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Cerebrovascular Disorders (D Jamieson, Section Editor)

Mobile Stroke Units: Bringing Treatment to the Patient

Mikel S. Ehntholt, MD[1]
Melvin Parasram, DO, MS[1]
Saad A. Mir, MD[1,2]
Mackenzie P. Lerario, MD[1,2,*]

Address
[1]Department of Neurology, Weill Cornell Medicine, New York, NY, USA
[*,2]New York-Presbyterian Mobile Stroke Treatment Unit Program, New York, NY, USA
Email: mpl9005@med.cornell.edu

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Mikel S. Ehntholt and Melvin Parasram contributed equally to this work.
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Keywords Mobile stroke unit (MSU) · Recombinant tissue plasminogen activator (r-tPA) · Pre-hospital stroke treatment

Abbreviations *ARTSS-2* Argatroban r-tPa Stroke Study · *ASPECTS* Alberta Stroke Program Early CT Score · *BEST-MSU* The Benefits of Stroke Treatment Delivered Using a mobile stroke unit · *CI* Confidence interval · *CLEAR-ER* Combined approach to thrombolysis utilizing eptifibatide and recombinant tissue plasminogen activator in acute ischemic stroke enhanced regimen · *CT* Computed tomography · *CTA* Computed tomography angiography · *ED* Emergency department · *IV* Intravenous · *LVO* Large vessel occlusion · *MOST* Multi-arm Optimization of Stroke Thrombolysis · *mRS* Modified Rankin Score · *MSU* Mobile stroke unit · *NIHSS* National Institutes of Health Stroke Scale · *NPV* Negative predicative value · *OR* Odds ratio · *PHANTOM-S* Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients Study · *PHAST* The Cleveland Pre-Hospital Acute Stroke Treatment group · *POC* Point of care · *PPV* Positive predicative value · *PT* Prothrombin time · *QALYs* Quality-adjusted life years · *ROSIER* Recognition of Stroke in the Emergency Room · *rFVIIa* Recombinant Factor VIIa · *r-tPA* Recombinant tissue plasminogen activator · *SITS-EAST* Safe Implementation of Treatment in Stroke-East registry · *TCD* Transcranial doppler · *US* United States

Abstract

Purpose of review Mobile stroke units (MSUs) have revolutionized emergency stroke care by delivering pre-hospital thrombolysis faster than conventional ambulance transport and in-hospital treatment. This review discusses the history of MSUs technological development, current operations and research, cost-effectiveness, and future directions.
Recent findings Multiple prospective and retrospective studies have shown that MSUs deliver acute ischemic stroke treatment with intravenous recombinant tissue plasminogen activator (IV r-tPA) approximately 30 min faster than conventional care. The 90-day modified Rankin Scores for patients who received IV r-tPA on the MSU compared to

conventional care were not statistically different in the PHANTOM-S study. Two German studies suggest that the MSU model is cost-effective by reducing disability and improving adjusted quality-life years post-stroke. The ongoing BEST-MSU trial will be the first multicenter, randomized controlled study that will shed light on MSUs' impact on long-term neurologic outcomes and cost-effectiveness.

Summary MSUs are effective in reducing treatment times in acute ischemic stroke without increasing adverse events. MSUs could potentially improve treatment times in large vessel occlusion and intracranial hemorrhage. Further studies are needed to assess functional outcomes and cost-effectiveness. Clinical trials are ongoing internationally.

Introduction

Stroke is the leading cause of serious long-term disability in the USA, with the annual cost burden reaching $26.3 billion [1–3]. Acute stroke treatment with intravenous (IV) recombinant tissue plasminogen activator (r-tPA) and mechanical thrombectomy are time-sensitive interventions, with faster symptom onset to treatment times leading to improved neurologic outcomes [4, 5]. r-tPA is maximally effective if administered within 60 min of stroke onset, a treatment window commonly called the "golden hour" [4, 5]. Treatment with r-tPA in the golden hour as compared with treatment within 61 to 270 min is associated with increased odds of discharge to home, independent ambulation at discharge, freedom from disability at discharge, and reduced hemorrhagic complications or in-hospital mortality [6]. However, only 15–60% of acute stroke patients arrive at the hospital within 4.5 h after onset of symptoms, and less than 10% of all stroke patients receive r-tPA [7, 8, 9••]. Of the patients treated with thrombolysis for acute ischemic stroke in the emergency department (ED), approximately 1% received r-tPA within the golden hour [10].

Due to optimization of in-hospital acute stroke treatment workflows since the late 1990s, the largest delays in acute stroke care are now in the pre-hospital setting [11]. Identifying and mitigating pre-hospital delays in stroke care such as failure to recognize and respond to symptoms, lack of integration of emergency medical services (EMS), and poor access to hospitals are essential to advancing stroke care.

Fassbender et al. proposed a novel approach to acute stroke care called the mobile stroke unit (MSU) in 2003 [12•]. MSUs were based on the hypothesis that bringing stroke treatment to patients could reduce pre-hospital delays, improve thrombolysis times, and subsequently improve patient outcomes [12•]. The MSU consists of a state-of-the-art ambulance capable of basic and advanced life support needs, a built-in CT scanner, and a specialized, interdisciplinary team of paramedics, nurses, CT technologists, and physicians that can perform the complete diagnostic work-up and treatment of stroke in the field.

Since its conception, MSUs have rapidly expanded throughout the world. Over 30 programs have launched worldwide, with 20 units either in operation or in developmental planning stages in the USA [9, 13••]. This review aims to describe the MSU model, advantages of pre-hospital stroke treatment, current published and ongoing MSU clinical trials, cost-effectiveness, and future directions in pre-hospital stroke care.

The mobile stroke unit (MSU)

In 2010, Fassbender et al. launched the first MSU in Saarland, Germany, and demonstrated the safety and feasibility of r-tPA administration in the pre-hospital setting [14]. Grotta et al. launched the first MSU in the USA in 2014 in Houston [15•]. In 2016, New York-Presbyterian Hospital (NYP) launched the first MSU on the Eastern Coast of the USA and now includes three MSUs, which is the largest network currently operating in the USA [16••].

What is on-board? MSUs are outfitted for adult advanced life support and acute neurological care, including standard EMS formulary medications and equipment, r-tPA, IV anti-hypertensive agents, and point of care (POC) laboratory equipment capable of measuring hemoglobin and international normalized ratios (INR) that are comparable to central laboratory testing [12•, 15•, 17, 18]. Most importantly, MSUs house portable CT scanners capable of 8-slice image acquisition that is comparable to in-hospital CT image quality [19]. The resolution and slice thickness (1.25 mm) of the images safely enable neurologists and radiologists to exclude hemorrhage, estimate ischemic burden, and identify hyperdense vessels. MSUs are equipped with lead reinforced walls and floors, lead vests and personal radiation detectors are worn by staff, and protocols for staff and ambulance positioning are utilized to protect the staff members and the public from radiation exposure [14, 15•]. In one study, the 1-year cumulative occupational radiation exposure to a MSU CT technician was 1.14 mSv, below the 10% US occupational dose limit of 5 mSv. Radiation exposure to patients and MSU staff was equivalent to in-hospital CT scanners (< 2 mSv), and public radiation exposure was indirectly measured via internal monitors and resulted an exposure of approximately 1 mSv or less to any one member of the general public [20]. Overall, the radiation exposure is low and within safety limits. Some MSUs utilize on-board CT angiography (CTA), transcranial dopplers (TCD), or near-infrared spectroscopy cerebral oximeters for large vessel occlusion (LVO) detection.

Who is on-board? The team varies per MSU program but always includes EMS personnel, an appropriately credentialed clinician responsible for r-tPA treatment decisions, and a technologist to operate the CT scanner. The most common staffing paradigm in the USA includes two paramedics, a CT technologist, vascular neurologists who are either on-board or accessed via telemedicine, and a registered nurse with specialized stroke training.

Logistics and Emergency Management: Integration of MSUs into EMS varies on location and regulations and requires a coordinated effort from key stakeholders such as hospital administration, EMS leadership, and MSU staff. In general, EMS dispatch will identify, alert, and dispatch the MSU to any suspected acute stroke cases based on a phone interaction. A basic life support ambulance will be dual-dispatched in case the patient is a stroke mimic or does not meet transport criteria for the MSU. At NYP, three MSUs are docked at NYP hospitals in the boroughs of Queens, Brooklyn, and Manhattan. Each MSU will be dispatched to a stroke patient if conventional ambulance transport to nearby hospital is greater than the time for MSU arrival and evaluation [16••]. Each MSU program has individualized catchment area that is coordinated with EMS. Upon arrival, the MSU team will obtain the history and collateral information, identify the last known normal, examine the patient, and perform pre-hospital stroke assessments, commonly the Cincinnati Pre-hospital Stroke Scale (CPSS) or the Los Angeles Motor Scale (LAMS) in the USA [21, 22, 23••, 24••]. Staff members are trained to discuss r-tPA contraindications with patients and family members, while the MSU evaluation is occurring. CT non-contrast of the head is performed in the field and interpreted by both vascular neurologists and remote radiologists who receive the images by wireless transfer. If the vascular neurologist is connected via telemedicine, the patient and crew are able to see, hear, and interact with the neurologist through on-board monitors, cameras, speakers, and microphones. If the patient is deemed a candidate for r-tPA, the infusion is begun, and the patient is transported to the closest primary or comprehensive stroke center. If the patient is found to have a hemorrhagic stroke, intravenous antihypertensives such as labetalol or nicardipine are administered. In cases of suspected or confirmed LVO, the MSU can provide advanced pre-notification to the receiving facility and potentially bypass the emergency department for the endovascular suite.

MSU Evidence to Date

In 2012, Walter et al. published the first randomized control trial demonstrating that a MSU in Saarland, Germany, could reduce call-to-r-tPA time to 35 min, compared to 76 min in the conventional care group [25•]. The number of patients who received therapy within the "golden hour" from last known well also increased significantly from 4% (2 of 42 patients in the control group) to 57% (30 of 54 patients in the MSU group) [25•]. Subsequently, Ebinger et al. published the Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients Study (PHANTOM-S) which showed that ambulance-based thrombolysis using a MSU in Berlin, Germany, resulted in decreased time to treatment and a tenfold increase in the rate of "golden hour" thrombolysis versus conventional care [26•]. The high rate of "golden hour" thrombolysis with MSU implementation demonstrated in Germany has been shown to be reproducible in prehospital settings outside of Germany as well [26•].

The Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU) was launched in

Houston in May 2014 [27•]. The aim of this multicenter, cluster-randomized comparative effectiveness trial is to determine whether r-tPA eligible patients managed on MSUs have improved functional outcomes compared to those receiving standard emergency care, whether telemedicine assessment on the MSU is reliable and accurate, and to establish a formal cost-benefit analysis of MSU treatment [23•]. The BEST-MSU run-in phase study revealed that when compared with usual care, the use of ambulance-based thrombolysis results in decreased time to treatment without an increase in adverse events [27•]. The BEST-MSU study is ongoing, and the targeted end of recruitment is May 2020 (NCT02190500).

In Toledo and Lima, Ohio, Lin et al. showed that the first full-time, 24 h per day/7 days a week MSU could be successfully implemented with r-tPA administration rates and times comparable to other MSUs nationwide [28••]. Additionally, they demonstrated that MSUs could provide rapid triage and treatment in the field for non-stroke neurological emergencies, including status epilepticus [28••].

Multiple studies have demonstrated feasibility of the MSU model through improved triage capability and decreased time to imaging and endovascular therapy with low rates of technical failure [29•, 30•, 31–33, 34••]. In an early subpopulation analysis of the PHANTOM-S pilot study, the MSU was dispatched to 152 subjects, of which 77 had ischemic strokes and 45 were treated with r-tPA (average time 62 min) with 1 CT scan technical failure [29•]. Wendt et al. showed improved field triage of patients with confirmed acute stroke (as opposed to stroke mimics) to stroke centers when compared with standard ambulance [30]. In a small retrospective cohort of patients, Cerejo et al. found that MSUs may help triage and shorten time to intra-arterial therapy for LVOs with significant reduction of door to primary stroke center time, median door to CT time, and CT to groin puncture for intra-arterial therapy time compared to standard ambulance [31]. John et al. demonstrated the use of CTA in MSU in one patient with a left middle cerebral artery occlusion and its subsequent successful triage to a thrombectomy capable center [32]. Grunwald et al. demonstrated feasibility of the Alberta Stroke Program Early CT Score (ASPECT) on MSU CT scanners [33]. In a sub-study of BEST-MSU, MSU care was shown to significantly decrease door to groin puncture times for thrombectomy by 10 min in patients transported by a MSU compared to standard ambulance [35••].

Several studies have shown feasibility of telemedicine technology in MSUs without negative impact on patient care [36•, 37••, 38••]. The Cleveland Pre-Hospital Acute Stroke Treatment (PHAST) group sought to test the reliability of MSU equipped with telemedicine technologies and compared its management to standard ambulance [37••, 38••]. They found significant reduction in evaluation and treatment times with MSU treatment and low technical complications using telemedicine [37••, 38••]. In the BEST-MSU study, Wu et al. directly compared neurological evaluation and treatment of patients by a telemedicine neurologist versus an on-board vascular neurologist and found agreement in 88% of cases, suggesting reliability of telemedicine in MSUs [39•]. Bowry et al. directly compared times to decision and treatment with r-tPA using telemedicine versus on-board neurologist in MSUs and found similar result times and no delays with telemedicine assessment [40••]. Telemedicine enables vascular neurologists to cover multiple MSUs, which is more efficient and cost-effective as ambulances in a MSU networks increase [37••].

An ongoing concern for MSUs is the potential to treat more stroke mimics with r-tPA given faster symptom onset to evaluation times. In the PHANTOM-S cohort, 2% of r-tPA administrations were stroke mimics in comparison to 3.5% with conventional care [30]. These investigators were able to show that the MSU concept improved triage of patients with cerebrovascular disease with good diagnostic accuracy (sensitivity 89%, specificity 77%, positive predicative value (PPV) 79%, and negative predicative value (NPV) of 87%) comparable to the validation results of the Recognition of Stroke in the Emergency Room (ROSIER) scale used to differentiate acute strokes from mimics (sensitivity of 93%, specificity 83%, PPV 90%, and NPV 88%) [30, 41]. Based on the PHANTOM-S study, MSUs are able to reliably transport and treat confirmed stroke cases with comparable stroke mimic treatment rates as conventional care.

Functional Outcomes

In an observational study of the patients included in the PHANTOM-S trial and a subsequent registry, the primary outcome of a 90-day modified Rankin Score (mRS) of ≤1 for patients who received tPA on the MSU compared to conventional care nearly reached statistical significance (odds ratio (OR) 1.40, 95% confidence interval (CI) 1.00–1.97; $p = 0.052$) [42••]. Multiple pre-specified secondary outcomes were significantly positive in this study, including 90-day mortality and mRS ≤3 [45••].

Tsivgoulis et al. used the Safe Implementation of Treatment in Stroke- East (SITS-EAST) registry to compare the functional outcomes, mortality, and 90-day mRS of patients who received r-tPA within the "golden hour" on a MSU versus in the hospital via standard ambulance transport [43••]. In their analysis, 127 patients received thrombolysis within the golden hour on a MSU, and 136 patients received thrombolysis within the golden hour in the hospital; when compared, there were no significant differences in the rates of favorable functional outcome (OR 1.84; 95% CI, 0.86–3.96) [46••]. Given the known benefits of golden hour thrombolysis in the ED, these findings suggest that MSUs will be more likely to reach maximum effectiveness as more patients are treated in the golden hour.

Cost-Effectiveness

The costs of building and operating a MSU are significant. In the USA, the capital cost of a MSU is approximately $600,000 to $1,000,000, while operational costs (assuming 12 h daily schedules) are $950,000 to $1,200,000 annually [44]. There are two published studies examining the cost-effectiveness of MSU in Germany [45•, 46•]. Dietrich et al. modeled cost-benefit analyses using data from the first MSU clinical trial in 2012 [48•]. Within limitations of the modeling, they found the MSU model to be cost-effective across a variety of assumptions with a benefit-cost ratio of 1.96 [48•]. The benefit-cost ratios increased substantially with gradual reductions of staff, use of telemedicine, and with higher population density to maximum benefit-cost ratios between 2.16 and 6.85 [48•]. Gyrd-Hansen et al. analyzed the cost-effectiveness of the MSU in the PHANTOM-S trial and found that the annual cost of MSU operations was €963,954 ($1,071,299.92); however, the higher frequency of early r-tPA use on the MSU resulted in an annual expected health gain of avoidance of 18 cases of disability when compared to conventional care [49•]. Avoiding 18 cases of disability resulted in an improvement of 29.7 quality-adjusted life years (QALYs), leading to a calculated incremental cost-effectiveness ratio of €32,456 ($36,070.30) per QALY [49•]. As a reference, the willingness to pay by healthcare decision makers threshold is approximately €50,000 ($55,000), and cost-effectiveness of r-tPA has been shown to be $48,676 per QALY, indicating that MSU care in the PHANTOM-S trial was cost-effective by industry standards [47, 48, 49•]. Although preliminary studies have suggested tenable cost-effectiveness of MSUs, randomized clinical trials like BEST-MSU are needed to further explore this important aspect of pre-hospital stroke treatment.

Future Direction

MSUs may have the ability to further advance acute ischemic stroke treatment systems of care, including improved LVO detection, adjunctive therapies to r-tPA, novel thrombolytic agents, and early administration of neuroprotectants. MSU early stroke detection capability has opened up the possibility of improving diagnostic and triage capabilities by obtaining collateral information and medication reconciliation in addition to advanced neuroimaging within a pre-hospital acute stroke workflow. In the Cleveland Clinic MSU model, CTA was able to effectively triage LVO, resulting in substantial reduction of "door-to-puncture" time [32]. This has been further verified in the BEST-MSU sub-study data pre-analysis, which showed a 10-min improvement in ED door to groin puncture times in those patients transported on a MSU [35••]. Cerebral oximeters which use near-infrared spectroscopy can be mounted on-board a MSU to supplement clinical scores for LVO detection with >85% sensitivity [49••]. On-board TCDs could provide rapid assessment of cerebral hemodynamics, monitor recanalization in real time, and provide the potential for sonothrombolysis [50]. Improving pre-hospital LVO detection through any of these imaging modalities could increase triage accuracy of LVO patients directly to centers with endovascular capabilities. Furthermore, investigators in Toledo have recognized that there are distinct patterns for timing of activations of the MSU suggesting further study into optimization of operating shifts and allocation of resources that would improve overall diagnostic metrics and cost-effectiveness [51•].

Due to the high rate of golden hour intervention on MSUs, it may be prudent to revisit previous trials of acute stroke treatment to assess whether ultra-early initiation of therapy may produce incremental benefit beyond that of r-tPA alone. Prior studies including the argatroban r-tPA stroke study (ARTSS-2), combined approach to thrombolysis utilizing eptifibatide and recombinant tissue plasminogen activator in acute ischemic stroke enhanced regimen stroke trial (CLEAR-ER), and field administration of stroke therapy magnesium study (FAST-MAG) have all shown no significant improvement in functional outcome at 90 days [52–54]. However, the administration of adjunctive therapies was typically given greater than 1 hour from symptom onset. The Multi-arm Optimization of Stroke Thrombolysis (MOST) trial will be examining the functional outcomes of

Fig. 1. Photos of the NewYork-Presbyterian Mobile Stroke Treatment Unit (Copyright: NewYork-Presbyterian Hospital).

early administration of argatroban and eptifibatide in patients treated with r-tPA in acute ischemic stroke (NCT03735979). There may be opportunity to revisit these interventions with the utilization of the MSU networks, since pre-hospital thrombolysis for acute ischemic stroke has been found to be faster than conventional care.

Novel thrombolytic agents are currently being studied, and alternative routes of r-tPA administration have been recently documented. Tenecteplase was compared to alteplase in treatment of acute ischemic stroke and found that tenecteplase resulted in higher incidence of reperfusion and better functional outcome than alteplase [55]. Additionally, tenecteplase requires only a bolus, whereas alteplase requires a bolus and infusion. Therefore, tenecteplase could be more easily administered on the MSU without transfer of care issues during patient handoff at receiving hospitals. There have been multiple case reports of intraosseous r-tPA administered without adverse effects, which raises the question of the ideal or acceptable route of administration in the hyperacute period of stroke treatment [56].

MSUs can be further utilized for neurological emergencies other than acute ischemic stroke. Prior reports showed successful management of status epilepticus and acute intracerebral hemorrhage [28••, 30]. Acute intracerebral hemorrhage in patients using anti-coagulation remains problematic; however, with several reversal agents available, early administration is paramount in management. MSUs can be fitted with several reversal agents for

Table 1. Acute ischemic stroke treatment pathways of the mobile stroke unit compared to conventional stroke care via standard ambulance and emergency department management

Column1	*MSU*	*Standard ambulance*	*Emergency department*
Intervention			
Neurologic evaluation	Yes	Yes	Yes
Stroke diagnosis by MD	Yes	No	Yes
CT Head non-contrast	Yes	No	Yes
CT angiography head and neck	Yes	No	Yes
POC labs*	Yes	No	Yes
r-tPA administration	Yes	No	Yes
Cerebral oximeter application	Yes	No	Yes
Anti-epileptics** administration	Yes	No	Yes
Hypertension management	Yes	No	Yes
Anti-coagulation reversal	Yes	No	Yes
Triage to appropriate stroke center	Yes	Yes	No
Advanced notification to interventionists	Yes	No	No

*Excluding finger stick blood glucose
**Anti-epileptics excluding IV/IM/IO benzodiazepines

optimal management of intracerebral hemorrhage. Furthermore, the Recombinant Factor VIIa (rFVIIa) for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) trial will be assessing the use of rFVIIa in acute spontaneous intracerebral hemorrhage and will be utilizing the MSU and conventional care systems (NCT03496883). Enrollment in the FASTEST trial begins in 2020.

Lastly, in rural or remote areas where there is limited access to emergency medical services, there exists the potential to study alternative means of bringing the treatment to the patient. For example, establishing an Air-MSU by means of a specially designed aircraft with the ability to diagnose and treat acute ischemic stroke has been proposed [57••]. This concept of aeronautical doctoring is already in place in Australia as the Royal Flying Doctors Service which increases the catchment area through use of specialty aircraft, thus bringing emergency services to difficult to access populations faster [58]. Expanding this service to include a CT scanner, telemedicine, and acute medical interventions could be potentially proposed and further studied. Additionally, a rendezvous system, where a MSU meets a second ambulance halfway between the base location and the patient pick-up location, could expand the catchment area for pre-hospital thrombolysis.

Conclusion

MSUs bring acute stroke treatment directly to patients and are able to administer r-tPA 30 min faster than standard care. MSUs are able to treat a higher proportion of patients in the hyperacute “golden hour.”

While initial studies have not shown improved functional outcomes with MSUs, clinical trials are still ongoing, and the potential for pooled analyses from international collaboration is growing. MSUs have been suggested to be cost-effective in retrospective analyses. The MSU model could offer further areas of research in acute ischemic stroke diagnosis, treatment, and pre-hospital triage. Fig 1 and Table 1

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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