Mobile Stroke Units Becoming More Common Despite Cost-effectiveness Questions

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FRONTLINE MEDICAL NEWS

Mobile stroke units—specially equipped ambulances that bring a diagnostic computed tomography (CT) scanner and therapeutic thrombolysis directly to patients in the field—have begun to proliferate across the United States, although they remain investigational, with no clear proof of their incremental clinical value or cost-effectiveness.

The first US mobile stroke unit (MSU) launched in Houston, Texas in early 2014 (following the world's first in Berlin, Germany, which began running in early 2011), and by early 2017, at least eight other US MSUs were in operation, most of them put into service during the prior 15 months. United States MSU locations now include Cleveland, Ohio; Denver, Colorado; Memphis, Tennessee; New York, New York; Toledo, Ohio; Trenton, New Jersey; and Northwestern Medicine and Rush University Medical Center in the western Chicago, Illinois region. A tenth MSU is slated to start operation at the University of California, Los Angeles later this year.

Early data collected at some of these sites show that initiating care of an acute ischemic stroke patient in an MSU shaves precious minutes off the time it takes to initiate thrombolytic therapy with tissue plasminogen activator (tPA), and findings from preliminary analyses suggest better functional outcomes for patients treated this way. However, leaders in the nascent field readily admit that the data needed to clearly prove the benefit patients receive from operating MSUs are still a few years off. This uncertainty about the added benefit to patients from MSUs couples with one clear fact: MSUs are expensive to start up, with a price tag of roughly $1 million to get an MSU on the road for the first time; they are also expensive to operate, with one estimate for the annual cost of keeping an MSU on the street at about $500,000 per year for staffing, supplies, and other expenses.

"Every US MSU I know of started with philanthropic gifts, but you need a business model" to keep the program running long-term, James C. Grotta, MD, said during a session focused on MSUs at the International Stroke Conference sponsored by the American Heart Association. "You can't sustain an MSU with philanthropy," said Dr Grotta, professor of neurology at the University of Texas Health Science Center in Houston,

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Dr James C. Grotta answers questions about the Houston mobile stroke unit during the 2015 International Stroke Conference.

director and founder of the Houston MSU, and acknowledged "godfather" of all US MSUs.

"We believe that MSUs are very worthwhile and that the clinical and economic benefits of earlier stroke treatment [made possible with MSUs] could offset the costs, but we need to show this," admitted May Nour, MD, a vascular and interventional neurologist at the University of California, Los Angeles (UCLA), and director of the soon-to-launch Los Angeles MSU.

The concept behind MSUs is simple: Each one carries a CT scanner on board so that once the vehicle's staff identifies a patient with clinical signs of a significant-acute ischemic stroke in the field and confirms that the timing of the stroke onset suggests eligibility for tPA treatment, a CT scan can immediately be run on-site to finalize tPA eligibility. The MSU staff can then begin infusing the drug in the ambulance as it speeds the patient to an appropriate hospital.

In addition, many MSUs now carry a scanner that can perform a CT angiogram (CTA) to locate the occluding clot. If a large vessel occlusion is found, the crew can bring the patient directly to a comprehensive stroke center for a thrombectomy. If thrombectomy is not appropriate, the MSU crew may take the patient to a primary stroke center where thrombectomy is not available.

Another advantage to MSUs, in addition to quicker initiation of thrombolysis, is "getting patients to where

they need to go faster and more directly," said Dr Nour.

"Instead of bringing patients first to a hospital that's unable to do thrombectomy and where treatment gets slowed down, with an MSU you can give tPA on the street and go straight to a thrombectomy center," agreed Jeffrey L. Saver, MD, professor of neurology and director of the stroke unit at UCLA. "The MSU offers the tantalizing possibility that you can give tPA with no time hit because you can give it on the way directly to a comprehensive stroke center," Dr Saver said during a session at the meeting.

Early Data on Effectiveness

Dr Nour reported some of the best evidence for the incremental clinical benefit of MSUs based on the reduced time for starting a tPA infusion. She used data the Berlin group published in September 2016 that compared the treatment courses and outcomes of patients managed with an MSU to similar patients managed by conventional ambulance transport for whom CT scan assessment and the start of tPA treatment did not begin until the patient reached a hospital. The German analysis showed that, in the observational Pre-hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients–Study (PHANTOM-S), among 353 patients treated by conventional transport, the median time from stroke onset to thrombolysis was 112 minutes, compared with a median of 73 minutes among 305 patients managed with an MSU, a statistically significant difference.[1] However, the study found no significant difference for its primary endpoint: the percentage of patients with a modified Rankin Scale score of 1 or lower when measured 90 days after their respective strokes. This outcome occurred in 47% of the control patients managed conventionally and in 53% of those managed by an MSU, a difference that fell short of statistical significance

Dr Nour attributed the lack of statistical significance for this primary endpoint to the relatively small number of patients enrolled in PHANTOM-S. "The study was underpowered," she said.

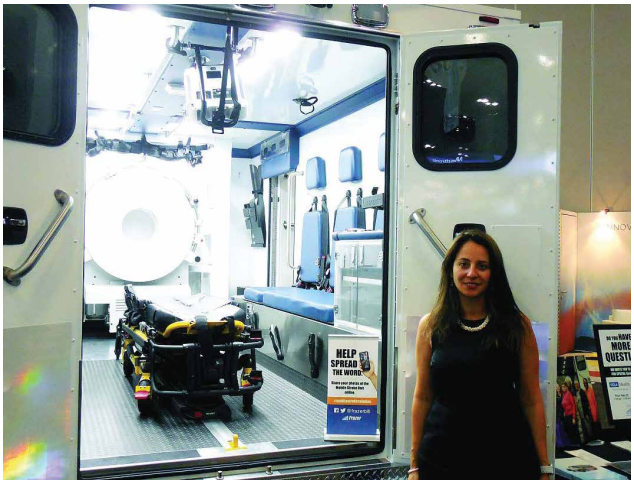
Dr Nour presented an analysis at the meeting that extrapolated the results out to 1,000 hypothetical patients and tallied the benefits that a larger number of patients could expect to receive if their outcomes paralleled those seen in the published results. It showed that among 1,000 stroke patients treated with an MSU, 58 were expected to be free from disability 90 days later, and an additional 124 patients would have some improvement in their 90-day clinical outcome based on their modified Rankin Scale scores when compared with patients undergoing conventional hospitalization.

"If this finding was confirmed in a larger, controlled study, it would suggest that MSU-based thrombolysis has substantial clinical benefit," she concluded.

Another recent report looked at the first 100 stroke patients treated by the Cleveland MSU during 2014. Researchers at the Cleveland Clinic and Case Western Reserve University said that 16 of those 100 patients received tPA, and the median time from their emergency call to thrombolytic treatment was 38.5 minutes faster than for 53 stroke patients treated during the same period at EDs operated by the Cleveland Clinic, a statistically significant difference.[2] However, this report included no data on clinical outcomes.

Running the Financial Numbers

Nailing down the incremental clinical benefit from MSUs is clearly a very important part of determining the value of this strategy, but another very practical concern is how much the service costs and whether it is financially sustainable.



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Dr May Nour and the UCLA mobile stroke unit that will soon hit the roads of Los Angeles.

"We did a cost-effectiveness analysis based on the PHANTOM-S data, and we were conservative by only looking at the benefit from early tPA treatment," Heinrich J. Audebert, MD, professor of neurology at Charité Hospital in Berlin and head of the team running Berlin's MSU, said during the MSU session at the meeting. "We

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did not take into account saving money by avoiding long-term stroke disability and just considered the cost of [immediate] care and the quality-adjusted life years. We calculated a cost of $35,000 per quality-adjusted life year, which is absolutely acceptable."

He cautioned that this analysis was not based on actual outcomes but on the numbers needed to treat calculated from the PHANTOM-S results. "We need to now show this in controlled trials," he admitted.

During his talk at the same session, Dr Grotta ran through the numbers for the Houston program. They spent $1.1 million to put their MSU into service in early 2014, and, based on the expenses accrued since then, he estimated an annual staffing cost of about $400,000 and an annual operating cost of about $100,000, for a total estimated 5-year cost of about $3.6 million. Staffing of the Houston MSU started with a registered nurse, CT technician, paramedic, and vascular neurologist, although, like most other US MSUs, the onboard neurologist has since been replaced by a second paramedic, and the neurological diagnostic consult is done via a telemedicine link.

Income from transport reimbursement, currently $500 per trip, and reimbursements of $17,000 above costs for administering tPA and of roughly $40,000 above costs for performing thrombectomy, are balancing these costs. Based on an estimated additional one thrombolysis case per month and one additional thrombectomy case per month, the MSU yields a potential incremental income to the hospital running the MSU of about $3.8 million over 5 years—enough to balance the operating cost, Dr Grotta said.

A key part of controlling costs is having the neurological consult done via a telemedicine link rather than by neurologist at the MSU. "Telemedicine reduces operational costs and improves efficiency," noted M. Shazam Hussain, MD, interim director of the Cerebrovascular Center at the Cleveland Clinic. "Cost-effectiveness is a very important part of the concept" of MSUs, he said at the session.

The Houston group reported results from a study that directly compared the diagnostic performance of an onboard neurologist with that of a telemedicine neurologist linked-in remotely during MSU deployments for 174 patients. For these cases, the two neurologists each made an independent diagnosis that the researchers then compared. The two diagnoses concurred for 88% of the cases, Tzu-Ching Wu, MD, reported at the meeting. This rate of agreement matched the incidence of concordance between two neurologists who independently assessed the same patients at the hospital,[3] said Dr Wu, a vascular neurologist and director of the telemedicine program at the University of Texas Health Science Center in Houston.

"The results support using telemedicine as the primary means of assessment on the MSU," said Dr Wu. "This may enhance MSU efficiency and reduce costs." His group's next study of MSU telemedicine will compare the time needed to make a diagnostic decision using the two approaches, which Dr Wu reported was something not formally examined in the study.

However, telemedicine assessment of CT results gathered in an MSU has one major limitation: the time needed to transmit the huge amount of information from a CTA.

The MSU used by clinicians at the University of Tennessee, Memphis, incorporates an extremely powerful battery that enables "full CT scanner capability with a moving gantry," said Andrei V. Alexandrov, MD, professor and chairman of neurology at the university. With this set up "we can do in-the-field multiphasic CT angiography from the aortic arch up within 4 minutes. The challenge of doing this is simple. It's 1.7 gigabytes of data," which would take a prohibitively long time to transmit from a remote site, he explained. As a result, the complete set of images from the field CTA is delivered on a memory stick to the attending hospital neurologist once the MSU returns.

Waiting for More Data

Despite these advances and the steady recent growth of MSUs, significant skepticism remains. "While mobile stroke units seem like a good idea and there is genuine hope that they will improve outcomes for selected stroke patients, there is not yet any evidence that this is the case," wrote Bryan Bledsoe, DO, in a January 2017 editorial in the *Journal of Emergency Medical Services*. "They are expensive and financially nonsustainable. Without widespread deployment, they stand to benefit few, if any, patients. The money spent on these devices would be better spent on improving the current EMS system, including paramedic education, the availability of stroke centers, and on the early recognition of ELVO [emergent large vessel occlusion] strokes," wrote Dr Bledsoe, professor of emergency medicine at the University of Nevada in Las Vegas.

Two other experts voiced concerns about MSUs in an editorial that accompanied a Cleveland Clinic report

in March.[4] "Even if MSUs meet an acceptable societal threshold for cost-effectiveness, cost-efficiency may prove a taller order to achieve return on investment for individual health systems and communities," wrote Andrew M. Southerland, MD, and Ethan S. Brandler, MD. They cited the Cleveland report, which noted that the group's first 100 MSU-treated patients came from a total of 317 MSU deployments and included 217 trips that were canceled prior to the MSU's arrival at the patient's location. In Berlin's initial experience, more than 2,000 MSU deployments led to 200 tPA treatments and 349 cancellations before arrival, noted Dr Southerland, a neurologist at the University of Virginia in Charlottesville, and Dr Brandler, an emergency medicine physician at Stony Brook (NY) University.

"Hope remains that future trials may demonstrate the ultimate potential of mobile stroke units to improve long-term outcomes for more patients by treating them more quickly and effectively. In the meantime, ongoing efforts are needed to streamline MSU cost and efficiency," they wrote.

Proponents of MSUs agree that what's needed now are more data to prove efficacy and cost-effectiveness, as well as better integration into EMS programs. The first opportunity for documenting the clinical impact of MSUs on larger numbers of US patients may be from the BEnefits of Stroke Treatment Delivered using a Mobile Stroke Unit Compared to Standard Management by Emergency Medical Services (BEST-MSU) Study, funded by the Patient-Centered Outcomes Research Institute. This study is collecting data from the MSU programs in Denver, Houston, and Memphis. Although currently designed to enroll 697 patients, Dr Grotta said he hopes to bring the number up to 1,000 patients.

"We are following the health care use and its cost for every enrolled MSU and conventional patient for 1 year," Dr Grotta explained in an interview. He hopes these results will provide the data needed to move MSUs from investigational status to routine and reimbursable care.

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Pulmonary Embolism Common in Patients With Acute Exacerbations of COPD

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FRONTLINE MEDICAL NEWS

About 16% of patients with unexplained acute exacerbations of chronic obstructive pulmonary disease (AECOPD) had an accompanying pulmonary embolism (PE), usually in regions that could be targeted with anticoagulants, according to a new systematic review and meta-analysis.

Approximately 70% of AECOPD cases develop in response to an infection, but about 30% of the time, an AE has no clear cause, the authors said in a report on their research. There is a known biological link between inflammation and coagulation, which suggests that patients experiencing AECOPD may be at increased risk of PE.

The researchers reviewed and analyzed seven studies, comprising 880 patients. Among the authors' reasons for conducting this research was to update the pooled prevalence of PE in AECOPD from a previous systematic review published in *Chest* in 2009.

The meta-analysis revealed that 16.1% of patients with AECOPD were also diagnosed with PE (95% confidence interval [CI], 8.3%-25.8%). There was a wide range of variation between individual studies (prevalence 3.3%-29.1%). In six studies that reported on deep vein thrombosis (DVT), the pooled prevalence of DVT was 10.5% (95% CI, 4.3%-19.0%).

Five of the studies identified the PE location. An analysis of those studies showed that 35% were in the main pulmonary artery, and 31.7% were in the lobar and interlobar arteries. Such findings "[suggest] that the majority of these embolisms have important clinical consequences," the authors wrote.

The researchers also looked at clinical markers that accompanied AECOPD and found a potential signal with respect to pleuritic chest pain. One study found a strong association between pleuritic chest pain and AECOPD patients with PE (81% vs 40% in those without PE). A second study showed a similar association (24% in PE vs 11.5% in non-PE patients), and a third study found no significant difference.

The presence of PE was also linked to hypotension, syncope, and acute right failure on ultrasonography, suggesting that PE may be associated with heart failure.

Patients with PE were less likely to have symptoms consistent with a respiratory tract infection. They also tended to have higher mortality rates and longer hospitalization rates compared with those without PE.

The meta-analysis had some limitations, including the heterogeneity of findings in the included studies, as well as the potential for publication bias, since reports showing unusually low or high rates may be more likely to be published, the researchers noted. There was also a high proportion of male subjects in the included studies.

Overall, the researchers concluded that PE is more likely in patients with pleuritic chest pain and signs of heart failure, and less likely in patients with signs of a respiratory infection. That information "might add to the clinical decision-making in patients with an AECOPD, because it would be undesirable to perform [CT pulmonary angiography] in every patient with an AECOPD," the researchers wrote.

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Norepinephrine Shortage Linked to Mortality in Patients With Septic Shock

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FRONTLINE MEDICAL NEWS

A national shortage of norepinephrine in the United States was associated with higher rates of mortality among patients hospitalized with septic shock, investigators reported.

Rates of in-hospital mortality in 2011 were 40% during quarters when hospitals were facing shortages and 36% when they were not, Emily Vail, MD, and her associates said at the International Symposium on Intensive Care and Emergency Medicine. The report was published simultaneously in *JAMA*.

The link between norepinephrine shortage and death from septic shock persisted even after the researchers accounted for numerous clinical and demographic factors (adjusted odds ratio, 1.2; 95% CI, 1.01 to 1.30; $P = .03$), wrote Dr Vail of Columbia University, New York.

Drug shortages are common in the United States, but few studies have explored their effects on patient outcomes. Investigators compared mortality rates among affected patients during 3-month intervals when hospitals were and were not using at least 20% less norepinephrine than baseline. The researchers used Premier Healthcare Database, which includes both standard claims and detailed, dated logs of all services billed to patients or insurance, with minimal missing data.

A total of 77% patients admitted with septic shock received norepinephrine before the shortage. During the lowest point of the shortage, 56% of patients received it, the researchers reported. Clinicians most often used phenylephrine instead, prescribing it to up to 54% of patients during the worst time of the shortage. The absolute increase in mortality during the quarters of shortage was 3.7% (95% CI, 1.5%-6.0%).

Several factors might explain the link between norepinephrine shortage and mortality, the investigators said. The vasopressors chosen to replace norepinephrine might result directly in worse outcomes, but a decrease in norepinephrine use also might be a proxy for relevant variables such as delayed use of vasopressors, lack of knowledge of how to optimally dose vasopressors besides norepinephrine, or the absence of a pharmacist dedicated to helping optimize the use of limited supplies.

The study did not uncover a dose-response association between greater decreases in norepinephrine use and increased mortality, the researchers noted. "This may be due to a threshold effect of vasopressor shortage on mortality, or lack of power due to relatively few hospital quarters at the extreme levels of vasopressor shortage," they wrote.

Because the deaths captured included only those that occurred in-hospital, "the results may have underestimated mortality, particularly for hospitals that tend to transfer patients early to other skilled care facilities," the researchers noted.

The cohort of patients was limited to those who received vasopressors for 2 or more days and excluded patients who died on the first day of vasopressor treatment, the researchers said.

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