Published in final edited form as:

J Emerg Med. 2011 August ; 41(2): 135–141. doi:10.1016/j.jemermed.2008.10.018.

IS THE DRIP-AND-SHIP APPROACH TO DELIVERING THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE SAFE?

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Abstract

Background—The drip-and-ship method of treating stroke patients may increase the use of tissue plasminogen activator (t-PA) in community hospitals.

Objective—The safety and early outcomes of patients treated with t-PA for acute ischemic stroke (AIS) by the drip-and-ship method were compared to patients directly treated at a stroke center.

Methods—The charts of all patients who were treated with intravenous (i.v.) t-PA at outside hospitals under the remote guidance of our stroke team and were then transferred to our facility were reviewed. Baseline NIHSS (National Institutes of Health Stroke Scale) scores, onset-to-treatment (OTT), and arrival-to-treatment (ATT) times were abstracted. The rates of in-hospital mortality, symptomatic hemorrhage (sICH), early excellent outcome (modified Rankin Scale [mRS] ≤ 1), and early good outcome (discharge home or to inpatient rehabilitation) were determined.

Results—One hundred sixteen patients met inclusion criteria. Eighty-four (72.4%) were treated within 3 h of symptom onset. The median estimated NIHSS score was 9.5 (range 3–27). The median OTT time was 150 min, and the median ATT was 85 min. These patients had an in-hospital mortality rate of 10.7% and sICH rate of 6%. Thirty percent of patients had an early excellent outcome and 75% were discharged to home or inpatient rehabilitation. When these outcome rates were compared with those observed in patients treated directly at our stroke center, there were no statistical differences.

Conclusions—In this small retrospective study, drip-and-ship management of delivering i.v. t-PA for AIS patients did not seem to compromise safety. However, a large prospective study comparing drip-and-ship management to routine care is needed to validate the safety of this approach to treatment.

Keywords

stroke; thrombolysis; health care; safety; outcomes

INTRODUCTION

Intravenous tissue plasminogen activator (t-PA) given within 3 h of symptom onset remains the only proven treatment for acute ischemic stroke (AIS), yet national rates of t-PA use among eligible patients remain < 5% (1,2). Many emergency physicians are concerned about administering t-PA in a setting without a stroke team or appropriate neurological and neurosurgical resources equipped to handle the complications of t-PA (3). The reluctance to treat patients in community hospitals is due in part to a lack of adequate intensive care services or Neurology and Neurosurgery coverage (3). Many hospitals, even those in small cities that neighbor large academic centers, do not have direct access to neurologists around the clock and do not have experience delivering t-PA for AIS. Other hospitals have emergency systems in place to access and consult a neurologist for patients with possible AIS via telephone or videotelemedicine (VTM) consults. When treatment with intravenous (i.v.) t-PA is recommended, the patients are initially treated at the outside hospital (OSH) and then transferred to a facility with Neurology and Neurosurgery staff available for continuation of care. This method of delivering t-PA to stroke patients has been termed “drip-and-ship.”

When the consultation for treatment recommendations is made by telephone, the neurologist cannot normally examine the patient or review the patient’s neuroimaging studies. Although studies have demonstrated that emergency physicians can accurately diagnose stroke and some feel comfortable treating stroke with t-PA without a neurologist being present, there is little evidence about the safety of treating patients with t-PA at a community hospital in consultation with a neurologist at a stroke center (3–5). To date, two groups have presented their experience with the feasibility of the drip-and-ship method in a total of 86 patients, collectively (6,7). To our knowledge, no previous studies have examined the safety and outcome of drip-and-ship patients in routine clinical practice compared with patients who present directly to and receive acute thrombolytic therapy at a stroke center. Despite a paucity of data on the safety of drip and ship, community hospitals across the United States are being encouraged to form relationships with stroke centers to increase the number of stroke patients treated by the drip-and-ship method (8).

Evidence that the drip-and-ship approach to delivering standard-dose i.v. t-PA is safe, especially when compared to routine treatments provided in a stroke center, may lead to increased physician comfort and higher treatment rates at community hospitals. The primary objective of this study was, therefore, to determine the safety and early outcomes of i.v. t-PA in patients treated at an OSH and transferred to our facility for further care. The t-PA treatment times, hemorrhagic complications, and early outcomes among patients treated with the drip-and-ship approach were compared with those who presented directly to our facility and received i.v. t-PA.

METHODS

Study Design

A retrospective study was developed to determine the safety and early outcomes of i.v. t-PA patients treated at an OSH and then transferred to our facility. This project was approved by the University of Texas–Houston Health Science Center Institutional Review Board.

Selection of Participants

All patients who presented to an OSH with AIS symptoms and were treated with i.v. t-PA and then transferred to our stroke center from January 2004 through November 2007 were identified. Patients were included if onset and treatment times were documented and if there was evidence that the decision to treat was made after consultation with our stroke team. All

AIS patients treated with i.v. t-PA within 3 h during the same time frame at our facility were identified to compare safety and early outcomes with the subset of patients treated within 3 h at OSH by the drip-and-ship method.

Setting

Our center, located in downtown Houston, serves as a hub for emergency departments (EDs) covering a radius of more than 100 miles. Our stroke team is available 24 h per day for telephone consultation on acute stroke patients and for VTM consultation at three regional hospitals. These forms of consultation are part of our routine clinical practice.

Methods of Measurement, Data Collection, and Processing

The medical records from the referring hospital were reviewed. The abstractors (SMS, HH, and AA) recorded onset, arrival, and t-PA bolus times and calculated pretreatment National Institutes of Health Stroke Scale (NIHSS) scores on a standardized abstraction form (9). The three NIHSS abstractors are certified in the NIHSS examination. Any part of the neurological examination not described by the emergency physicians was assumed to be normal. In cases where there was discrepancy between the times recorded at the OSH and our admission notes, the symptom-onset time recorded in our admission notes was considered the correct time, as this history was elicited by a stroke team member at the receiving hospital. The time of OSH arrival and t-PA bolus times recorded in the OSH medical records were considered the correct times. All other reported data, including adverse events and outcomes, were obtained from our prospective stroke registry. Our registry data were acquired prospectively by trained abstractors who had a detailed code book that defines each variable. We have an ongoing quality control program to monitor the accuracy of our data. The abstractors for our registry were not involved in the generation of this project and, thus, were blinded to our hypothesis.

Admission history and physical examination upon arrival to our facility were reviewed to evaluate for response to t-PA. All neuroimaging tests performed within 3 days of t-PA treatment were reviewed to identify evidence of hemorrhagic transformation using the criteria established in the European-Australasian Acute Stroke Study trial, and to evaluate for evidence of infarction on diffusion-weighted imaging or follow-up computed tomography (CT) imaging, if magnetic resonance imaging (MRI) was not performed (10). Hemorrhage was considered symptomatic (sICH) if any decline in neurological condition led to CT or MRI brain imaging that revealed the presence of a parenchymal hematoma (PH) that was likely to have caused the deterioration. A PH2 hemorrhage is defined as a confluent area of blood occupying at least one-third of the infarct volume with mass effect or parenchymal hemorrhage outside of the area of infarction (10).

Outcome Measures

The primary outcome measure was in-hospital mortality. Secondary outcome measures were the proportion of patients with sICH, discharge modified Rankin Scale (mRS) score, and discharge disposition. Excellent outcome was defined as mRS ≤ 1 . Good outcome was defined as discharge to home or inpatient rehabilitation.

Statistical Analyses

Outcome analyses—Outcomes are described with measures of central tendency among the three patient populations: 1) OSH within 3 h, 2) OSH between 3 and 6 h, and 3) the stroke center within 3 h. Measures of central tendency included mean, standard deviation, median, and interquartile range. Onset-to-treatment (OTT) and arrival-to-treatment (ATT) times and the rates of adjuvant intra-arterial therapy (IAT) utilization and neuroimaging

confirmation of stroke were calculated. We compared each of these variables, as well as baseline demographics and stroke severity (NIHSS scores), in patients treated within 3 h at OSH and at our center.

As secondary analyses, multivariate logistic regression with in-hospital mortality, excellent outcome, good outcome, and sICH were used as outcome variables to explore the relationship between transfer status (drip-and-ship vs. treatment at our center) and early outcomes while adjusting for baseline NIHSS and OTT time. Age at admission was a priori selected as a clinically important covariate when assessing outcomes, yet was not statistically different between OSH and our center's patients in this cohort.

Because this was an exploratory study, no adjustments for multiple comparisons were made. A *p*-value of 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 15 (SPSS Inc., Chicago, IL).

RESULTS

There were 116 patients meeting inclusion criteria who came from 37 OSHs covering a maximum radius of 403 miles (Figure 1). The mean distance patients traveled between transfer and receiving hospital was 77 miles (SD 45 miles). The median time from symptom onset to arrival at our hospital was 6 h; the mean time was 382 min (SD 173 min). The median time from t-PA bolus at an OSH to arrival at our hospital was 3 h among the transferred patients; the mean time was 212 min (SD 132 min). Twenty-three of the 116 (20%) transferred patients were treated after VTM guidance.

Patients Treated at OSH within Three Hours of Symptom Onset

Only 84/116 transfer patients (72%) were treated within 3 h of onset. This was similar to the percentage of patients treated within 3 h of onset at our institution (69%; data not shown). Table 1 demonstrates that the proportion of patients treated within 3 h at OSH over the study period increased, and overall represented 21.2% of post-t-PA stroke patients managed at our center during the study period. Table 2 shows the baseline demographics and t-PA treatment times of the transferred patients who received i.v. t-PA within 3 h (*n* = 84) and within 3–6 h (*n* = 31), and patients treated at our hospital within 3 h of symptom onset (*n* = 312). We found no difference in age or gender, but a significantly higher proportion of transfers were white (*p* < 0.0001). Among patients treated within 3 h of symptom onset, the median baseline NIHSS score was 9.5 for those treated at OSH. This was significantly lower than for patients treated at our hospital (median baseline NIHSS = 12, *p* = 0.005). OTT times were available in all cases. Arrival times to OSH were available in 63/84 cases; ATT time could not be calculated in the remaining cases. The median OTT and ATT times of drip-and-ship patients were 150 and 85 min, respectively. These times were significantly longer than patients treated at our center (OTT 135 min, *p* = 0.027; ATT 64 min, *p* < 0.0001).

Drip-and-ship patients were treated with adjuvant IAT in only 6% of cases, compared to 15.1% of patients presenting directly to our center (*p* = 0.029). The mean time from symptom onset to arrival at our hospital was nearly 6 h (355 min, SD 144 min) even among drip-and-ship patients treated within 3 h of symptom onset, who might have been considered for adjuvant IAT. The percentage of patients with a confirmed stroke was 82% when treated at our hospital, vs. 75% in the drip-and-ship population.

Patient Safety and Early Outcomes (Figure 2)

Patients treated at OSH had a 6% rate of sICH, whereas patients treated at our center had a 4.5% rate of sICH. This was not statistically significant, but we did not have sufficient

power to detect a difference in this sample. Both rates are within the rates observed in clinical trials of i.v. t-PA for AIS (11).

The primary outcome measure, in-hospital mortality rate, was nearly identical in patients treated at our center (10.6%) and patients treated at OSH (10.7%). When controlling for pre-t-PA NIHSS score and OTT, in-hospital mortality rate in drip-and-ship patients was not statistically different from patients treated at our center. About 30% of patients treated at OSH had an excellent early outcome. Nearly 75% of patients had a good discharge disposition. There was no difference in the functional outcome of excellent mRS on discharge between the two groups of patients, nor was there a significant difference in the rate of favorable discharge disposition, even when controlling for pre-treatment NIHSS score and OTT. Figure 2 shows a comparison of the point estimates with 95% confidence intervals (CI) of various different outcomes. Comparing outcomes of patients treated at the OSH vs. directly at our center, the mean difference in proportions with 95% CI, respectively, was 0.01 (−0.13 to 0.12) for ≥ 4 -point NIHSS improvement; 0.03 (−0.14 to 0.07) for mRS 0–1; 0.05 (−0.17 to 0.07) for mRS 0–2; 0.07 (−0.19 to 0.04) for good discharge disposition; 0.01 (−0.08 to 0.07) for mortality; and 0.02 (−0.07 to 0.04) for sICH. None of these differences was significant.

Treatment beyond Three Hours

Of the 32 transfer patients treated after 3 h, 10 were treated within 190 min. Twenty-nine of the 32 patients were treated within 4 ½ h of symptom onset. Three patients were thought to have been treated within 3 h of symptom onset, but additional history obtained upon arrival to our hospital placed them out of the window. One additional patient who woke up with a stroke, with an NIHSS score of 30, was treated 12 h after the last time the patient was known to be normal. None of these 4 patients had sICH. The median NIHSS score of patients treated 3–6 h from symptom onset was 8 (range 4–25). The median OTT time of patients treated 3–6 h after onset was 216 min (interquartile range 190–240 min). The sICH and mortality rates were 6.5% (2/31). Twelve of the 32 patients (37.5%) treated beyond 3 h of symptom onset had an excellent outcome (mRS ≤ 1). Twenty-one patients (65.6%) were discharged to home or inpatient rehabilitation.

DISCUSSION

The drip-and-ship method for delivering AIS therapy increases the number of patients who may benefit from i.v. t-PA (6,7). Patient selection for i.v. t-PA with the drip-and-ship approach involves a discussion between an emergency physician at the local hospital and a stroke physician at the hub. The decision to treat also relies upon a community radiologist to interpret baseline neuroimaging studies. Safety concerns may limit the widespread application of treatments by this approach. Our data, however, are in agreement with prior studies demonstrating that rates of in-hospital mortality and sICH using the drip-and-ship method are similar to those in patients treated within clinical trials. Our study also suggests that the in-hospital mortality rate in the drip-and-ship patients is nearly identical to that of patients treated at our comprehensive stroke center in our routine clinical practice. The rate of sICH was higher in drip-and-ship patients, but the difference did not reach statistical significance. Our small sample size may have precluded the ability to detect a clinically meaningful and statistically significant increase in sICH.

The percentage of patients who ultimately were found to have a stroke on neuroimaging studies was not statistically different between OSH and our center's treated patients, further supporting the accuracy of emergency physicians to diagnose suspected acute stroke (12). Prior studies have used the neurologist's diagnosis of stroke as the gold standard to which the emergency physician's diagnosis was compared (13). Our study used radiographic

confirmation of an infarct. A majority of the MRI scans were performed within 24 h of the ictus, and might not have detected cerebral ischemic events that were effectively reversed by early complete recanalization, actual transient ischemic attacks, or very small infarcts, particularly in the posterior circulation (14).

Drip-and-ship patients were treated later than patients treated at our center, largely due to delays in ATT. The median ATT in drip-and-ship patients was 25 min longer than the target set by the National Institute of Neurological Disorders and Stroke. Given that nearly 2 million neurons die each minute during a middle cerebral artery stroke, improvements are needed in the process of acute stroke evaluation and treatment at OSH (15). It also should be acknowledged that the telephone or VTM consultations actually may have contributed to the delay. Additional studies are therefore needed to determine the factors that contribute to the extended ATT time.

Utilization of the drip-and-ship method of t-PA delivery for stroke is likely to increase, and it is critically important that more safety data are accumulated. No large studies have been performed, and no randomized studies comparing adverse events and outcomes with those achieved at stroke centers are likely to be performed due to poor feasibility of consenting and randomizing in the field and the cooperation that would be required of community hospitals and emergency transporting services. A non-randomized, prospective study, however, would be feasible and would provide stronger evidence of the relative safety of the drip-and-ship method.

Limitations

Our study has important limitations. First, we assumed that any part of the neurological examination not documented at the OSH was normal. Therefore, the NIHSS scores abstracted from the medical records at the OSH may have underestimated the full extent of neurological deficits. If the true NIHSS scores were substantially higher, this might at least partially explain the higher rate of sICH, but there was still no difference in mortality or functional outcome. Second, the number of patients is small, and thus, this study is underpowered to detect small differences among outcomes and safety rates comparing those observed in drip-and-ship patients with patients treated at our center. Our study is also limited by its retrospective nature, and our results require validation in a prospective, equivalency study, although, as previously stated, a randomized study of sufficient magnitude is unlikely to be undertaken. Finally, this study did not evaluate the outcomes of patients who remained at the treating OSH facility after treatment with i.v. t-PA. However, there is evidence that poor outcomes, complications, and lengths of stay may be reduced by treatment in a stroke unit within a stroke center (16).

CONCLUSIONS

Emergency physicians at community hospitals may or may not be comfortable giving t-PA, however, our data suggest that once treated at OSH, AIS patients' early outcomes are similar if they are transferred to a stroke center after t-PA treatment vs. if the patients had gone directly to the stroke center and were treated with t-PA within 3 h of onset. Our study lends support to the American Heart Association/American Stroke Association policy statement advocating the creation of drip-and-ship arrangements between local hospitals and stroke centers (8).

ARTICLE SUMMARY

1. Why is this topic important?

The drip-and-ship approach to delivering t-PA to acute stroke patients may increase the treatment rate in community hospitals.

2. What does this study attempt to show?

We reviewed our center's experience treating patients by the drip-and-ship approach to determine the safety of t-PA in this setting.

3. What are the key findings?

Drip-and-ship patients had the same mortality rate as patients treated directly in our center's Emergency Department. The rate of symptomatic intracerebral hemorrhage was insignificantly higher in drip-and-ship patients, but is within the expected rate.

4. How is patient care impacted?

Our data suggest that the safety of t-PA for treating stroke is not compromised by the drip-and-ship method when guided by an experienced stroke team.

Acknowledgments

Drs. Martin-Schild, Barreto, and Abraham are supported by training grant 5-T32-NS007412-09 from the National Institutes of Health to the University of Texas–Houston Medical School Stroke Program.

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Figure 1.
Location of Houston stroke center and distribution of transfer hospitals.

Figure 2.

Point estimates of adverse events and early outcome rates in patients treated at outside hospitals (OSH) and in patients treated directly at our stroke center within 3 h of symptom onset. Error bars represent 95% confidence intervals around point estimates. NIHSS = National Institutes of Health Stroke Scale.

Table 1

t-PA Treatments within 3 Hours of Symptom Onset Over Study Period

Year	Treated at Our Center < 3h	Treated at OSH < 3 h	OSH % Total Treatments < 3 h
2004	88	15	14.6
2005	76	16	17.4
2006	103	27	20.8
2007*	45	26	36.6
Total	312	84	21.2

* Only cases with complete registry entries by December 1, 2007 were included.

OSH = outside hospital.

Table 2

Baseline Variables and Treatment Process

Variable	Treated at Our Center < 3 h from Onset n = 312	Treated at OSH < 3 h from Onset n = 84
Age, years, mean (SD)	65 (15)	65 (15)
Race, %		
White	46.2	78.6
Black	37.5	9.5
Hispanic	14.4	11.9
Other	1.9	0
Male, %	44.6	44.0
NIHSS pre-tPA		
Mean (SD)	13.1 (6.7)	10.7 (5.8)
Median (range)	12 (0–38)	9.5 (3–27)
	n = 312	n = 69
OTT, minutes		
Median	135	150
IQR	105–157	117–165
	n = 312	n = 84
ATT, minutes		
Median	64	85
IQR	50–78	66–120
	n = 308	n = 63
Adjuvant IAT rate, %	15.1	6.0

OSH = outside hospital; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation; OTT = onset-to-treatment time; ATT = arrival-to-treatment time; IQR = interquartile range; IAT = intra-arterial therapy.