

## Research Article

# The Cooperative Attempt of teLestroke-based Drip and ship Emergent Referral - the Aso (CALDERA) model

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## Special Issue on

## Ischemic Stroke: A Cerebrovascular Accident

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## Abstract

In the Aso area of Kumamoto Prefecture in Japan there are no hospitals where stroke patients can receive acute-period revascularization treatments. As transfer to an out-of-area hospital takes approximately an hour, the interval between stroke onset and arrival at the distant care facility is long and of 11 patients transferred in 2010, only one received recombinant tissue plasminogen activator (rt-PA) therapy. Therefore, to make it possible to deliver rt-PA therapy at the primary emergency hospital we developed a telemedicine system that uses smartphones for communication between the out-of-area comprehensive stroke center and the primary emergency hospital. Patients with acute ischemic stroke are taken to the primary emergency hospital where the physician in charge uses the smartphone "RDICOM" application to upload the NIH stroke scale and a head CT image on a server. The stroke neurologist at the comprehensive stroke center then assesses the case and uses "RDICOM" information to make it possible to deliver rt-PA therapy at the primary hospital ("drip"). Patients requiring special treatment are transferred to a comprehensive stroke center ("ship"); during transfer rt-PA is delivered via intravenous drip infusion. Between June 2012 and August 2013, fourteen patients with acute ischemic stroke were taken to a primary emergency hospital in the Aso area. Of these, 6 underwent successful rt-PA therapy under the telemedicine-facilitated direction of an out-of-area stroke neurologist. At the time of admission, the mean NIH stroke scale of these 6 patients was 14.5. After rt-PA treatment it was 3.2. No patients suffered hemorrhagic complications. With the remote support provided by our smartphone telemedicine system it is possible to deliver rt-PA therapy even in areas where such treatment was formerly not possible.

## ABBREVIATIONS

**RT-PA:** Recombinant Tissue Plasminogen Activator; **Nih:** National Institutes Of Health; **Ct:** Computed Tomography; **Mrs:** Modified Rankin Score; **Mri:** Magnetic Resonance Imaging; **Mra:** Magnetic Resonance Angiography; **Caldera:** Cooperative Attempt Of Telestroke-Based Drip And Ship Emergent Referral - The Aso

## INTRODUCTION

In Japan, transvenous recombinant tissue plasminogen

activator (rt-PA) therapy has been covered by medical insurance since October 2005. However, of stroke patients living in Japan only (2.5%) received rt-PA therapy in 2009 [1]. This may be attributable to the lack of stroke specialists at the admitting hospital or to the failure of patients to report to the nearest medical facility despite the presence of stroke symptoms.

The Aso medical district is located in northeastern of Kumamoto Prefecture in Japan. It is in an area surrounded by an outer rim of mountains that encloses highlands 400-800

meters above sea level. The population in Aso is approximately 70,000 and rt-PA treatment is not performed at local hospitals. Most acute stroke patients are taken 40 km by ambulance to a secondary emergency hospital near Kumamoto City; the transportation time is approximately one hour. During 2010, of 35 patients with suspected acute stroke, 11 suffered acute cerebral infarcts and were transported to undergo rt-PA therapy at secondary hospitals within 3 hours from onset. However, only one patient arrived in time to receive rt-PA treatment. In the other 10 the interval between stroke onset and their arrival at the secondary hospital was too long for effective rt-PA therapy.

This indicated that a new system for the administration of immediate drip rt-PA therapy at local primary emergency hospitals was needed in this geographic area ("drip"). Then these patients can be transported ("shipped") to a comprehensive stroke center for the completion of rt-PA treatment. We designate this method the "drip and ship" system and its system was called Cooperative Attempt of teLestroke-based Drip and ship Emergent Referral - the Aso (CALDERA) (Figure 1). The Aso area had the most famous CALDERA in the world.

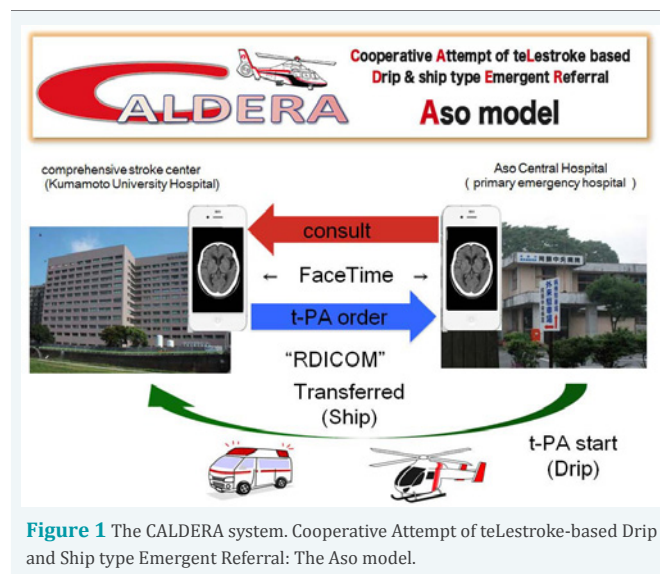
## MATERIALS AND METHODS

Our case in point is a patient who was transported to the local primary emergency hospital (Aso Central Hospital) within 3 hours of stroke onset (4.5 hours since September 2012). At the time of admission a blood test and neurological examinations were performed to determine the NIH stroke scale. Then chest X-ray- and head CT studies were performed and the images were uploaded on the server. Simultaneously, a stroke specialist at the comprehensive stroke center of Kumamoto University Hospital was contacted by smartphone to determine whether the patient should be transferred for further neurological examinations. The stroke specialist referred to the CT images provided by the "RDICOM" smartphone application to determine whether there were early ischemic changes or other abnormal findings and submitted a preliminary assessment. With the iPhone 4S smartphone it was possible to connect to Wi-Fi via the primary hospital's wireless LAN system and data were available via a 3G circuit. The system, produced by TRIART Co. (Fukuoka, Japan), also transferred the NIH stroke scale.

To rule out contraindications for the administration of rt-PA, the patient's eligibility for thrombolytic therapy is established at the primary hospital. For additional treatment at Kumamoto University Hospital, weather permitting, the patient is transferred by helicopter; in bad weather or at night transportation is by ambulance. If no improvements are seen by the time the patient arrives at Kumamoto University Hospital, an MRI scan is acquired to determine the appropriateness of thrombectomy using Merci or Penumbra systems. In the absence of large hyperintensity areas on diffusion-weighted images and the existence of a mismatch between diffusion- and perfusion-weighted images thrombectomy is performed within 8 hours after stroke onset.

## RESULTS

CALDERA was started in June 2012. By August 2013, 19 patients (10 males, 9 females, age range 40 - 93 years) suspected of having suffered a stroke within the preceding 3 hours (4.5



hours since September 2012) were admitted to Aso Central Hospital (Table 1). The diagnosis at the time of local admission was cerebral hemorrhage in 5 and cerebral infarction in 14 patients. The NIH stroke scale in the 19 patients ranged from 1 - 29 (mean 10.0). In these patients, six patients received rt-PA treatment. The NIH stroke scale in the 6 patients ranged from 6 - 29 (mean 14.5). Between 5 - 42 min (mean 20.3 min) elapsed between their admission at Aso Central Hospital and the acquisition of CT studies. As the interval between CT and rt-PA delivery was 20 - 119 min.

The NIH stroke scale was 3 - 12 (mean 6.2) 24 hours after rt-PA administration; at the time of discharge it ranged from 0 - 9 (mean 3.2). The modified Rankin score (mRS) 3 months after rt-PA treatment was 0 - 1 in 3 cases, 3 in one case, and 4 - 5 in 2 cases (Table 2).

## CASE PRESENTATION

A 40-year-old female Aso resident (case 12 in Table 1, case 4 in Table 2) sustained a fall in her kitchen at 06:45. She was admitted to a local hospital where a CT scan showed no bleeding. She was drowsy and manifested global aphasia and complete right hemiparesis. At 09:40 she arrived by ambulance at Aso Central Hospital without a change in her right paralysis and aphasia. A CT scan showed no early CT signs (Figure 2) and an Edaravone drip was started. Her NIH stroke scale was 20. As rt-PA delivery was not contraindicated it was started at 10:05 (3 hr 20 min after her fall).

With a physician on board she was transported by helicopter to Kumamoto University Hospital where she arrived at 11:21. Although her right paralysis was improved, her speech disturbance was not and her NIH stroke scale was 11. Diffusion-weighted MRI showed a small hyperintensity area in the left insular cortex. Magnetic resonance angiography (MRA) yielded a poor image of the left middle cerebral artery branches (Figure 3). Therefore additional interventional treatment targeting the left middle cerebral artery branches was delivered with the aid of a Penumbra system. Post-treatment angiography showed complete recanalization of the left middle cerebral artery

**Table 1:** Summary of 19 patients suspected of having suffered a stroke within the preceding 3 hours (4.5 hours since September 2012) were admitted to Aso Central Hospital.

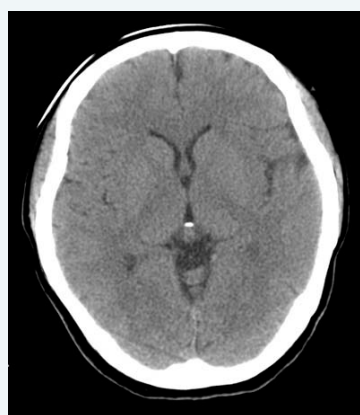
Case No.	Age	Sex	NIH Stroke Score	Diagnosis	Rt-PA
1	89	M	11	cerebral infarction	+
2	84	F	15	cerebral hemorrhage	-
3	93	M	12	cerebral infarction	+
4	83	M	4	cerebral hemorrhage	-
5	79	M	1	cerebral infarction	-
6	74	F	6	cerebral hemorrhage	-
7	74	M	1	cerebral infarction	-
8	85	F	9	cerebral hemorrhage	-
9	72	M	3	cerebral infarction	-
10	87	F	6	cerebral infarction	+
11	41	F	23	cerebral hemorrhage	-
12	40	F	20	cerebral infarction	+
13	89	F	22	cerebral infarction	-
14	68	M	1	cerebral infarction	-
15	80	F	9	cerebral infarction	+
16	77	M	29	cerebral infarction	+
17	92	F	6	cerebral infarction	-
18	71	M	9	cerebral infarction	-
19	79	M	3	cerebral infarction	-

NIH: National Institutes of Health.

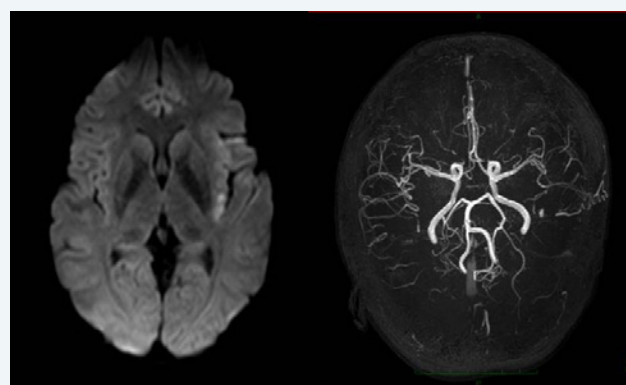
**Table 2:** Summary of six patients received rt-PA treatment.

Case No.	Age	Sex	attack - treatment (min)				ASPECTS	NIH stroke score			mRS (at 3 months after)
			Attack-Admission (min)	Admission ~ CT (min)	CT ~ treatment (min)	admission ~ Treatment (min)		On admission	After 24 hours	At discharge	
1	89	F	175				10	11	6	3	4
			122	18	35	53					
2	93	M	87				10	12	12	9	5
			35	17	35	52					
3	87	F	133				10	6	4	0	0
			77	25	31	56					
4	40	F	200				7	20	8	1	1
			175	5	20	25					
5	80	F	194				10	9	4	5	3
			33	42	119	161					
6	77	M	101				10	29	3	1	1
			60	15	26	41					

**Abbreviations:** CT: computed tomography, ASPECT: Alberta stroke program early CT, NIH: National Institutes of Health, mRS: modified Rankin scale.



**Figure 2** A CT scan showed no early CT signs at admission to Aso Central Hospital.



**Figure 3** Left: Diffusion-weighted MRI showed a small hyperintensity area in the left insular cortex. Right: MRA yielded a poor image of the left middle cerebral artery branches.

branches at 13:47 (7 hr 2 min after onset) (Figure 4). After 24 hr her speech disturbance disappeared and her NIH stroke scale was 8; at discharge it was 1 and her mRS was 1 three months later.

## DISCUSSION

In Japan, the administration of intravenous rt-PA therapy within 3 hours of acute ischemic stroke onset has been approved since 2005. However, relatively few patients have received rt-PA treatment. In September 2012, the approved interval between the occurrence of acute cerebral infarction and rt-PA delivery was extended to 4.5 hours. Although the patient age and possible contraindications must be considered, we expect an increase in the number of patients who would benefit from rt-PA treatment. In rural areas there are few facilities that can deliver this therapy because specialist in treating acute stroke patients tend to congregate in urban areas. Consequently, to help acute stroke patients living in remote areas, an information-technology-based system that facilitates a remote diagnosis is needed.

The usefulness, reliability, and safety of telemedicine systems have been investigated [2-8] (Table 3) and the ability to transfer DICOM images for viewing on monitors is highly valuable. However, such systems require large capital investments and they tend to be cumbersome. As our system uses a smartphone to view the images and a server for the fast and easy uploading of images, it can be implemented at a relatively low cost. Even when an acute stroke specialist is not available at the stroke center, contact can be made via the smartphone.

The usefulness of remotely-performed stroke examinations with the aid of smartphones and the FaceTime application installed on iPhone 4 has been reported [9,10]. These instruments facilitate the transfer of the NIH stroke scale and of CT images to specialists at the comprehensive stroke center and allow the oral and visual presentation of patient data and of the patient's condition by non-specialists at the primary emergency hospital.

The "drip and ship" approach to treat patients with acute stroke has been evaluated in the literature [11-13]. We found that the interval between our patients' arrival at the emergency hospital and the inception of rt-PA administration was approximately 64.7 minutes. This complies with the international guidelines of the American Heart Association [14]. Although our study population was small, none of our patients presented with symptomatic intracranial hemorrhage and 3 of 6 patients



**Figure 4** Left: A left internal cerebral artery angiogram (lateral view) showing obstruction of the left middle cerebral artery branches. Center: The Penumbra system was used to address the left middle cerebral artery branches. Right: A left internal cerebral artery angiogram (lateral view) showing recanalization of the left middle cerebral artery branches.

**Table 3:** Comparison of telemedicine systems for stroke.

	Hub/Spoke	Data transfer	System	Cost
TEMPiS	2/12	Picture transfer	Videoconfer-ence	-
REACH	1/8	DICOM data transfer	Television + video camera + microphone	10000 dollar
TESS	1/7	DICOM data transfer	Television + video camera + microphone	8000 dollar
STARR	1/2	-	Television + video camera + microphone	-
STRoKE DOC	1/4	DICOM data transfer	Television + video camera + microphone	-
CALDERA	1/1	iPhone 4S (RDICOM)	iPhone 4S (Face Time)	2500 dollar

**TEMPiS:** Telemedical Project for Integrative Stroke Care, **REACH:** Remote Evaluation for Acute Ischemic Stroke, **TESS:** Telemedicine in Stroke in Swabia, **STARR:** Stroke Telemedicine for Arizona Rural Residents, **STRoKE DOC:** Stroke Team Remote Evaluation Using a Digital Observation Camera, **CALDERA:** Cooperative Attempt of teLestroke-based Drip and ship Emergent Referral - the Aso.

**Table 4:** Comparison of telemedicine systems for treatment of RT-PA.

	Martin-Schild et. al	Pervez et. al	Lazaridis et. al	CALDERA
Age (mean)	65	73.6	68	77.7
Man percentage	44	42.9	47.8	33.3
Case number	84	84	185	6
attack - treatment (min)	150	140	152	148.3
attack-admission (min)	65	-	60	83.7
admission-treatment (min)	85	-	90	64.7
NIH stroke scale				
On admission	10.7	13	10	14.5
After 24 hours	-	-	-	6.8
At discharge	-	-	-	3.2
additional IVR treatment(%)	6	0	0	16.7
mRS (3 months after) (%)	30	-	-	50
symptomatic intracranial hematoma (%)	6	4.8	1.6	0

**NIH:** National Institutes of Health, **mRS:** modified Rankin scale, **CALDERA:** Cooperative Attempt of telestroke-based Drip and ship Emergent Referral - the Aso.

manifested a mRS score below 2 three months after suffering the insult.

## CONCLUSION

The "drip and ship" method to deliver rt-PA treatment to patients with remotely-diagnosed acute stroke is of great value, especially with reference to patients living in remote areas without stroke specialists. Advances in information technology

render this method scalable and may eliminate regional differences in the administration t-PA therapy to stroke patients.

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