQR)	74.5 (65.3–81.8)	75.0 (67.5–83.5)	74.0 (65.5–81)	0.804
Drip and ship, *n*	37 (37.8%)	31	6	<0.001
Helicopter transportation, *n*	41 (41.8%)	31	10	<0.001
Symptom onset-to-needle time, min median (IQR)	160 (133–186)	167 (131–198)	152 (134–183)	0.202
Symptom onset-to-door time, min median (IQR)	64 (40–90)	40 (30–68)	70 (46–97)	0.001
Door-to-needle time, min median (IQR)	84 (68–112)	110 (93–134)	78 (53.5–96.5)	<0.001
Initial NIHSS median (IQR)	15.0 (8.0–20.8)	16.0 (8–20.5)	15.0 (8–20.5)	0.848
Large vessel occlusion, *n* (%)	73 (74.5)	21 (67.7)	52 (77.7)	0.297
Occlusion site				0.897
ICA	22	5	17	
M1	28	10	18	
M2	14	4	10	
BA	9	2	7	
Toast classification				0.978
Large artery atherosclerosis	20	7	13	
Cardioembolism	55	19	36	
Small vessel occlusion	8	2	6	
Other determined etiology	7	1	6	
Undetermined etiology	8	2	6	
Endovascular treatment, *n* (%)	33 (33.7)	7 (22.6)	26 (38.8)	0.087
sICH, *n* (%)	4 (4.1)	0	4 (6.0)	0.212
mRS 0–2 at 90 days, *n* (%)	60 (61.2)	17 (54.8)	43 (64.2)	0.865
Mortality during admission, *n* (%)	2 (2.0)	1 (3.2)	1 (4.5)	0.623

BA: basilar artery, ICA: internal carotid artery, IQR: interquartile range, M1: M1 segment of the middle cerebral artery, M2: M2 segment of the middle cerebral artery, min: minutes, mRS: modified Rankin Scale, n: number, NIHSS: National Institutes of Health Stroke Scale, sICH: symptomatic intracranial hemorrhage.

The rate of patients achieving favorable outcomes (mRS score ≤2) was 54.8% in the Islands group and 64.2% in the Mainland group (Table 3); there were no significant differences between the groups. No patients experienced worsened neurologic symptoms during helicopter transport.

Results of EVT combined with IV rt-PA

Endovascular therapy was performed in seven patients in the Islands group (22.6%) and 26 patients in the Mainland group (38.8%) (Table 3). The DSR method was performed for all seven patients in the Islands group but only three patients in the Mainland group (Table 3). In seven patients transported from the islands, the DSR method was performed (five using HEMS and two using an FDP helicopter). In all seven patients, the delivery time from symptom onset to arrival at our hospital was within 6 h and four patients had successful recanalization (mTICI grade 2b or 3). Symptom onset-to-puncture time in the Islands group was longer than that in the Mainland group, and the percentage of patients with successful recanalization in the Islands group (57.1%) was lower than that in the Mainland group (96.2%) (Table 3).

Risk factors of unfavorable outcomes

Among 98 patients, 38 patients (38.8%) had an unfavorable outcome. To identify the factors associated with the risk for unfavorable outcome, we carried out univariate and multivariate analysis of 98 patients with stroke. Multivariate analysis revealed that age (78 years and more), symptom onset-to-needle time (over 143 minutes), and NIHSS score (17 and more) were independent determinants of unfavorable outcome (Table 4), with similar results in other reports.[11,12] Patients living on these isolated islands did not show increased risks of unfavorable outcomes (Table 4). Furthermore, we confirmed a model for prediction of unfavorable outcome, using a stepwise logistic regression analysis. Our results showed that age (78 years and more), symptom onset-to-needle time (over 143 minutes), and NIHSS score (17 and more) remained in the final equation (Table 5).

Discussion

DS approach and teleradiology

Coordination between the hub-and-spoke institutes is critical, because there is limited time for treatment in AIS. Our hospital is part of a hub-and-spoke type network with nine hospitals on the remote islands of Nagasaki Prefecture. Several previous studies have compared patients treated on arrival at a primary emergency department with patients treated using the DS paradigm.[13–16] The DS method is currently used for one in four patients treated with IV rt-PA

Table 3 Endovascular treatment combined with intravenous recombinant tissue plasminogen activator in the Islands and Mainland groups

	Islands	Mainland	*P*-value
Number of cases	7	26	
Sex			1.000
Male, *n* (%)	5	17	
Female, *n* (%)	2	9	
Age (years), median (IQR)	77.0 (70.5–81.5)	78.0 (65.0–81.8)	0.758
Initial NIHSS median (IQR)	17 (15.5–21.5)	16.5 (13.0–21.0)	0.675
Occlusion site			0.960
ICA	2	10	
M1	2	11	
M2	2	3	
BA	1	2	
Drip, ship, and retrieve, *n*	7	4	<0.001
Helicopter transportation, *n*	7	3	<0.001
Symptom onset-to-puncture time, min Median (IQR)	318 (228–322)	212.5 (151.2–255.0)	0.002
Successful reperfusion (mTICI 2b or 3), *n* (%)	4 (57.1)	25 (96.2)	0.023
mRS 0–2 at 90 days, *n* (%)	3 (42.9)	17 (65.4)	0.257

BA: basilar artery, ICA: internal carotid artery, IQR: interquartile range, M1: M1 segment of the middle cerebral artery, M2: M2 segment of the middle cerebral artery, min: minutes, mRS: modified Rankin Scale, mTICI: modified thrombolysis in cerebral infarction, n: number, NIHSS: National Institutes of Health Stroke Scale.

Table 4 Factors associated with risks for unfavorable outcomes among 98 patients treated with intravenous recombinant tissue plasminogen activator, according to univariate and multivariate logistic regression analysis

Variables	Univariate analysis			Multivariate analysis		
	b (SE)	Crude OR (95% CI)	*P*-value	*b* (SE)	Adjusted OR (95% CI)	*P*-value
Age ≥ 78	1.22 (0.44)	3.40 (1.44–8.01)	0.005	1.42 (0.71)	4.14 (1.02–16.78)	0.047
Male, against female	0.05 (0.42)	1.05 (0.46–2.39)	0.905	0.71 (0.70)	2.03 (0.52–7.98)	0.312
Drip and ship	0.12 (0.43)	1.13 (0.49–2.60)	0.780	−1.89 (1.79)	0.15 (0.01–5.05)	0.291
Helicopter transportation	0.55 (0.42)	1.72 (0.75–3.94)	0.194	−1.23 (1.22)	0.29 (0.03–3.15)	0.310
Symptom onset-to-needle > 143 min	1.82 (0.55)	6.17 (2.12–17.97)	0.001	2.60 (0.80)	13.46 (2.81–64.43)	0.001
NIHSS ≥ 17	2.27 (0.48)	9.67 (3.74–24.97)	<0.001	2.29 (0.72)	9.88 (2.41–40.54)	0.001
Large vessel occlusion	1.52 (0.59)	4.58 (1.43–14.66)	0.010	0.96 (1.03)	2.62 (0.35–19.82)	0.351
Large artery atherosclerosis	−0.48 (0.54)	0.62 (0.21–1.77)	0.369	−21.43 (>100)	-	1.000
Cardioembolism	1.10 (0.44)	3.00 (1.26–7.13)	0.013	−20.60 (>100)	-	1.000
Small vessel occlusion	−0.69 (0.84)	0.50 (0.10–2.62)	0.412	−20.33 (>100)	-	1.000
Other determined etiology	−1.41 (1.10)	0.24 (0.03–2.11)	0.199	−39.88(>100)	-	0.999
Undetermined etiology	−1.59 (1.10)	0.21 (0.02–1.73)	0.146	−22.20 (>100)	-	1.000
Endovascular treatment	0.04 (0.44)	1.04 (0.44–2.45)	0.929	−0.50 (0.74)	-	0.503
sICH	21.77 (>100)	-	0.999	38.14 (>100)	-	0.999
Islands against Mainland	0.39 (0.44)	1.48 (0.62–3.51)	0.379	3.52 (2.19)	33.86 (0.46–>100)	0.108

CI: confidence interval, min: minutes, NIHSS: National Institutes of Health Stroke Scale, OR: odds ratio, SE: standard error, sICH: symptomatic intracranial hemorrhage.

Table 5 Final fitting model associated with risks of unfavorable outcomes among 98 patients treated with intravenous recombinant tissue plasminogen activator, according to stepwise logistic regression analysis

variables	Stepwise logistic regression model		
	b (SE)	Adjusted OR (95% CI)	*P*-value
Age ≥ 78	1.15 (0.56)	3.17 (1.05–9.53)	0.040
Symptom onset-to-needle > 143 min	2.62 (0.72)	13.69 (3.35–55.91)	<0.001
NIHSS ≥ 17	2.83 (0.62)	17.00 (5.02–24.97)	<0.001

CI: confidence interval, min: minutes, NIHSS: National Institutes of Health Stroke Scale, OR: odds ratio, SE: standard error.

in the United States (US).[8] The present study is unique for its focus on the comparison between patients with treatment initiated on remote islands and those treated on the mainland. Symptomatic ICH was not observed in the Islands group. We found no differences between the two groups regarding the percentage of favorable patient outcomes. Since 1991, we have used a teleradiology system between our hospital and nine hospitals on these isolated islands. Telemedicine and telestroke have been used in the US since the 1990s and were evaluated with Class 1 level of evidence by the American Heart Association in 2018.[17]

Helicopter transport

Transport by helicopter has been reported to be safe in animal experimental models as well as in human patients with stroke.[18–20] Currently, we use a 24-h helicopter transportation system consisting of three types of helicopter: HEMS, an MSDF helicopter, and an FDP helicopter. Helicopter transport from the islands to our hospital using an MSDF helicopter was started in the 1970s. Helicopter systems for transferring patients began in 1970 in Europe and the US.[5] The usefulness of the helicopter system in patients with AIS was first reported in the 1990s in that country.

In Japan, HEMS transport began in 2001. HEMS began in Nagasaki Prefecture in 2006, and our hospital serves as the base hospital. In the present study, no patients experienced worsened neurological symptoms during helicopter transport. Importantly, the present study showed that patients living on isolated islands did not have increased risks for unfavorable outcomes.

DSR approach

Other previous studies have reported the safety and effectiveness of the DSR approach in AIS.[7,21] In this study, seven patients living on the islands were treated via the DSR method; of these, three patients had favorable outcomes, and four of seven patients transported via the DSR method in the Islands group had successful reperfusion (Table 3).

All seven patients were delivered to our hospital within 6 h of symptom onset. Recently, the DEFUSE 3 and DAWN trials have extended the therapeutic time window for EVT.[22,23] In the near future, more patients living on remote islands might be able to receive EVT.

Our study has some limitations that are inherent to its retrospective design, and was restricted by its relatively small sample size. The analyses were also limited to the protocol of a single hospital. In the future, a larger prospective study will be needed to evaluate any differences between the Islands and Mainland groups.

Conclusion

The DS method appears to be feasible and safe for use in patients living on isolated islands of Nagasaki Prefecture, Japan.

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Conflicts of Interest Disclosure

The authors declare no conflicts of interest regarding this manuscript.

References

1) Berkhemer OA, Fransen PS, Beumer D, et al.: A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 372: 11–20, 2015
2) Goyal M, Menon BK, van Zwam WH, et al.: Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 387: 1723–1731, 2016
3) Saver JL, Goyal M, van der Lugt A, et al.: Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 316: 1279–1288, 2016
4) Kawahara I, Fujimoto T, Takahata H, et al.: "Drip-and-ship" method of IV-tPA by helicopter transportation for acute ischemic stroke patients in the isolated islands in Nagasaki prefecture. *Jpn J Stroke* 34: 69–75, 2012
5) Conroy MB, Rodriguez SU, Kimmel SE, Kasner SE: Helicopter transfer offers a potential benefit to patients with acute stroke. *Stroke* 30: 2580–2584, 1999
6) Ishihara H, Oka F, Oku T, et al.: Safety and time course of drip-and-ship in treatment of acute ischemic stroke. *J Stroke Cerebrovasc Dis* 26: 2477–2481, 2017
7) Pfefferkorn T, Holtmannspötter M, Schmidt C, et al.: Drip, ship, and retrieve: cooperative recanalization therapy in acute basilar artery occlusion. *Stroke* 41: 722–726, 2010
8) Sheth KN, Smith EE, Grau-Sepulveda MV, Kleindorfer D, Fonarow GC, Schwamm LH: Drip and ship thrombolytic therapy for acute ischemic stroke: use, temporal trends, and outcomes. *Stroke* 46: 732–739, 2015
9) Adams HP Jr, Bendixen BH, Kappelle LJ, et al.: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 24: 35–41, 1993
10) Zaidat OO, Yoo AJ, Khatri P, et al.: Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 44: 2650–2663, 2013
11) Koga M, Shiokawa Y, Nakagawara J, et al.: Low-dose intravenous recombinant tissue-type plasminogen activator therapy for patients with stroke outside European indications: Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry. *Stroke* 43: 253–255, 2012
12) Lees KR, Bluhmki E, von Kummer R, et al.: Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 375: 1695–1703, 2010

13) Qureshi AI, Chaudhry SA, Rodriguez GJ, Suri MF, Lakshminarayan K, Ezzeddine MA: Outcome of the 'drip-and-ship' paradigm among patients with acute ischemic stroke: results of a statewide study. *Cerebrovasc Dis Extra* 2: 1–8, 2012
14) Mansoor S, Zand R, Al-Wafai A, Wahba MN, Giraldo EA: Safety of a "drip and ship" intravenous thrombolysis protocol for patients with acute ischemic stroke. *J Stroke Cerebrovasc Dis* 22: 969–971, 2013
15) Tekle WG, Chaudhry SA, Hassan AE, Rodriguez GJ, Suri MF, Qureshi AI: Drip-and-ship thrombolytic treatment paradigm among acute ischemic stroke patients in the United States. *Stroke* 43: 1971–1974, 2012
16) Kageji T, Obata F, Oka H, et al.: Drip-and-ship thrombolytic therapy supported by the telestroke system for acute ischemic stroke patients living in medically under-served areas. *Neurol Med Chir* (*Tokyo*) 56: 753–758, 2016
17) Jauch EC, Saver JL, Adams HP Jr, et al.: Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 44: 870–947, 2013
18) Leira EC, Zaheer A, Schnell T, et al.: Effect of helicopter transport on neurological outcomes in a mouse model of embolic stroke with reperfusion: AIR-MICE pilot study. *Int J Stroke* 10: 119–124, 2015
19) Faine BA, Dayal S, Kumar R, Lentz SR, Leira EC: Helicopter "drip and ship" flights do not alter the pharmacological integrity of rtPA. *J Stroke Cerebrovasc Dis* 27: 2720–2724, 2018
20) Leira EC, Stilley JD, Schnell T, Audebert HJ, Adams HP Jr.: Helicopter transportation in the era of thrombectomy: the next frontier for acute stroke treatment and research. *Eur Stroke J* 1: 171–179, 2016
21) Hiyama N, Yoshimura S, Shirakawa M, et al.: Safety and effectiveness of drip, ship, and retrieve paradigm for acute ischemic stroke: a single center experience. *Neurol Med Chir* (*Tokyo*) 56: 731–736, 2016
22) Albers GW, Marks MP, Kemp S, et al.: Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 378: 708–718, 2018
23) Nogueira RG, Jadhav AP, Haussen DC, et al.: Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 378: 11–21, 2018

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