Prehospital thrombolysis in acute stroke

Results of the PHANTOM-S pilot study

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ABSTRACT

Objective: Beneficial effects of IV tissue plasminogen activator (tPA) in acute ischemic stroke are strongly time-dependent. In the Pre-Hospital Acute Neurological Treatment and Optimization of Medical care in Stroke (PHANTOM-S) study, we undertook stroke treatment using a specialized ambulance, the stroke emergency mobile unit (STEMO), to shorten call-to-treatment time.

Methods: The ambulance was staffed with a neurologist, paramedic, and radiographer and equipped with a CT scanner, point-of-care laboratory, and a teleradiology system. It was deployed by the dispatch center whenever a specific emergency call algorithm indicated an acute stroke situation. Study-specific procedures were restricted to patients able to give informed consent. We report feasibility, safety, and duration of procedures regarding prehospital tPA administration.

Results: From February 8 to April 30, 2011, 152 subjects were treated in STEMO. Informed consent was given by 77 patients. Forty-five (58%) had an acute ischemic stroke and 23 (51%) of these patients received tPA. The mean call-to-needle time was 62 minutes compared with 98 minutes in 50 consecutive patients treated in 2010. Two (9%) of the tPA-treated patients had a symptomatic intracranial hemorrhage and 1 of these patients (4%) died in hospital. Technical failures encountered were 1 CT dysfunction and 2 delayed CT image transmissions.

Conclusions: The data suggest that prehospital stroke care in STEMO is feasible. No safety concerns have been raised so far. This new approach using prehospital tPA may be effective in reducing call-to-needle times, but this is currently being scrutinized in a prospective controlled study.

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GLOSSARY

AIS = acute ischemic stroke; **PHANTOM-S** = Pre-Hospital Acute Neurological Treatment and Optimization of Medical care in Stroke; **STEMO** = stroke emergency mobile unit; **tPA** = tissue plasminogen activator.

Keeping the time lapse from symptom onset to therapy of acute ischemic stroke (AIS) patients as short as possible is crucial for achieving good outcome.[1] This is reflected in international guidelines.[2,3] Several factors can lead to substantial delays, prolonging the call-to-needle time in prehospital[4,5] as well as in-hospital management.[6–8] Only in 11% of AIS patients treated with tissue plasminogen activator (tPA) in the International Stroke Thrombolysis Registry (mainly European) was tPA started within the first 90 minutes after symptom onset (of those patients treated within the 3-hour time window).[9]

Major efforts have been made to reduce delays in treatment of AIS.[10–13] Although considerable improvements have been achieved, e.g., by introducing point-of-care coagulation measurement in the emergency room[14] or implementing an all-points alarm,[15] onset-to-treatment times often remain unsatisfactory because prehospital delays are widely unaffected.[12] It may thus be time to rethink the way we organize stroke management in general. The Pre-Hospital Acute Neurological Therapy and Optimization of Medical care in Stroke patients (PHANTOM-S) concept features a

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Supplemental data at www.neurology.org

Supplemental Data

Podcast

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newly designed ambulance, the so-called stroke emergency mobile unit (STEMO), which is deployed when patients suspected of having stroke are identified at the dispatch center with a specialized stroke identification interview algorithm.[16] We report the results of the pilot study of an ongoing project to show a relevant reduction in time from emergency call to treatment.[17] This study was focused on feasibility and technical reliability but also assessed preliminary safety and call-to-needle times in patients who received tPA treatment in the prehospital setting.

METHODS

Details of the PHANTOM-S study (NCT01382862) have been described previously.[17] The pilot study of the PHANTOM-S was conducted in the emergency medical services system of the city of Berlin during the period from February 8, 2011 to April 30, 2011.

Stroke emergency mobile unit. STEMO (see figure 1) is designed as a mobile intensive care unit additionally equipped with a CT scanner (CereTom® 8-slice mobile CT scanner; NeuroLogica®, Danvers, MA), a point-of-care laboratory (Micros 60, ABX Diagnostics; CoaguChek XS Plus, Roche Diagnostics Germany; and i-STAT Portable Clinical Analyzer, American Screening Corporation, Shreveport, LA), and the telemedicine infrastructure for remote imaging reading as well as video-conferencing support (MEYTEC GmbH, Seefeld, Germany) for evaluating patients with suspected AIS. The CT scanner is locked in a resting position when the vehicle is moving and unlocked for scanning during examination. The CT scanner is run from a small lead-shielded compartment inside the vehicle. Radiation shielding had been calculated beforehand, and technical procedures were tested during a 2-week simulation period before starting patient examinations. STEMO is staffed by a team consisting of a physician with at least 4 years of training in clinical neurology and additional qualification in emergency medicine (neurologist), a paramedic of the fire brigade (similar to Emergency Medical Technician–Paramedic),[18] and a radiographer (radiology technician with at least 2.5 years of clinical experience and specially trained in the use of the CereTom scanner) with additional paramedic qualification (similar to Emergency Medical Technician–Intermediate).[18] The radiographer and the physician (who both stay inside the protected compartment in the vehicle during CT examination) were provided with a dosimeter to record the radiation exposure caused by the CT scanner. The STEMO is based at a fire brigade station close to the center of Berlin. The operating range was defined by a previously calculated 75% probability to arrive at the scene within 16 minutes and covers more than 1,000,000 inhabitants. In the pilot study, STEMO was supposed to operate from 7:00 AM to 6:30 PM from Monday to Friday every week (11.5 hours daily). The only exception was time required for maintenance, technical upgrades, and several official engagements and presentations.

Figure 1 The stroke emergency mobile unit with CT scanner on board

Note the CT scanner in the back of the cabin and the separated shielded workstation on the right behind the door.

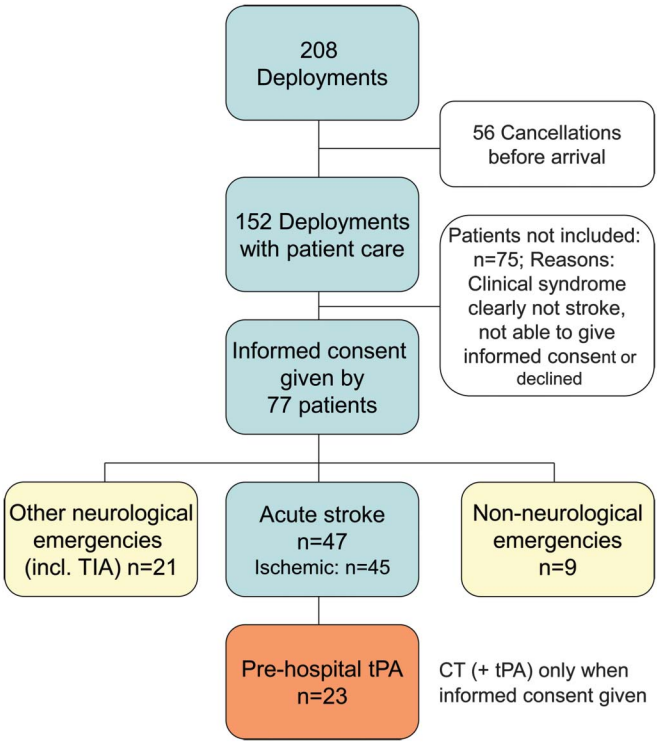
Dispatcher. The dispatch center of the fire brigade used a previously validated interview algorithm[16] to identify patients with a high probability of stroke within 4 hours after symptom onset or with unknown time of onset. In this case, STEMO was deployed if available. STEMO was assisted by a regular ambulance at all times to avoid delays in the treatment of patients in case a technical problem associated with STEMO occurred.

Patients and procedures. Basic medical care including specific neurologic expertise was offered to all patients who were managed by the STEMO team. Exclusion criteria for STEMO-specific procedures (CT scan and point-of-care laboratory) were age younger than 18 years and possible or known pregnancy. Prehospital diagnostics were started on-site or in the STEMO ambulance. Stroke diagnosis was made clinically by the neurologist. In case of a suspected acute stroke, a brain CT was conducted (with the STEMO in the parking position) after phone consultation with a radiologist. CT was performed only if it was considered to be helpful for a therapeutic decision in the STEMO. After completion of the scan, image data were sent to the radiologist on call via a teleradiology system using bundled 3G standard (universal mobile telecommunications system bandwidth: high-speed packet access). Additional analyses of blood glucose concentration, blood count, international normalized ratio, and electrolytes were performed simultaneously. The radiologist conveyed the CT results to the neurologist on board the STEMO by mobile phone. The final decision for tPA treatment was made by the STEMO physician after a short telephone consultation with the project's senior neurologist. Decision about eligibility for tPA was made on the basis of the drug license except for exclusion of patients older than 80 years (for detailed information, see http://www.strokeforum.com). In case of AIS, patients were admitted to the closest "appropriate hospital" equipped with a stroke unit.

Data collection including follow-up documentation and statistics. Data were collected from prehospital sources (database of the dispatch center and STEMO operation protocols), from hospital sources (medical reports), as well as from a 3-month follow-up telephone survey including a structured interview regarding the modified Rankin scale and living conditions. Data were analyzed only when patients had given informed consent for the use and publication of individual data.

If patients were unavailable at the 3-month follow-up, the registration office was contacted to ascertain whether the patient had survived. All data are presented in a descriptive manner and

Figure 2 Number of patients with prehospital recognition of stroke and treatment with tissue plasminogen activator (tPA) obtained



the analysis was performed with SPSS Statistics 19 statistical software (IBM Corporation, Armonk, NY).

Ethics approval. The study was approved by the Data Protection Commissioner and the Ethics Committee of the Charité Universitätsmedizin. For the new setting of a mobile CT scanner and prehospital thrombolysis, CT examination and specific stroke treatment could be offered only to patients who were able to give informed consent for STEMO-specific procedures personally or by a legally authorized representative. Data were analyzed only if patients gave informed consent for the use and publication of the individual data.

RESULTS

Calculation of times in regular care. To provide an estimate of times to treatment in regular care, we refer to the procedure times that were used in the power calculation for the prospective controlled study (NCT01382862). Mean time from call-to-needle in regular care had been calculated in an analysis of 50 consecutive patients with AIS who presented directly to the Campus Benjamin Franklin of the Charité Hospital and were treated with tPA in 2010. The mean call-to-door time was 44 ± 13 minutes (median: 40 [37–48] minutes) and the door-to-needle time was 54 ± 22 minutes (median: 48 [39–68] minutes). This resulted in a call-to-needle time of 98 ± 27 minutes (median: 92 [79–112] minutes) and an onset-to-needle time of 146 ± 67 minutes (median: 134 [103–176] minutes). In a sensitivity analysis comprising only patients treated at the same times of day and week as in the STEMO pilot study, time intervals were slightly shorter (call-to-admission: 42 ± 9 minutes; door-to-needle: 52 ± 21 minutes; and call-to-needle: 95 ± 25 minutes).

Deployment and study inclusion. On 52 days from February 8, 2011 to April 30, 2011, the dispatchers deployed STEMO for 208 suspected stroke emergencies after using the interview algorithm (figure 2). The operation was canceled 56 times (27%) before arriving on-site (in most cases because of additional information given by the accompanying ambulance team, which arrived first and decided that no special stroke treatment was necessary). Specific medical management was provided by the STEMO team for 152 patients. Forty-four patients were unable to give informed consent during the emergency management because of impaired consciousness or communication disorders. No additional informed consent for scientific use of individual data was collected from another 31 patients because of obvious nonstroke disease (16 patients), lack of time for consent procedures (14 patients), or patient decline (1 patient refused to give informed consent for data utilization). Hence, we report data from 77 patients.

Technical and conceptual reliability. Noncontrast brain CT was performed in 64 patients (83%), and an additional cranial CT angiography in 1 patient with suspected proximal middle cerebral artery occlusion. Eight brain CT examinations (12%) displayed motion artifacts with moderately impaired reading quality in 5 (8%) as stated by the radiologist. No technical failures occurred in the vehicle itself, the point-of-care laboratory, or the other medical instruments except for 1 case of CT dysfunction. Because of a CT motion blockage, 1 patient had to be transported by a regular ambulance to the nearest stroke unit (accompanied by the physician) where the patient received tPA after CT examination. In 2 cases, the CT image transmissions were delayed (>5 minutes but both <15 minutes) because of temporarily low transmission rates in the mobile telecommunication system. The radiation levels recorded by the dosimeters remained within normal limits over the entire period.

Diagnosis and treatment of patients. On the basis of medical history and neurologic examination, the neurologist established a prehospital diagnosis of stroke in 56 patients and TIA in 5 patients. This prehospital diagnosis was confirmed in 53 cases (87%) (45 AIS, 7 TIAs, 1 hemorrhagic stroke) by the final in-hospital diagnosis. The other 8 patients were diagnosed in hospital with headache (3 patients), infection (2 patients), dysarthria with unknown etiology (1 patient), intoxication (1 patient), and brain tumor (1 patient). However, 14 of 16 patients (88%) with a prehospital provisional nonstroke diagnosis had a final nonstroke diagnosis in hospital. The other 2 patients had an in-hospital diagnosis of subarachnoidal hemorrhage (1 patient) and TIA (1 patient). Eighty-eight percent (68 patients) eventually had a neurologic disorder; these disorders consisted

of 47 strokes (45 ischemic and 2 hemorrhagic), 8 TIAs, 4 epileptic seizures, 2 brain tumors, 1 facial nerve palsy, and 6 headaches (figure 2). Mean transportation time in STEMO to hospital was 12 ± 11 minutes (median: 9 [7–13] minutes).

Twenty-three (51%, 14 men, 9 women; mean age 75 years) of the 45 patients with prehospital as well as final AIS diagnoses received tPA (22 in the prehospital setting and 1 patient after hospital admission because of CT malfunction in the STEMO). The mean onset-to-call time was 55 minutes (median: 34 [13–92] minutes). The mean call-to-needle time was 58 minutes (median: 58 [50–63] minutes) for patients with prehospital tPA treatment and 62 minutes (median: 58 [51–65] minutes) including the patient who received delayed tPA treatment in the hospital. This resulted in a mean onset-to-needle time of 117 minutes (median: 97 [69–156] minutes) in all AIS patients treated with tPA. Four patients (17%) were treated within 60 minutes. Two patients (8%) treated with tPA experienced an intracranial hemorrhage during the first 7 days after stroke onset. Whereas clear neurologic deterioration was observed in 1 patient, the other patient developed a mild somnolence and the hemorrhage was detected in regular follow-up imaging. This patient (88 years old) died in the hospital with sepsis on day 16. One additional patient who had a prehospital diagnosis of acute stroke with sudden onset of dysarthria and weakness in one arm was treated with tPA, but was finally diagnosed with sepsis; no side effects of treatment occurred in this patient. The reasons for not treating with tPA in 22 patients with AIS included onset-to-therapy decision time of more than 4.5 hours (n = 13), severe disability pre-onset (n = 2), anticoagulation (n = 2), no disabling deficit at the time of therapy decision (n = 1), a tumor with uncertain significance (n = 1), and symptoms of severe stroke with fixed gaze deviation and hemiplegia (n = 3).

After ambulance transport, no other serious adverse events were recorded in stroke or nonstroke patients during the first 7 days or up to hospital discharge. The clinical characteristics, the time parameters of the prehospital stroke treatment, and functional outcome of patients with AIS are shown in the table. Telephone follow-up data of all AIS patients with thrombolytic treatment are summarized in the table. Of those patients, 43% reached a modified Rankin scale score of 0 or 1.

Table Characteristics of patients with acute ischemic insult

	Patients with AIS mean (SD), median [IQR]	Patients with AIS without tPA treatment mean (SD), median [IQR]	Patients with AIS who received tPA mean (SD), median [IQR]	Patients of the reference group in 2010 mean (SD), median [IQR]
No. of patients	n = 45	n = 22	n = 23	n = 50
Call-to-arrival on-site time, min	14 (6), 13 [10–16]	16 (7), 15 [11–20]	13 (6), 13 [10–16]	8 (5), 7 [5–10]
On-site time, min	63 (22), 62 [50–71]	60 (30), 56 [44–69]	65 (13), 62 [60–74]	NA
Call-to-needle time, min			62 (21), 58 [50–65]	98 (28), 92 [79–112]
On-site-to-needle time, min			48 (22), 42 [37–52]	91 (49), 84 [73–101]
Call-to-hospital time, min	85 (20), 86 [74–92]	83 (29), 78 [73–86]	86 (12), 87 [78–95]	44 (14), 40 [37–48]
Age, y	74 (12), 77 [66–82]	73 (12), 75 [66–82]	75 (12), 79 [70–85]	70 (21), 75 [71–83]
Initial NIHSS score	7 [4–12]	6 [3–9]	8 [5–12]	8 [5–16]
Pre-onset mRS score	1 [0–3]	3 [0–3]	1 [0–3]	NA
Pre-onset mRS score >1, %	42	45	39	NA
Symptomatic secondary hemorrhage within 7 d, n (%)	2 (4)	0 (0)	2 (9)	3 (6)[a]
Dead within 7 d, n (%)	1 (2)	0 (0)	1 (4)	4 (8)[a]
No. of patients	n = 34	n = 11	n = 23	n = 50
mRS score <2 after 3 mo, n (%)	14 (41)	5 (45)	9 (39)[b]	NA
Dead within 3 mo, n (%)	5 (15)	1 (5)	4 (17)	NA

Abbreviations: AIS = acute ischemic stroke; IQR = interquartile range; mRS = modified Rankin scale; NA = not applicable; NIHSS = NIH Stroke Scale; tPA = tissue plasminogen activator.
[a] Data at time of discharge (median: 7 days [6–10 days]).
[b] Or 57% (8 of 14) of those with pre-onset mRS score of 0 or 1.

DISCUSSION The results of our study indicate that specific stroke management including diagnostic setup and thrombolytic treatment is feasible in the prehospital setting. Using a stroke identification algorithm at the dispatching level, a specialized stroke ambulance can be sent specifically to patients with acute neurologic diseases. With the exception of 1 CT failure, the mobile technology was stable and thrombolytic treatment could be applied to a high proportion of patients. Compared with previously collected control data, the new approach promises a relevant time saving in call-to-needle times. By accelerating the diagnostic setup, onset-to-needle times were less than 90 minutes in 48% of our patients compared with 11% of the patients treated within the 3-hour time window in the International Stroke Thrombolysis Registry.[9] Albeit small, our pilot study has not raised safety concerns.

The idea of a specialized stroke emergency vehicle equipped with a CT scanner[19] was first realized in the Mobile Stroke Unit project of the University of Saarland, Germany, and the results of a controlled study comprising 100 patients (53 in the active cohort with 12 prehospital tPA treatments) were recently published.[20,21] The time from call to treatment was substantially reduced by prehospital thrombolysis compared with regular care. In comparison to the Mobile Stroke Unit project, STEMO was deployed in a different population setting (urban area in contrast to a more rural area) with a high number of patients potentially eligible for treatment. In contrast to the Mobile Stroke Unit project, an additional emergency physician was called to the stroke emergencies only in case of vital threat (and therefore to be at the scene at the same time), and radiology was performed via teleradiology instead of having a radiologist on board of the vehicle. In addition, patients with acute emergencies were transported in the STEMO to the hospital whereas the transport was done by a regular ambulance in the Mobile Stroke Unit project.

Our series of prehospital tPA treatments seems encouraging. Although tPA was restricted to patients able to give informed consent, we managed to treat 23 patients in a short time period of 52 days. The high frequency of specific stroke treatment is relevant when taking into account the significant financial and personnel efforts of such a new infrastructure.

Two studies have reported the use of specialized mobile medical services in emergency medicine,[22,23] one for myocardial infarction and one for stroke care by a mobile intensive care unit. Both suggested faster and more reliable care for patients compared with standard procedures but the mobile stroke intensive care unit did not provide prehospital brain imaging or thrombolytic therapy.

So far, the results have not raised safety concerns that prehospital treatment with tPA might lead to a higher rate of serious complications such as intracranial hemorrhage or death compared with in-hospital use of tPA.[24,25] This is in agreement with previous publications that did not report higher rates of secondary hemorrhage when tPA was started in smaller hospitals and transferral to a referral stroke center was initiated immediately ("drip and ship").[26–30]

The present study has limitations. Given that the study was designed as a pilot and feasibility study, our sample size is too small to provide sufficient evidence for safety. With previously collected control data only, any statement regarding effective time saved should be made with caution. Hence, within the framework of PHANTOM-S, a controlled study is currently underway comparing the effects of prehospital and conventional stroke management between randomly assigned calendar periods with and without STEMO availability.[17]

The new concept requires substantial human and financial resources that need to be analyzed in a health economy evaluation. Whether such a concept is more appropriate for rural or urban settings is under debate. However, the new approach of prehospital stroke management may offer additional benefits such as a prehospital triage with directed admission to the most appropriate hospital.[20] It may also create a new infrastructure for research of innovative stroke treatments. STEMO combines specialized equipment and a highly qualified stroke team, both available in a very early time window after stroke onset.

The feasibility and technical reliability of prehospital acute stroke work-up including thrombolytic treatment before hospital arrival has been shown. In addition, our results indicate that STEMO may be effective in the reduction of call-to-treatment time.

AUTHOR CONTRIBUTIONS

Joachim E. Weber, MD: Study concept and design, drafted manuscript, acquisition, analysis, and interpretation of data. Martin Ebinger, MD, PhD: Study concept and design, acquisition, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Michal Rozanski, MD, Carolin Waldschmidt, MD, Matthias Wendt, MD, and Benjamin Winter, MD: Acquisition, analysis and interpretation of data. Philipp Kellner, MD: Critical revision of the manuscript for important intellectual content. André Baumann, PhD: Study concept and design. Jochen B. Fiebach, MD, Kersten Villringer, MD, Sabina Kaczmarek, and Matthias Endres, MD: Critical revision of the manuscript for important intellectual content. Heinrich J. Audebert, MD: Study concept and design, study supervision, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

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DISCLOSURE

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REFERENCES

1. 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 2010;375:1695–1703.
2. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation 2007;115:e478–e534.
3. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457–507.
4. Bouckaert M, Lemmens R, Thijs V. Reducing prehospital delay in acute stroke. Nat Rev Neurol 2009;5:477–483.
5. Buck BH, Starkman S, Eckstein M, et al. Dispatcher recognition of stroke using the National Academy Medical Priority Dispatch System. Stroke 2009;40:2027–2030.
6. Jungehulsing GJ, Rossnagel K, Nolte CH, et al. Emergency department delays in acute stroke: analysis of time between ED arrival and imaging. Eur J Neurol 2006;13:225–232.
7. Tveiten A, Mygland A, Ljostad U, Thomassen L. Intravenous thrombolysis for ischaemic stroke: short delays and high community-based treatment rates after organisational changes in a previously inexperienced centre. Emerg Med J 2009;26:324–326.
8. Rose KM, Rosamond WD, Huston SL, Murphy CV, Tegeler CH. Predictors of time from hospital arrival to initial brain-imaging among suspected stroke patients: the North Carolina Collaborative Stroke Registry. Stroke 2008;39:3262–3267.
9. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768–774.
10. Kwan J, Hand P, Sandercock P. Improving the efficiency of delivery of thrombolysis for acute stroke: a systematic review. QJM 2004;97:273–279.
11. Schwamm LH, Pancioli A, Acker JE, et al. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. Circulation 2005;111:1078–1091.
12. Kohrmann M, Schellinger PD, Breuer L, et al. Avoiding in hospital delays and eliminating the three-hour effect in thrombolysis for stroke. Int J Stroke 2011;6:493–497.
13. Audebert HJ, Schwamm L. Telestroke: scientific results. Cerebrovasc Dis 2009;27:15–20.
14. Walter S, Kostopoulos P, Haass A, et al. Point-of-care laboratory halves door-to-therapy-decision time in acute stroke. Ann Neurol 2011;69:581–586.
15. Nolte CH, Malzahn U, Kuhnle Y, et al. Improvement of door-to-imaging time in acute stroke patients by implementation of an all-points alarm. J Stroke Cerebrovasc Dis Epub 2011 Sep 7.
16. Krebes S, Ebinger M, Baumann AM, et al. Development and validation of a dispatcher identification algorithm for stroke emergencies. Stroke 2012;43:776–781.
17. Ebinger M, Rozanski M, Waldschmidt C, et al. PHANTOM-S: the prehospital acute neurological therapy and optimization of medical care in stroke patients—study. Int J Stroke 2012;7:348–353.
18. Clark WR Jr. Emergency medical services education and licensure: a road map for the future. J La State Med Soc 2009;161:290–292.
19. Fassbender K, Walter S, Liu Y, et al. "Mobile stroke unit" for hyperacute stroke treatment. Stroke 2003;34:e44.
20. Kostopoulos P, Walter S, Haass A, et al. Mobile stroke unit for diagnosis-based triage of persons with suspected stroke. Neurology 2012;78:1849–1852.
21. Walter S, Kostopoulos P, Haass A, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. Lancet Neurol 2012;11:397–404.
22. Roberts MJ, McNeill AJ, MacKenzie G, Adgey AA. Time delays to lytic therapy and outcome in 100 consecutive patients with a history suggestive of acute myocardial infarction in an area with access to a mobile coronary care unit. Eur Heart J 1994;15:594–601.
23. Sablot D, Magnaudeix M, Akouz A, et al. Impact of mobile intensive care units on treating stroke within the 3-hour time window in a semi-rural area [in French]. Presse Med 2008;37:401–405.
24. Micieli G, Marcheselli S, Tosi PA. Safety and efficacy of alteplase in the treatment of acute ischemic stroke. Vasc Health Risk Manag 2009;5:397–409.
25. Heuschmann PU, Kolominsky-Rabas PL, Roether J, et al. Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. JAMA 2004;292:1831–1838.
26. Pervez MA, Silva G, Masrur S, et al. 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 2010;41:e18–e24.
27. Pfefferkorn T, Holtmannspotter M, Schmidt C, et al. Drip, ship, and retrieve: cooperative recanalization therapy in acute basilar artery occlusion. Stroke 2010;41:722–726.
28. Martin-Schild S, Morales MM, Khaja AM, et al. Is the drip-and-ship approach to delivering thrombolysis for acute ischemic stroke safe? J Emerg Med 2011;41:135–141.
29. Silverman IE, Beland DK, Chhabra J, McCullough LD. The "drip-and-ship" approach: starting IV t-PA for acute ischemic stroke at outside hospitals prior to transfer to a regional stroke center. Conn Med 2005;69:613–620.
30. Chalela JA, Kasner SE, Jauch EC, Pancioli AM. Safety of air medical transportation after tissue plasminogen activator administration in acute ischemic stroke. Stroke 1999;30:2366–2368.