Drip-and-Ship Thrombolytic Therapy Supported by the Telestroke System for Acute Ischemic Stroke Patients Living in Medically Under-served Areas

Teruyoshi KAGEJI,1 Fumiaki OBATA,2 Hirofumi OKA,3 Yasuhisa KANEMATSU,3 Ryo TABATA,4 Kenji TANI,4 Hiroyasu BANDO,2 and Shinji NAGAHIRO5

1Department of Neurosurgery, Tokushima Prefectural Kaifu Hospital, Tokushima, Japan; 2Department of Internal and General Medicine, Tokushima Prefectural Kaifu Hospital, Tokushima, Japan; 3Department of Regional Neurosurgery, Tokushima University Hospital, Tokushima, Japan; 4Department of General Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan; 5Department of Neurosurgery, School of Medicine, The University of Tokushima, Tokushima, Japan

Abstract

There are a few stroke specialists in medically under-served areas in Japan. Consequently, in remote area patients may not receive thrombolysis with intravenous recombinant tissue plasminogen activator (iv rt-PA), the standard treatment for acute ischemic stroke. Using a mobile telestroke support system (TSS) that accesses the internet via a smart phone, we implemented iv rt-PA infusion therapy under a drip-and-ship protocol to treat the stroke patients in medically under-served areas. The physicians at the Tokushima Prefectural Kaifu Hospital (TPKH), located in rural Japan, can relay CT or MRI scans and other patient data via their smart phone to off-site stroke specialists. In the course of 34 months, we used the TSS in 321 emergencies. A total of 9 of 188 (4.8%) with acute ischemic stroke, received iv rt-PA infusion therapy using a mobile TSS; in 5 among these (55.6%), we obtained partial or complete recanalization of occluded arteries. None suffered post-treatment hemorrhage and their average NIH stroke score fell from 14.6 at the time of admission to 6.8 at 24 h post-infusion. The drip-and-ship protocol contributed to the safe and effective treatment of the stroke patients living in medically under-served rural areas.

Key words: drip-and-ship protocol, recombinant tissue plasminogen activator, telemedicine, telestroke, stroke

Introduction

Recombinant tissue plasminogen activator (rt-PA) infusion therapy is effective in patients with hyper-acute cerebral infarction.1,3 The early thrombolytic treatment of patients with acute ischemic stroke is associated with the lower mortality rates, higher rates of independent ambulation at discharge, and discharge to home.3,2

In Japan, the rt-PA treatment of patients seen within 3 h of stroke onset has been possible since 2005.3,5 The use of alteplase in the extended therapeutic time window (within 4.5 h of symptom onset) became covered by insurance in August 2012.9 However, the stroke specialists are needed for the appropriate treatment of such patients, and in rural areas without such experts, the delivery of intravenous (iv) rt-PA is difficult. A national survey conducted in 2010 showed that lesser than 5% of eligible Japanese patients had received rt-PA therapy and that by 2009, 44 of 348 emergency medical service areas (12.6%) did not deliver the iv rt-PA treatment.3

In some areas of Japan, the care of acute stroke patients is suboptimal and there are significant disparities in rural communities. Kaifu is a depopulated remote region in the southern Tokushima Prefecture; 23,021 persons live in a 525 km² area and their medical care is delivered by the 38 physicians (1.7% of the population). It is under-served with respect to medical and especially acute stroke care, and the rate of iv rt-PA therapy is low.6–10

Tokushima Prefectural Kaifu Hospital (TPKH) is located in the center of Kaifu. The distance to the closest comprehensive stroke center at Tokushima

Received March 28, 2016; Accepted May 27, 2016
University Hospital (TUH) is 80 km. TPKH has 105 beds; the patients are attended by the general physicians and orthopedic surgeons. It has no stroke specialists, and till 2013, it had no experience with iv rt-PA infusion therapy for acute ischemic stroke. Between October 1, 2009 and September 30, 2010, the transport of stroke patients from Kaifu to TUH required an average of 136 min, i.e. 96 min more than that of patients living around TUH in Tokushima city.11)

The use of telemedicine for stroke care has spread in Western countries.8,12–14) In 2009, the American Heart Association recommended telestroke systems for the neurological assessment and primary prevention of stroke.15) We established the telestroke support system (TSS) in our medically under-served area. It involves the standard portable communication devices and the relay of clinical information and high-quality neuroimages to off-site stroke specialists for a real-time clinical diagnosis and treatment advice.

Methods

In collaboration with Tokushima University Hospital (TUH) and Tokushima Red Cross Hospital (TRCH), we developed a drip-and-ship protocol for the initial treatment of off-site patients with acute ischemic stroke. It involves the TSS (called the “k-support system”) and the delivery of iv rt-PA infusion therapy at TPKH under the direction of a stroke specialist at TUH and TRCH. After the iv injection of a single alteplase dose of 0.6 mg/kg (not exceeding 60 mg), a 10% dose-bolus is delivered at TPKH. This is followed by the continuous infusion of the remainder of alteplase during transport by ambulance or helicopter from TPKH to a stroke center of TUH or TRCH for post-thrombolytic care.

Our k-support system features an exclusive application developed for smart devices and a dedicated server connected to a picture archiving and communication system (PACS) at TPKH (Fig. 1). The real-time extramural access is via a virtual private network (VPN) connection by wireless LAN, it can deliver patient information, CT-, MR-, and 3D-CTA images, and animated- and 3D-images to the smartphone of a registered physician located off-site. The time-course is established automatically based on individual patients. The communication via a Twitter-style closed communication system is also possible.

The k-support team of our TSS (Fig. 2) consists of emergency medical technicians (EMTs) in the Kaifu area, the physicians at TPKH, and the stroke specialists at the TUH and TRCH stroke center (Table 1). The on-site EMTs send patients’ information (time of stroke onset, neurological findings, and vital signs) to TPKH. Upon patient arrival at TPKH, the MRI studies are performed immediately and the findings are conveyed via a smart device to the stroke specialists at TUH and TRCH. If they deem thrombolysis by immediate iv rt-PA therapy appropriate, the patient is transported to the comprehensive stroke center at TUH under the drip-and-ship protocol.

The patient status is evaluated using the National Institutes of Health stroke scale (NIHSS) at the time of admission and 24 h after the start of iv rt-PA infusion.16) The recanalization of occluded vessels is recorded using the thrombolysis in cerebral infarction (TICI) classification.17)

Results

Between February 2013 and December 2015, we used the TSS in 321 emergencies (acute stroke in 161 (50%), head injury in 51 (16%), gastrointestinal

Fig. 1 (A) Components of the system (SYNAPSE Erm) for connecting off- and on-site medical care providers. (B) Display of the diagnostic and treatment data on mobile devices.
Drip-and-Ship Thrombolytic Therapy for Stroke Patients

Fig. 2 Concept of the telemedicine “k-support” system. The emergency technicians relay patient information to a physician at TPKH who is in contact with a stroke specialist at TUH. The drip-and-ship protocol for iv rt-PA infusion therapy is implemented at TPKH before patient transport to the stroke center. EMTs: Emergency Medical Technicians, TPKH: Tokushima Prefectural Kaifu Hospital.

Table 1 Member and number of smart devices in our k-support team

| Member of k-support team | Number of smart devices |
|--------------------------|-------------------------|
| Physicians               |                         |
| TPKH                     |                         |
| General physician        | 5                       |
| Cardiologist             | 2                       |
| Orthopedic surgeon       | 2                       |
| Respiratory physician    | 1                       |
| Neurosurgeon             | 1                       |
| TUH                      |                         |
| Neurosurgeon             | 2                       |
| EMTs in Kaifu area       | 3                       |
| Stroke center            | 2 (TUH, TRCH)           |

EMTs: emergency medical technicians, TPKH: Tokushima Prefectural Kaifu Hospital, TRCH: Tokushima Red Cross Hospital, TUH: Tokushima University Hospital.

disease in 38 (12%), and cardiovascular disease in 22 (7%). We delivered iv rt-PA infusion therapy under the drip-and-ship protocol supported with a mobile TSS (k-support system) to 9 of 188 (4.8%) patients with acute ischemic stroke. All the nine patients are presented with cardiogenic embolism due to atrial fibrillation. For the immediate care of all patients, the general physicians at TPKH consulted with the stroke specialists at TUH via TSS; 5 patients were treated by the general physicians alone at TPKH. The complete (TICI 3) and partial (TICI 2B) recanalization was observed in 4 and 1 patient(s), respectively; in three stroke patients with internal carotid artery occlusion, there was no recanalization (TICI 0). The average NIHSS score was 14.4 (range 3–40); 24 h post-iv rt-PA infusion, it was 6.8 (range 2–15). None of the 9 patients suffered post-treatment intracerebral hemorrhage.

The interval between the stroke onset to arrival at TPKH ranged from 30 to 97 min, the door-to-needle time from 59 to 125 min, the stroke onset-to-needle from 108 to 173 min, and the average transport time from TPKH to TUH from 27 to 86 min (Table 2).

Discussion

Many patients with acute ischemic stroke are initially seen by the general or emergency physicians, consequently, the treatment is heavily dependent on their diagnostic acumen and the stroke patients may not receive emergent iv rt-PA therapy. A similar problem exists in medically under-served remote areas of Japan, where there are few stroke specialists. Before 2013, TPKH, located in southern...
Tokushima Prefecture, had never delivered iv rt-PA infusion therapy.

The early thrombolytic treatment of patients with acute ischemic stroke is associated with the reduced rates of mortality and symptomatic intracranial hemorrhage. However, the transfer of patients from a general hospital to a regional stroke center delays the start of rt-PA treatment. Therefore, we implemented a protocol at TPKH, whereby the delivery of iv rt-PA infusion is started locally before the transport of the stroke patients to a comprehensive stroke center at TuH or TRCH for post-thrombolytic care. This strategy is now known as “drip-and-ship,” which has been used in 17% of the stroke patients treated by rt-PA infusion therapy living in remote areas of the USA, and the patient discharge rate and the rate of patients able to return to independent living was high. In 2009, The American Heart Association/American Stroke Association promulgated a statement advocating the use of the telestroke system and the drip-and-ship protocol in patients with acute ischemic stroke. The others subsequently reported that in stroke patients, the immediate delivery of rt-PA infusion therapy under this protocol, supported by telemedicine technology, is safe and effective. The smart devices with applications adapted to TSS appear to be useful for mobile communications. A large study by Sheth et al. found that after the risk adjustment, the rate of in-hospital mortality and symptomatic intracranial hemorrhage was only slightly higher in “drip-and-ship”-treated patients than in patients directly admitted at a stroke center.

The standard real-time cellular video phone can be used to obtain the NIHSS score in patients with acute stroke who present at remote hospitals. The interpretation of the head CT scans sent via smartphone teleradiology to off-site vascular neurologists was in excellent agreement with the reading of on-site radiologists. Takao et al. developed a system that uses smart devices for the real-time relay of patient data, the diagnostic images, and the clinical management information among members of Japanese stroke teams located in remote areas and at stroke centers.

In 2009, The American Heart Association/American Stroke Association promulgated a statement advocating the use of the telestroke system and the drip-and-ship protocol in patients with acute ischemic stroke. The others subsequently reported that in stroke patients, the immediate delivery of rt-PA infusion therapy under this protocol, supported by telemedicine technology, is safe and effective. The smart devices with applications adapted to TSS appear to be useful for mobile communications. A large study by Sheth et al. found that after the risk adjustment, the rate of in-hospital mortality and symptomatic intracranial hemorrhage was only slightly higher in “drip-and-ship”-treated patients than in patients directly admitted at a stroke center.

The standard real-time cellular video phone can be used to obtain the NIHSS score in patients with acute stroke who present at remote hospitals. The interpretation of the head CT scans sent via smartphone teleradiology to off-site vascular neurologists was in excellent agreement with the reading of on-site radiologists. Takao et al. developed a system that uses smart devices for the real-time relay of patient data, the diagnostic images, and the clinical management information among members of Japanese stroke teams located in remote areas and at stroke centers.

### Table 2 Patients profile of drip and ship protocol of intravenous rt-PA infusion therapy in TPKH

| Case | Age | Sex | Onset-to-arrival (min) | Door-to-needle (min) | Onset-to-needle (min) | Transport time (min) | Occlusion vessel | NIHSS on admission | TICI classification | NIHSS 24 h after infusion |
|------|-----|-----|------------------------|----------------------|----------------------|----------------------|------------------|-------------------|--------------------|---------------------|
| 1    | 89  | M   | 30                     | 123                  | 153                  | 44                   | MCA              | 10                | 3                  | 2                   |
| 2    | 96  | M   | 73                     | 89                   | 162                  | 55                   | ICA              | 18                | 0                  | 8                   |
| 3    | 91  | M   | 85                     | 59                   | 144                  | 62                   | MCA              | 10                | 2B                 | 6                   |
| 4    | 84  | F   | 58                     | 50                   | 108                  | 34                   | ICA              | 17                | 0                  | 15                  |
| 5    | 93  | M   | 97                     | 53                   | 150                  | 67                   | ICA              | 18                | 0                  | 15                  |
| 6    | 78  | F   | 53                     | 77                   | 130                  | 27                   | MCA              | 9                 | 3                  | 6                   |
| 7    | 70  | M   | 48                     | 125                  | 173                  | 31                   | PCA              | 3                 | 3                  | 2                   |
| 8    | 97  | F   | 54                     | 97                   | 151                  | 77                   | –                | 5                 | NE                 | 3                   |
| 9    | 69  | F   | 87                     | 73                   | 160                  | 86                   | BA               | 40                | 3                  | 4                   |

BA: basilar artery, ICA: internal cerebral artery, MCA: middle cerebral artery, NIHSS: National Institute of Health stroke scale, PCA: posterior cerebral artery, TICI: thrombolysis in cerebral infarction, TPKH: Tokushima Prefectural Kaifu Hospital.

**Conclusion**

The drip-and-ship protocol for iv rt-PA infusion therapy supported by a mobile TSS such as our “k-support system” may benefit patients with acute ischemic stroke living in the remote areas without the stroke centers or the stroke specialists.
Conflicts of Interest Disclosure

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

References

1) Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 333: 1581–1587, 1995

2) Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K; Stroke Acute Management with Urgent Risk-factor Assessment and Improvement Study Investigators: Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke 40: 3591–3595, 2009

3) Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y; Japan Alteplase Clinical Trial (J-ACT) Group: Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 37: 1810–1815, 2006

4) Toyoda K, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Naganuma M, Nishiyama K, Minematsu K; Stroke management with routine risk-factor assessment and improvement (SAMURAI) rt-PA registry: general results and subanalyses. Jpn J Stroke 32: 756–761, 2010 (Japanese)

5) Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, Olson DM, Hernandez AF, Peterson ED, Schwamm LH: Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA 309: 2480–2488, 2013

6) Minematsu K, Toyoda K, Hirano T, Kimura K, Kondo R, Mori E, Nakagawara J, Sakai N, Shiokawa Y, Tanahashi N, Yasaka M, Katayama Y, Miyamoto S, Ogawa A, Sasaki M, Suga S, Yamaguchi T; Guidelines for the intravenous application of recombinant tissue-type plasminogen activator (Alteplase), the second edition, October 2012: a guideline from the Japanese stroke society. J Stroke Cerebrovasc Dis 222: 571–600, 2013

7) Okada A, Minematsu K, Ogawa A, Imanaka Y, Sekimoto M, Hashi K, Yamaguchi T; Nation-wide survey of use of intravenous rt-PA (alteplase) therapy during the first four years after approval: overcoming regional gaps. Jpn J Stroke 32: 365–372, 2010 (Japanese)

8) Saler M, Switzer JA, Hess DC: Use of telemedicine and helicopter transport to improve stroke care in remote locations. Curr Treat Options Cardiovasc Med 13: 215–224, 2011

9) Martin-Schild S, Morales MM, Khaja AM, Barreto AD, Hallevi H, Abraham A, Sline MR, Jones E, Grotta JC, Savitz SI: Is the drip-and-ship approach to delivering thrombolysis for acute ischemic stroke safe? J Emerg Med 41: 135–141, 2011

10) Pervez MA, Siva G, Masrur S, Betensky RA, Furie KL, Hidalgo R, Lima F, Rosenthal ES, Rost N, Viswanathan A, Schwamm LH: Remote supervision of IV-tpa for acute ischemic stroke by telemedicine or telephone before transfer to a regional stroke center is feasible and safe. Stroke 41: e18–e24, 2011

11) Mizobuchi Y, Satomi J, Okazaki T, Kageji T, Nagahiro S, Nishimura M: Evaluating stroke treatment in the south Tokushima medical areas without stroke specialists. Shikoku Acta Medica 68: 35–40, 2012 (Japanese)

12) Gonzalez MA, Hanna N, Rodrigo ME, Saltiel LF, Waksman R: Reliability of prehospital real-time cellular video phone in assessing the simplified National Institutes of Health Stroke scale in patients with acute stroke: a novel telemedicine technology. Stroke 42: 1522–1527, 2011

13) Takao H, Murayama Y, Ishibashi T, Karagiozov KL, Abe T: A new support system using a mobile device (smartphone) for diagnostic image display and treatment of stroke. Stroke 43: 236–239, 2012

14) Demaerschalk BM, Vargas JE, Channer DN, Noble BN, Kiernan TE, Gleason EA, Vargas BB, Ingall TJ, Aguilar MI, Dodick DW, Bobrow BJ: Smartphone teleradiology application is successfully incorporated into a telestroke network environment. Stroke 43: 3098–3101, 2012

15) Schwamm LH, Holloway RG, Amarenco P, Audebert HJ, Bakas T, Chumbler NR, Handschu R, Jauch EC, Knight WA 4th, Levine SR, Mayberg M, Meyer BC, Meyers PM, Skalabrin E, Wechsler LR; American Heart Association Stroke Council; Interdisciplinary Council on Peripheral Vascular Disease: A review of the evidence for the use of telemedicine within stroke system of care: a scientific statement from the American Heart Association/American Stroke Association. Stroke 40: 2616–2634, 2009

16) Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J: Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke 25: 2220–2226, 1994

17) Higashida RT, Furlan AJ, Roberts H, Tompkins C, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D; Technology Assessment Committee of the American Society of Interventional and Therapeutic Neuroradiology; Technology Assessment Committee of the Society of Interventional Radiology: Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke 34: e109–e137, 2003

18) Morgenstern LB, Lisabeth LD, MecoZZi AC, Smith MA, Longwell PJ, McFarling DA, Risser JM: A population-based study of acute stroke and TIA diagnosis. Neurology 62: 895–900, 2004

Neurol Med Chir (Tokyo) 56, December, 2016
19) Rymer MM, Thurtchley D, Summers D: Expanded modes of tissue plasminogen activator delivery in a comprehensive stroke center. *Stroke* 34: 58–60, 2003

20) Akins PT, Delemos C, Wentworth D, Byer J, Schorer SJ, Atkinson RP: Can emergency department physicians safely and effectively initiate thrombolysis for acute ischemic stroke? *Neurology* 55: 1801–1805, 2000

21) Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM: Why are stroke patients excluded from tPA therapy? An analysis of patient eligibility. *Neurology* 56: 1015–1020, 2001

22) Switzer JA, Hess DC: Development of regional programs to speed treatment of stroke. *Curr Neurol Neurosci Rep* 8: 35–42, 2008

23) 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

24) 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

*Address reprint requests to: Teruyoshi Kageji, MD, Department of Neurosurgery, Tokushima Prefectural Kaifu Hospital, 75-1, Nakamura, Mugi-cho Kaifu-gun, Tokushima, 775-0006, Japan.*

e-mail: kageji@hotmail.co.jp