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Safety and Effectiveness of Drip, Ship, and Retrieve Paradigm for Acute Ischemic Stroke: a Single Center Experience

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Abstract

This study analyzed the efficacy and safety of the "drip, ship, and retrieve (DSR)" approach used to improve patient access to thrombectomy for acute stroke. Methods: The study participants were 45 patients who underwent thrombectomy following intravenous tissue plasminogen activator between September 2013 and August 2015. Patients were divided into two groups according to whether they were transferred from another hospital (DSR group; *n* = 33) or were brought in directly (Direct group; *n* = 12). The two groups were compared based on their baseline characteristics, time from stroke onset to reperfusion, outcome, and adverse events. Results: There were no significant differences in baseline characteristics. Time from onset until admission to our facility was significantly shorter in the Direct group (56.9 min) than in the DSR group (163.5 min) (*P* <0.0001). Conversely, time from arrival at the hospital to arterial puncture was significantly shorter in the DSR group (25.0 min) than in the Direct group (109.5 min) (*P* <0.0001). Time from onset to reperfusion did not differ significantly between the groups. There was no significant difference in patient outcomes, with a modified Rankin scale score of 0–2 (44.8% in DSR group versus 48.7% in Direct group). Moreover, there was no difference in the incidence of adverse events. Discussion: Despite the time required to transfer patients in the DSR group between hospitals, reducing the time from arrival until commencement of endovascular therapy meant that the time from onset to reperfusion was approximately equivalent to that of the Direct group. Conclusion: Time-saving measures need to be taken by both the transferring and receiving hospitals in DSR paradigm.

Key words: thrombectomy, acute stroke, endovascular treatment, drip and ship, telemedicine

Introduction

Endovascular thrombectomy is indicated in Japan for acute ischemic stroke due to large vessel occlusion where tissue plasminogen activator (t-PA) is either not indicated or ineffective. Until recently, however, there was no evidence attesting to the efficacy of this procedure. This changed in 2015 with the announcement of findings from 5 randomized, controlled trials (RCTs)[1–5] demonstrating the efficacy of endovascular thrombectomy. The U.S. Guidelines on early endovascular treatment of acute ischemic stroke have also been modified, with the 2015 Focused Update by the American Heart Association/American Stroke Association (AHA/ASA) now recommending the use of endovascular therapy with a stent retriever in patients who meet all of the following 6 criteria (Class I; Level of Evidence A): (a) prestroke modified Rankin scale (mRS) score 0 to 1; (b) receiving intravenous t-PA within 4.5 hours of stroke onset; (c) causative occlusion of the internal carotid artery or proximal MCA (M1); (d) age ≥18 years; (e) National Institute of Health Stroke Scale (NIHSS) score of ≥6; (f) Alberta Stroke Program Early CT score (ASPECTS) of ≥6; and (g) treatment can be initiated within 6 hours of symptom onset.[6] In Japan, however, there are limitations on the number of facilities that can perform this procedure on a permanent basis and on the types of patients that can undergo it.

Pfefferkorn et al. proposed a treatment protocol to transfer acute stroke patients to a facility capable of performing thrombectomy. The authors referred to this protocol as "drip, ship, and retrieve" (DSR) based on

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the steps of administering intravenous t-PA ("drip"), transferring the patient ("ship"), and retrieving the thrombus ("retrieve").[7] This cooperative protocol offers the advantage of increased patient access to thrombectomy, but it also has the disadvantage of being time-consuming compared to the direct transport of patients to a thrombectomy-capable facility. For this reason, transferred patients reportedly have poor outcomes compared to those who are transported directly.[8] Initiatives to reduce the time spent at the transferring facility and the time until starting endovascular therapy at the receiving facility are therefore essential when transferring acute stroke patients.

In the present study, the efficacy and safety of DSR were analyzed by comparing patients treated with this approach and patients transported directly.

Materials and Methods

The study participants were 45 patients who underwent thrombectomy following intravenous t-PA at our hospital between September 2013 and August 2015. During this period, 41 patients were transferred to our hospital via drip and ship paradigm, and 33 received thrombectomy (80.5%). In this study, the patients treated by thrombectomy were divided into two groups according to whether they were transferred from another hospital (DSR group; n = 33) or were brought in directly (Direct group; n = 12).

Patient demographic and baseline characteristics including age, sex, past medical history, severity of neurological deficit (NIHSS score), and extent of the stroke on CT imaging (ASPECTS) were compared between the two groups. Other compared variables were the recanalization rate based on the Thrombolysis in Cerebral Infarction (TICI) grade, modified Rankin scale (mRS) score at 3 months post-treatment, and adverse event incidence. Compared variables related to treatment time were time from stroke onset to reperfusion, time to diagnostic imaging, time from diagnostic imaging to t-PA administration, time from arrival at the receiving facility until the arterial puncture, and time from an arterial puncture to reperfusion.

Magnetic Resonance Imaging (MRI)

All included patients underwent MRI (1.5 Tesla, Intera Achieva Pulsar; Philips, Amsterdam, NED). Images included diffusion-weighted imaging (DWI), axial fluid-attenuated inversion recovery, 3-dimensional time-of-flight magnetic resonance angiography. DWI was performed using echo planar imaging techniques. The DWI lesion volume was determined by manually tracing the edge of the hyperintense signal on each slice of the trace DWI scans.

DWI–the Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS)[9] on admission was assessed by stroke specialist.

Endovascular Therapy (EVT)

Patients without significant reperfusion on cerebral angiography after receiving t-PA underwent endovascular treatment using a suction catheter (Penumbra system, Penumbra, Alameda, CA, USA) or stent retriever (Solitaire FR, Medtronic Neurovascular, Irvine, CA, USA; Trevo ProVue, Stryker Neurovascular, Fremont, CA, USA) under local anesthesia.

Evaluation of Clinical Outcomes

Patient outcomes were evaluated using the mRS score at 90 (±10) days after onset. Favorable outcomes were defined as mRS scores of 0–2.

Results

There were no significant differences between the groups in any of the patient demographic or baseline characteristics (Table 1).

Time from onset until admission to our facility was significantly shorter in the Direct group (56.9 min) than in the DSR group (163.5 min) (P <0.0001). Conversely, time from arrival at the hospital to arterial puncture was significantly shorter in the DSR group (25.0 min) than in the Direct group (109.5 min) (P <0.0001). Time from stroke onset to reperfusion did not differ significantly between the DSR group (268.0 min) and the Direct group (244.5 min) (Table 2, Fig. 1).

Significant reperfusion (TICI 2b-3) was achieved in 30 of 33 patients (90.9%) in the DSR group and 11 of 12 patients (91.7%) in the Direct group. There was no significant difference between the groups in the percentage of favorable outcomes (mRS score 0-2) (odds ratio: 0.92, 95% confidence interval: 0.20-4.17) (Fig. 2). There was also no difference in the incidence of adverse events such as intracranial hemorrhage and procedure-related complications. Two patients in the DSR group required decompressive craniectomy. There was one death in DSR group and two in Direct group; there was no significant difference in mortality (Table 3). No adverse events occurred in the DSR group during transfer.

Discussion

In the DSR approach used in the present study, the time taken to transfer DSR group patients after intravenous t-PA significantly prolonged their time from

Table 1 Baseline characteristics of the patients treated by thrombectomy via drip and ship or direct transfer

Baseline characteristics	DSR (n = 33)	Direct (n = 12)	P
age–yr			
Median	74.2 (66–82)	78(67–86)	0.92
Female sex–no.(%)	12 (36.4)	8 (66.7)	0.69
Medical history–no.(%)			
Atrial fibrillation	21 (63.6)	10 (83.3)	0.20
Diabetes Mellitus	6 (18.2)	0 (0)	0.11
Hypertension	18 (30.3)	6 (50)	0.78
modified Rankin Scale–no.(%)			
0	27 (81.8)	8 (66.7)	0.47
1	1 (3)	0 (0)	
2	1 (3)	1 (8.3)	
3–5	4 (12.1)	3 (25)	0.48
NIHSS*			
Median(Interquartile range)	18 (15–26)	22 (15–27)	
Range	5–40	5–40	0.44
ASPECTS**			
median(Interquartile range)	7(5–8)	8 (7–9)	0.48
Site of occlusion–no.(%)			
Internal Carotid Artery	15 (45.5)	1 (8.3)	0.012
Middle Cerebral Artery	14 (42.4)	10 (83.3)	0.011
Basilar Artery	4 (12.1)	1 (8.3)	0.53

ASPECTS, Alberta Stroke Program Early CT score; NIHSS, National Institute Health Stroke Scale.

Table 2 Time metrics from stroke onset to reperfusion

Process measures (min)	DSR	Direct	P
Onset to door	163.5 (54.0–344.0)	56.9 (26.0–161.0)	<0.0001
Door to puncture	25.0 (16.3–27.8)	109.5 (61.8–159.5)	<0.0001
Onset to reperfusion	268.0 (224.0–330.0)	244.5 (186.5–267.3)	0.21

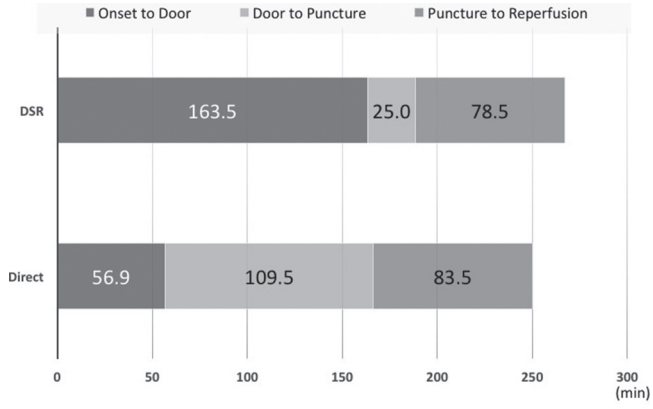

Fig. 1 Comparison of time metrics of the acute stroke patients in the Drip, Ship and Retrieve (DSR) group and Direct group. Time from onset until admission to our facility is significantly shorter in the Direct group (56.9 min) than in the DSR group (163.5 min). Conversely, time from arrival at the hospital to arterial puncture is significantly shorter in the DSR group (25.0 min) than in the Direct group (109.5 min). Time from onset to reperfusion does not differ significantly between the DSR group (268.0 min) and the Direct group (244.5 min).

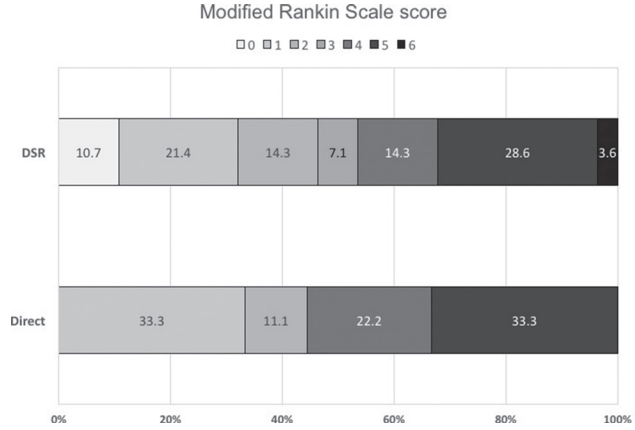

Fig. 2 Comparison of clinical outcomes of the acute stroke patients in the DSR group and Direct group.

stroke onset until admission to our hospital. However, our efforts to reduce the time from their arrival until commencement of thrombectomy meant that the time from stroke onset to reperfusion was almost equivalent to that of the Direct group. There were also

Table 3 Adverse events

Event–no.(%)	DSR	Direct	*P*
Death	1 (3%)	2 (16.7%)	0.13
Hemorrhagic transformation (total)	12 (36.4%)	4 (33.3%)	0.79
Hemorrhagic infarction	9 (3%)	4 (33.3%)	0.69
Parenchymal hematoma	3 (9%)	0 (0%)	0.47
Symptomatic hemorrhage	1 (3%)	1 (8.3%)	0.16
Intraoperative adverse events (total)	2 (6%)	1 (8.3%)	0.79
Perforation of the intracranial artery	1 (3%)	0 (0%)	0.42
Embolization in new territory	1 (3%)	1 (8.3%)	0.48
Decompressive hemicraniectomy	2 (6%)	0 (0%)	0.25

no significant differences between the groups in terms of patient outcomes and adverse events, suggesting that the DSR approach is both safe and effective.

There is a considerable amount of literature pointing to the safety and efficacy of transfer-based treatment of acute stroke patients. A study by Sheth et al. analyzing data from 44,667 patients with ischemic stroke treated with IV t-PA in the U.S. reported that drip and ship (D&S) was performed in 10,475 (23.5%) of these patients.[10] Tekle et al. used a U.S. database of insured medical care to compare the data from 22,243 acute ischemic stroke patients transported directly to the hospital with the data of 4,474 patients treated by the D&S method, and they found that the rate of in-hospital death was lower and the rate of home discharge/self-care was higher in the D&S group.[11]

On the other hand, previous studies have also highlighted the issues surrounding the D&S approach, such as the pronounced trend towards symptomatic intracranial hemorrhage in the D&S group reported by Sheth et al. Moreover, a study in South Korea comparing the data from 78 D&S patients with that of 317 directly-transported patients found that the percentage of poor prognosis cases (mRS score of 3-6 at 90 days post-treatment) was higher in the D&S group.[8] The results of analysis in these studies indicated that hospital transfers delayed the initiation of treatment, suggesting the need to implement time-saving measures. Meanwhile, in the study by Tekle et al., "retrieve" procedures only accounted for 4,474 patients—just 7%—of the entire study population,[11] so this study can hardly be described as an analysis of DSR. On the other hand, the present study differs to that of previous literature in that it was concerned solely with the analysis of DSR patients. As such, the present study is the first of its kind to investigate the safety and efficacy of the DSR approach since the introduction of the stent retriever.

Since thrombectomy is currently known to be an effective stroke treatment, improving its rate of adoption is a pressing issue. However, there are limitations on the number of facilities in Japan that can perform thrombectomy 24 hours a day and on the types of patients that can undergo this procedure. Under these circumstances, the DSR approach could help to improve the rate of thrombectomy procedures. However, increases in hospital transfer times can prolong the time to reperfusion, suggesting that significant improvements in prognosis may not be feasible even when reperfusion is achieved with thrombectomy. Sudden changes in the patient's condition during transfer can lead to deterioration of outcomes, while the failure of the initial treating physician to accompany patients being treated with the DSR approach can also lead to worsening of symptoms during transport. Accordingly, when implementing the DSR approach, measures to reduce the additional time of transfer are essential for improving patient prognosis.

In the present study, there was no difference between DSR and directly-transported patients in the time to commencement of endovascular therapy as a result of reductions in the time spent at the transferring hospital and the time until the commencement of endovascular treatment at the receiving hospital. These time-saving measures require the expedited sharing of data on tests performed at the transferring hospital with the receiving hospital. The recent use of information and communication technology (ICT) between transferring and receiving facilities has enabled real-time transmission of CT, MRI, and other imaging data. In the U.S., the use of specialized telemedicine systems for exchanging information on stroke patients is known as "telestroke". As of 2012, there were 38 telestroke programs operating in 27 states.[12] A study by Yaghir et al. reported a high rate of good treatment outcomes in transferred stroke patients treated with the aid of a telestroke program, suggesting the efficacy of this form of telemedicine.[13] However, there have also been issues associated with this technology, as shown by a study which found that 23% of patients diagnosed via telemedicine were in fact stroke mimics.[14] There were no stroke mimics in the present study because the initial diagnosis was performed directly by a stroke specialist. However, the occurrence of stroke mimics could increase in the future with the spread of ICT.

While none of the patients in our study experienced sudden changes or adverse events during transfer, it is crucial for the physician to accompany and constantly monitor the patient.

The limitations of this study include the retrospective nature of the analyses and the limited study population. The analyses were also limited to the DSR protocol of a single transferring hospital, so a prospective study of multiple facilities should be conducted in the future. A large-scale prospective study with the aim of clarifying the efficacy and issues of the DSR approach is essential given that this coordinated approach will be indispensable for enabling increased access to thrombectomy among stroke patients in Japan.

Conclusion

The study findings suggest that time-saving initiatives adopted by transferring and receiving hospitals can reduce the time to reperfusion among DSR patients to approximately that of directly-transported patients.

Conflicts of Interest Disclosure

N. Hiyama, M. Shirakawa, K. Uchida, Y. Oki, S. Shindo, and K. Tokuda have no conflicts of interest.

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References

1) Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW; MR CLEAN Investigators: A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 372: 11–20, 2015

2) Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD; ESCAPE trial investigators: randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 372: 1019–1930, 2015

3) Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM; EXTEND-IA Investigators: Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 372: 1009–1018, 2015

4) Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Devlin TG, Lopes DK, Reddy V, du Mesnil de Rochemont R, Jahan R; SWIFT PRIME Investigators: Solitaire™ with the Intention for thrombectomy as primary endovascular treatment for acute ischemic stroke (SWIFTPRIME) trial: protocol for a randomized, controlled, multicenter study comparing the solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. *Int J Stroke* 10: 439–448, 2015

5) Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A; REVASCAT Trial Investigators: Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 372: 2296–2306, 2015

6) Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, Johnston KC, Johnston SC, Khalessi AA, Kidwell CS, Meschia JF, Ovbiagele B, Yavagal DR; American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 46: 3020–3035, 2015

7) Pfefferkorn T, Holtmannspötter M, Schmidt C, Bender A, Pfister HW, Straube A, Mayer TE, Brückmann H, Dichgans M, Fesl G: Drip, ship, and retrieve:

cooperative recanalization therapy in acute basilar artery occlusion. *Stroke* 41: 722–726, 2010
8) Cha JK, Nah HW, Kang MJ, Kim DH, Park HS, Kim SB, Jeong EH, Huh JT: Outcomes after tissue plasminogen activator administration under the drip and ship paradigm may differ according to the regional stroke care system. *J Stroke Cerebrovasc Dis* 23: 160–163, 2014
9) Aoki J, Kimura K, Shibazaki K, Sakamoto Y: DWI-ASPECTS as a predictor of dramatic recovery after intravenous recombinant tissue plasminogen activator administration in patients with middle cerebral artery occlusion. *Stroke* 44: 534–537, 2013
10) 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
11) 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
12) Silva GS, Farrell S, Shandra E, Viswanathan A, Schwamm LH: The status of telestroke in the United States: a survey of currently active stroke telemedicine programs. *Stroke* 43: 2078–2085, 2012
13) Yaghi S, Harik SI, Hinduja A, Bianchi N, Johnson DM, Keyrouz SG: Post t-PA transfer to hub improves outcome of moderate to severe ischemic stroke patients. *J Telemed Telecare* 21: 396–399, 2015
14) Ali SF, Viswanathan A, Singhal AB, Rost NS, Forducey PG, Davis LW, Schindler J, Likosky W, Schlegel S, Solenski N, Schwamm LH: Partners Telestroke Network: The TeleStroke mimic (TM)-score: a prediction rule for identifying stroke mimics evaluated in a Telestroke Network. *J Am Heart Assoc* 23: e000838, 2014

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