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Mobile stroke units: filling gaps in prehospital stroke care

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MOBILE STROKE UNITS:

FILLING GAPS IN PREHOSPITAL STROKE CARE

by

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ABSTRACT

Acute ischemic stroke (AIS) is a major cause of death and disability in the United States. With advancements in therapeutic reperfusion, it has become clear that improving time-to-treatment is among the most important factors in yielding better outcomes for patients. When AIS occurs in the community, away from readily available interventions, timely recognition and transport are paramount to decreasing the time-to-treatment and ultimately increasing rates of reperfusion and reducing morbidity and mortality.

Over the past several years, investigations have launched studying the efficacy of mobile stroke units (MSU) in reducing the morbidity and mortality burden of AIS. MSUs are specially designed transport vehicles, run by trained expert stroke management personnel, and stocked with diagnostic imaging equipment in the form of computed tomography scanners and fibrinolytic therapy. In a number of prospective study designs comparing MSUs to standard management by emergency medical services, researchers have utilized several endpoints including time-to-treatment, rates of symptom resolution, and long-term recovery from AIS. These studies have generally demonstrated better outcomes with MSUs and provided evidence for the efficacy of the MSU model in treating AIS. However, most studies have been limited to metropolitan regions of the country, and no randomized-controlled trials have been completed, although one is currently underway.

There is little evidence, however, evaluating the cost-effectiveness of MSUs in the management of AIS. The expense of constructing and operating these specialized vehicles over ten years has been estimated to be millions of dollars, while the cost of a single case of AIS can range anywhere from the cost of the emergency department visit to the inclusion of long-term care from resultant sequelae depending on the patient outcome. It remains unclear to what degree the upfront investment in quicker management for AIS is capable of producing downstream cost savings for the healthcare system in the setting of demonstrated improved outcomes.

In this study, I propose a method of cost-effectiveness analysis to compare the MSU model to standard management of AIS occurring in metropolitan communities to determine whether MSUs are cost-effective, or possibly cost-saving.

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LIST OF ABBREVIATIONS

AIS	Acute Ischemic Stroke
ACLS	Advanced Cardiac Life Support
BLS	Basic Life Support
CEA	Cost-effectiveness Analysis
CSC	Comprehensive Stroke Center
CT	Computed Tomography
ED	Emergency Department
EMS	Emergency Medical Services
LVO	Large-vessel Occlusion
mRS	Modified Rankin Scale
MRI	Magnetic Resonance Imaging
MSU	Mobile Stroke Unit
PSC	Primary Stroke Center
RN	Registered Nurse
SM	Standard Management
tPA	Tissue Plasminogen Activator
uw-mRS	Utility-Weighted Modified Rankin Scale
VN	Vascular Neurologist

INTRODUCTION

Background

Stroke is the fifth leading cause of death and a significant source of adult disability in the United States.[1,2] The repercussions of stroke can be monumental, both to the patient and the medical system. Morbidity from ischemic stroke is common, often leading to an increased reliance on the healthcare system for the remainder of a patient's life. As a result, the enormous burden of stroke is carried by the patient, their family, and the many facets of the medical system involved in their resultant acute, and potentially chronic, healthcare needs.

Within the past decade, researchers have explored bringing the emergency department to the patient. By equipping ambulatory care vehicles with computed tomography (CT) scanners and qualified personnel to identify and treat cases of acute ischemic stroke (AIS), mobile stroke units (MSU) are currently under investigation as a means to diagnose, differentiate, and manage AIS in the field. However, questions still circulate around the feasibility of this new model given the high startup and operational costs.

Statement of the Problem

Negative outcomes of AIS can be mitigated if the underlying etiology is identified, properly triaged, and/or managed earlier in the chain of care during the prehospital stroke response. While hospital management of stroke has undergone optimization since the introduction of definitive treatments for AIS to reduce the time-to-treatment, prehospital stroke management has remained largely unchanged over the same period.

Patient deterioration during transport time, or upon reception at an inappropriate facility incapable of definitive treatment, has the potential for life-altering and costly sequelae. While evidence in favor of MSU efficacy is accumulating, their high upfront and operational costs remain barriers to their ubiquitous usage.

Hypothesis

Mobile stroke units provide a cost-effective adjunct to hospital management of AIS as compared to traditional transport by ambulance.

Objectives and specific aims

We set out to propose methods for determining parameter ranges at which MSUs reach threshold cost-effectiveness and/or cost-savings as an adjunct to hospital management of AIS.

Specific aims are to:

- Explore the evidence of MSU efficacy compared to traditional hospital transport in the setting of AIS and the impact of early intervention on recovery from AIS
- Propose models of threshold cost-effectiveness analysis that can be run with evidence both currently available as well as future data still under investigation

REVIEW OF THE LITERATURE

Overview

Stroke is the fifth leading cause of death and carries a significant burden of morbidity in the United States.[1,2] While preventative measures like statins and antihypertensives have contributed to a decrease in the rates of new and recurrent stroke in recent years, stroke remains a major cause of preventable mortality.[3]

Stroke is a neurologic emergency defined by the loss of blood flow to a region of brain tissue secondary to either upstream vascular occlusion (acute ischemic stroke [AIS]) or bleed (acute hemorrhagic stroke).[4] In both etiologies of stroke, neuronal infarct begins over the course of minutes and continues until either: a) perfusion is restored or b) tissue regionally supplied by the non-perfused blood vessel(s) is entirely infarcted.

Community cases of stroke are first identified in the emergency department (ED). Standard management of stroke relies on a clinical diagnosis of stroke symptoms, followed by CT or magnetic resonance imaging (MRI) of the head to assess for the presence or absence of intracranial blood to differentiate ischemic and hemorrhagic etiology.[5] If hemorrhage is ruled out by imaging, and barring any contraindication, tissue plasminogen activator (tPA) can be administered to promote lysis of the fibrin clot suspected of blocking cerebral perfusion. In the case of a large vessel occlusion (LVO), tPA alone is often insufficient management, necessitating recanalization by neurovascular thrombectomy.[6]

Although advances in medical and surgical treatment options to recanalize ischemic blood vessels have dramatically improved stroke care, outcomes of stroke that occur in the community are negatively impacted by time lost to transport to the hospital for definitive care. Outcomes from AIS have markedly improved following the introduction of tPA and the advent of neurovascular thrombectomy, in the case of LVO.[6,7]

However, time elapsed from the onset of stroke symptoms until reception at an appropriate facility capable of definitive treatment remains a major limiting factor for further improvement of post-AIS outcomes. Under current prehospital care, emergency medical services (EMS) receive a call to 911 from the community describing symptoms typical for a possible stroke, and an ambulance is dispatched with basic and/or advanced cardiac life support (BLS/ACLS) providers to respond, assess, and transport the patient to the nearest receiving facility based on field triage. Research has shown that tPA efficacy markedly decreases 270 minutes from the onset of symptoms.[5] This window of time birthed the expression "time is brain," which echoes how crucial the period is in the timely recognition, triage, and treatment of stroke to prevent the progression of neuronal infarction, and ultimately preservation of brain function.

In an attempt to shorten this timeframe, several studies have been launched over the past few years to investigate the benefit of early prehospital intervention. Researchers have outfitted ambulances with the imaging and staff necessary to recognize and manage cases of AIS. Currently, mobile stroke units (MSUs) are under investigation as a means to diagnose, differentiate, and manage AIS in the field.

Existing research

The first MSU was established in the United States in 2013 by Parker, et. al..[8] Over the course of approximately twelve months, researchers fund-raised, built, integrated, and launched an MSU in metropolitan Houston, Texas. Over the following twelve months, a staff comprised of a neurology-trained nurse, two Houston-licensed paramedics, one in-person vascular neurologist (VN), and one telemedically-linked VN responded to over one hundred calls for stroke-like symptoms from the Houston dispatch office for EMS. The data recorded during the trial included elapsed time from when the patient first contacted EMS (called 911) to the administration of tPA, as well as the door-to-puncture time for percutaneous neurovascular thrombectomy in the case of LVO.

By expediting the speed with which patients are able to receive a head CT scan during hyper-acute stroke, the Houston MSU was able to identify AIS reliably in the field, leading to quicker administration of tPA, shorter door-to-puncture times for patients experiencing LVO, and ultimately better long term outcomes for MSU-managed stroke patients.[8] Patients' recovery from stroke symptoms was logged on the modified Rankin scale (mRS) where a score of 0-2 represents functional independence (**Table 1)**.[9] Within the study, mRS was 0-1 in 33% of patients, greater than 1 in 23% of cases, and within 1 point of baseline for 58% of patients with previously identified comorbidities affecting their function. In regards to whether recovery was improved in MSU-treated patients, Parker., et. al. did not include comparative recovery data for patients treated by standard management (SM) via conventional ambulance. At the time of publication, the study was not designed to answer that question which would be better addressed by a two-armed trial comparing MSU to SM.

Table 1. Modified Rankin scale.[9]

Score	Clinical significance
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assitance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk or attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Deceased

The nearest point of comparison might come from a retrospective study out of Berlin that compared data from 427 MSU-treated patients to 505 patients who received SM via conventional ambulance transport.[10] Researchers observed when examining the ratio of patients with a mRS score of 1 or lower, there was no significant statistical difference between those receiving MSU care compared to SM. However, the authors concluded that functional outcomes may still be improved by starting thrombolytics in the field prior to reception at a hospital. Due to the differences in the study populations and the omission of baseline mRS in the study by Kunz, et. al., the data of the two studies cannot be directly compared. As Kunz, et. al. suggested in their conclusion, a prospective, double-blind trial remains the best vehicle for comparing management by MSU and SM in order to generate higher quality MSU recovery data.

A short-coming of the Parker, et. al. study was the indeterminate efficacy of telemedicine alone aboard the MSU. Telemedicine is a long-term goal the authors posit would contribute greatly to the cost-effectiveness and feasibility of MSUs in general. By eliminating the need for a dedicated VN aboard the MSU, medical resources could be more efficiently allocated over the entire healthcare network. Over the course of their study, the in-person vascular neurologist and the remote, telemedically-linked VN agreed on the etiology of the strokes in 91% of cases.[8] At the time of publication, research was ongoing to determine whether telemedicine could reliably replace in-person vascular neurologist.

A challenge the researchers encountered concerned construction of the MSU; the CT scanner adopted for use aboard the MSU faced difficulty moving along its tracks when the ambulance was on an incline.[8] The authors note this was rarely encountered on the flat streets of Houston and so did not impact patient care, however, the generalizability of this blueprint for future MSUs operating in geographically disparate regions of the country is called into question. Additional engineering may be necessary to adapt conventional CT scanners for use in an ambulatory setting that can be subject to forces not seen in stationary radiology labs.

An ongoing challenge for Parker et. al. at the time of publication was the communication network between the MSU and the Houston EMS system. EMS dispatch is the first link in the chain of prehospital care and, as such, the sensitivity of its stroke triaging determines broadly which patients will be seen by the MSU as opposed to managed by conventional ambulance. In this study, the MSU staff received calls from Houston EMS dispatch when their triaging algorithm determined stroke was possible.[6] In addition to calls received from dispatch, the MSU directly communicated with EMS paramedics in the field to recruit new patients into the study. Paramedics would inform the MSU of patients who they concluded met Houston EMS criteria for stroke on-scene (home, work, etc.) but were not originally dispatched as patients with symptoms concerning for stroke.[8] Authors argued that within an iteration of the EMS system that comprehensively includes the MSU, there would be additional opportunities to intercept patients experiencing possible strokes that may not have been identified by the dispatcher.

Furthermore, there remains a question about generalizing the results of this study which looked at the Houston metropolitan area to rural parts of the country, or more congested cities, where prehospital dispatch-to-door times may vary. In rural areas, the distances covered by ambulances could eclipse those discussed in this study ten times over.[8] In these settings, the authors suggest that MSUs could function as a rendezvous service for conventional ambulances that depart the scene of a stroke before the MSU can arrive.[8] In this way, patients who experience AIS in rural areas would be candidates for either intravenous tPA by the MSU, or in the case of an LVO discovered on CT angiography, advanced triage to a comprehensive stroke center (CSC) where neurovascular thrombectomy can be performed.

A weakness arose in the evaluation of the total and running costs of the MSU project. Parker et. al. included estimates for the ambulance, telemedical equipment, CereTom CT scanner, and standard ALS outfitting but excluded the costs of staffing and tPA (supplied by Genentech). The authors explain that staffing costs were excluded because, as opposed to the six members staffing their trial MSU, they expect that future iterations could evolve to include just a three-person combination of paramedics, EMTs, and a trained nurse to operate the CT scanner, report with the remote VN, and assist with patient care.[8] Similarly, the cost of tPA was excluded on the premise that a practical net cost could not be evaluated without a structure for reimbursement for the drug. While these costs were indeed moving targets at the time of publication, the cost analysis of launching and operating an MSU remained incomplete at the conclusion of the study.

In 2017, Fassbender et. al. published a large scale meta-analysis to investigate the benefits and challenges MSUs have faced since the establishment of the first MSU in Houston in 2013.[11] The authors of this meta-analysis, which looked at eleven independent studies, agreed with the Parker et. al. finding that time-to-treat was reduced in MSU-managed patients. The authors found that "bringing the hospital to the patient" in the form of an MSU shortened patients' time-to-treatment compared to SM by ambulance transport, followed by EMS handoff to the ED, non-contrast CT scan in a radiology lab, CVA triaging and treatment or transport to a more appropriate facility capable of neurovascular thrombectomy (comprehensive stroke center) in the case of LVO.[11] Whether patients were treated with a) tPA in eligible cases of AIS, b) blood pressure modification and/or Warfarin reversal for intracranial hemorrhage (ICH), or c) definitive intra-arterial treatment in case of LVO at a CSC, the median time-to-treat was quicker in MSU-managed cases compared to SM cases.[11] The authors cited a reduction in the time from onset of symptoms to treatment of 72 minutes using MSUs compared to times in excess of 120 minutes in previous studies on prehospital stroke management.

In addition to providing patients with quicker access to non-contrast CT scans for detection of AIS, investigators found MSUs benefited some patients experiencing LVO due to access to CT angiography. Patients receiving SM for AIS are triaged using one of many existing prehospital stroke scales that help determine whether the patient's symptoms are due to true CVA (as opposed to a stroke mimic) and the etiology of the stroke to guide treatment. Compared to clinically useful stroke scales for predicting the presence or absence of LVO, CT angiography is favored due to better sensitivity and specificity in its detection.[11] Fassbender et. al. discuss several internationally utilized stroke scales including the Los Angeles Motor Scale, Rapid Arterial Occlusion Evaluation scale, Field Assessment Stroke Triage for Emergency Destination scale, and Prehospital Acute Stroke Severity scale which have varying levels of sensitivity and specificity; however, they report that all research suggests a significant number of LVOs are not discovered by clinical scores. In turn, the authors make the case that given its gold-standard levels of sensitivity and specificity in the case of LVO, CT angiography allows for the best possible triage for patients experiencing stroke to the most appropriate receiving facility.

Under the traditionally accepted time-is-brain framework, any decrease in the delay to definitive treatment has the potential to improve outcomes. Fassbender, et. al.

cite results from the PHANTOM-S trial in which patients found to have LVO were transported to a hospital unequipped to intervene with neurosurgery at a 32% decreased rate when transported by MSU compared to SM with a conventional ambulance.[11]

Treatment teams at receiving hospitals could also be equipped to treat stroke mimics earlier with the aid of an accurate diagnosis via a CT scan obtained during transport. Fassbender, et. al. postulate that MSUs may have the uninvestigated secondary benefit of identifying conditions that mimic stroke such status epilepticus and traumatic brain injury.[11] As with the management of LVO, prehospital imaging has demonstrated its aid in triaging these patients to facilities with appropriately staffed neurology departments and diverting from others that are incapable of managing them.

Additionally, the authors regard telemedicine as an important tool to reduce staffing demands and increase cost-effectiveness of future MSUs. In an additional study cited by the investigators authored by Wu et. al., an agreement rate of 88% was found between remote vascular neurologists and onboard VNs compared to the 91% agreement rate observed by Parker et. al. in the first established MSU in Houston.[8,12] Fassbender et. al. point out the rate of agreement between the VNs is the same as that observed between two hospital-based VNs seeing the same patients for live evaluation in the emergency department.[11] With equal comparability and a 98% satisfaction rate for the connection quality of the telemedical technology used in the study, the authors assert that “absolutely reliable telecommunication connectivity” allows for the replacement of an in-person VN with one remotely linked by telemedicine.[11]

While telemedicine appears increasingly reliable and effective at filling the role of an in-person VN, an issue remains with their argument -- 98% satisfactory connectivity is not the same as absolute reliability. The authors do not address the discrepancy, presumably because the difference is subjectively small; however, any disparity between in-person and remote VN evaluation leaves room for incongruent stroke management and different clinical outcomes for patients. A remaining question from the Fassbender, et. al. study is whether the cost-savings offered by a remote VN increases the availability of the MSU model so that more patients ultimately receive the service than are denied it due to dissatisfactory telemedicine connections.

Furthermore, Fassbender, et. al. note the research potential that MSUs provide in the form of a rolling neurology laboratory. Take for instance transcranial ultrasound, which has demonstrated promise for identifying certain subsets of CVAs, as well as some stroke mimics.[13] With a CT scanner, MSU researchers are able to diagnose or rule out AIS in the hyper-acute phase of symptoms and are, thus, better able to study other cutting-edge diagnostic techniques for the detection of these and other acute neurological disorders rarely encountered in inpatient and ED populations.

In a discussion of the long-term clinical outcomes of patients treated with tPA onboard MSUs, the authors report mixed results. According to Fassbender, et. al., there was no difference in 7-day mRS and National Institutes of Stroke Scale (NIHSS) scores observed in the initial randomized trial conducted by Walter et. al.; however, Fassbender et. al. state that the study was not appropriately powered to detect a significant difference in these measures.[11,14] In a later study conducted on 90-day mRS data obtained from 2011 to 2015, Fassbender et. al. report that the raw data did not demonstrate a significant recovery benefit, as measured by 90-day mRS scores of 0 or 1. This was particularly surprising because 37% of the 305 patients treated aboard MSUs received thrombolytic therapy within 60 minutes of symptom onset.[11] However, they argue that when the groups were adjusted for population differences the MSU-treated population had better rates of recovery. Fassbender et. al. exposed a potential weakness in their analysis by not discussing the methods used by the authors of that study to standardize the two groups, as any heterogeneity in the study arms may bias the results. Ultimately, Fassbender et. al. determined that additional evidence in the form of controlled trials are required to accurately compare clinical outcomes of patients receiving care by MSU and SM.

In an effort to produce more robust evidence comparing MSU care to standard management (SM), a prospective, multicenter cluster-randomized trial was started in 2015 in Houston, TX to explore clinical outcomes and cost-effectiveness of MSUs. This trial, authored by Yamal et. al. and dubbed Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU), was designed to recruit tPA-eligible patients from as many as twenty operating MSU sites across the United States into two arms: those managed by an MSU and those receiving SM by conventional ambulance transport to the most appropriate receiving facility.

Sample size was determined in order to power the study to detect differences in 90-day recovery reported in a utility weighted modified Rankin scale (uw-mRS), which incorporates important quality of life metrics based on patient perception.[15] The trial will utilize a two-sample t-test to identify significant difference between the MSU and SM groups.[16] The study is powered to detect the difference observed between tPA and placebo treated arms in two previous studies, one out of Berlin by Kunz et. al. and another, the NINDS tPA trial. By powering the study to observe differences in clinical recovery and quality of life (via the uw-mRS) outside of ranges found in placebo trials, Yamal et. al. positioned the BEST-MSU study to supply both a statistically significant and clinically useful comparison of 90-day recovery data between the MSU and SM arms. The authors are interested in using this metric as a means of providing higher quality evidence of long-term clinical outcomes than what has been previously reported.

At the time of publication in the International Journal of Stroke in March 2018, the study had recruited 288 patients eligible for tPA treatment under American Heart Association guidelines (173 in the MSU arm and 115 in the SM arm).[16] Investigators state patient recruitment is blinded and bias-limited by using the same evaluators and guidelines to assess patients for stroke, regardless of their enrollment into the MSU or SM arms. However, the authors mention that on weeks where patients receive SM, patients may be evaluated by either the MSU research nurse or VN in the emergency department after conventional transport, whereas on weeks the MSU operates, patients are seen by the entire MSU team which includes the addition of a paramedic and a certified CT technologist.[16] Alarmingly, Yamal et. al. do not propose a protocol to ensure that the RN and VN evaluate a proportional number of patients independently or posit a control for such a confounder. The lack of consistency between MSU and SM weeks that could result from inconsistent stroke assessment is concerning because it may contribute to heterogeneity between the groups and lessen comparability. In an effort to minimize bias from such pragmatically challenging issues, the authors propose that biases are reviewed by an independent committee. They add that, presently, this committee has not expressed any concerns about the comparability of the study arms, however, the credentials of the committee and its methodology are not detailed in the publication.[16] Yamal et. al. expect patient recruitment to conclude and endpoint analysis of the study's two primary outcomes, 90-day recovery and cost-effectiveness, to begin in September 2019.

Once commenced, analysis of primary clinical outcomes will be measured using the uw-mRS 90 days after patients received AIS management by MSU or SM. The authors explain that the uw-mRS has an advantage over the standard mRS used in previous studies because it simultaneously looks at clinical effects and patient perception as it relates to quality of life. In essence, the authors believe the uw-mRS is a more granular and complete observation of patient recovery from stroke at ninety days post-care compared to the standard mRS, which has been used in previous studies. However, for cross-study comparison the standard 90-day mRS will be analyzed as part of the BEST-MSU study as a secondary outcome.

The co-primary outcome, cost-effectiveness, will help determine whether MSUs save costs to healthcare long term, a proposition the authors believe will help justify the large upfront costs and augmented reimbursement from healthcare payers, such as Medicare. Their cost-effectiveness analysis (CEA) will compare post-stroke healthcare costs to fixed costs of introducing and operating an MSU, as well as quality-adjusted life years of enrolled patients. The tool the authors will use to compare the rates at which

Medicare will reimburse for post-stroke costs is the resource utilization form (RUF), which includes costs accrued from the time of arrival of EMS to home healthcare after the patient is discharged. As a result of exhaustive cost-listing and incremental collection of RUFs at three month intervals for the first year after stroke, the RUF represents a strong tool for the researchers to compare healthcare cost utilization between the MSU-managed and SM groups.[16]

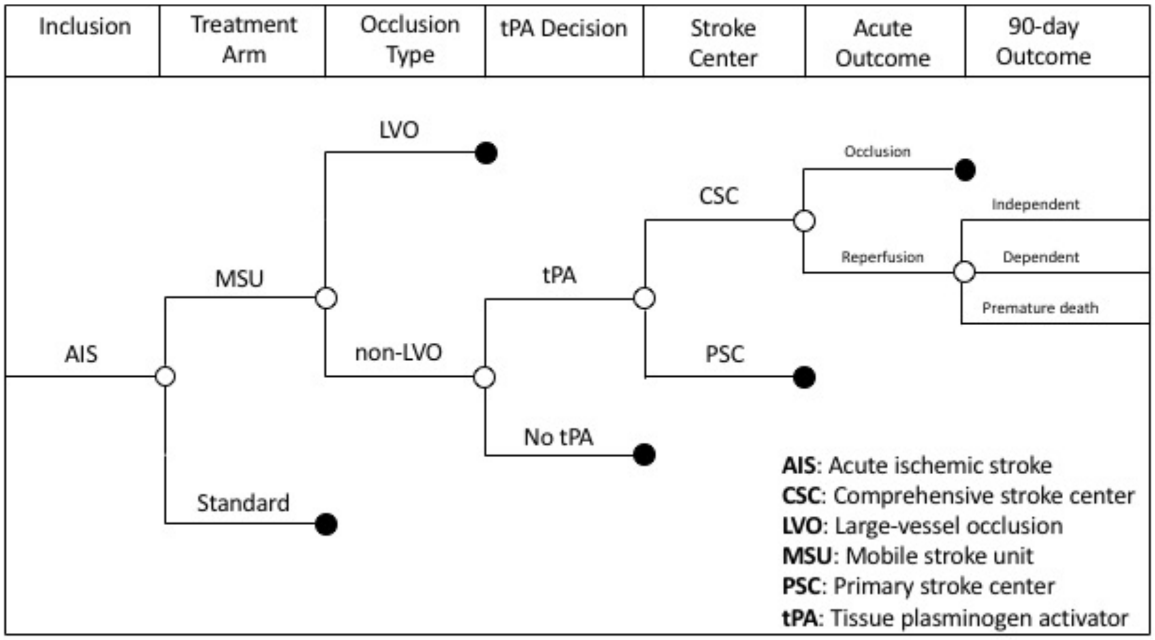
In summary, the review of the literature on MSU treatment of AIS compared to standard prehospital care has demonstrated reduction in time-to-treatment, benefits to long-term recovery, and obstacles in scalability. One of the remaining questions surrounding MSU operations is the cost as it compares to current management of AIS. To answer this question, studies have looked at a range of ways to inventory MSU costs, but few have looked at actually comparing those costs to the current prehospital system.

METHODS

Overview

A decision tree model (**Figure 1**) was created (Microsoft PowerPoint v16.16) to explore the cost consequences of different treatment strategies for prehospital AIS in the United States. The model can be used to compare two treatment arms: 1) MSU treatment and transport with hospital standard of care; and 2) standard ambulance treatment and transport with hospital standard of care. Using this framework, a population of 1000 adults (18 years or older) can be modeled from the time of base-hospital contact for stroke-like symptoms until 90 days post-AIS diagnosis. The 90-day cutoff was used to allow for comparison of 90-day mRS/uw-mRS data as a measure of patient recovery. The model will utilize an age-adjusted regional life-expectancy based on the mean age at the time of AIS and average life-expectancy post-AIS. MSU cost-of-treatment and cumulative health maintenance costs associated with AIS will be based on the most recent estimates from the BEST-MSU trial as soon as they become available.[15] Standard ambulance treatment and transport will be based on regional averages. All health outcomes will be measured in disability-adjusted life years (DALY) which accounts for both years lived with disability and earlier than expected death. DALYs will be based on median age of first stroke. Comparisons of cost-effectiveness will be made using incremental cost-effectiveness ratio (ICER), which represents the proportion of net costs per DALY averted by the intervention performed.[16] Cost parameters for the MSU arm can be obtained from completed, ongoing, or prospective studies on the MSU model.

Figure 1: Decision tree model. MSU + hospital standard of care. The decision to give tPA is based on absolute and relative contraindications.



Analytic approach

The decision tree was created to look at both possible treatment arms: 1) MSU treatment and transport with hospital standard of care and 2) standard ambulance treatment and transport with hospital standard of care. To factor in all eligible prehospital interventions, the framework begins at the time of dispatch for stroke-like symptoms. Costs of different modes of acute and chronic treatment include the treatment arm (MSU start-up costs versus standard ambulance), tPA decision, stroke center, and financial costs of managing adverse sequelae.

Cases of AIS that are eligible for tPA can then either be triaged to a PSC or CSC depending on the existence or absence of LVO, which helps determine the need for mechanical thrombectomy. In the acute hospital setting, the patient is either determined to have complete, partial, or no reperfusion after treatment. For the purposes of studying long term cost-benefits, 90-day recovery data in the form of mRS or uw-mRS can be compared to demonstrate the change in the level of functional dependence and corresponding change in DALY and ICER values.

Model parameters

Epidemiological parameters will need to be adjusted based on the region of interest. These values will be determined by literature review and expert opinion. Parameters will be held constant between arms as they do not depend on the treatment modality. The reimbursement for MSU administered tPA is not well defined and will need to be estimated.

Outcome measures

The primary outcomes of the study are threshold values for treatment effectiveness and cost. Thresholds are specified as the rate of effectiveness and net cost at which the MSU model becomes the more cost-effective choice. The secondary outcome is the ICER, or the ratio of incremental costs per DALY prevented by the treatment option. The ICER can be evaluated based on the differences of costs and DALYs between these two strategies to compare MSU treated and transported patients with SM. The ICER threshold will be defined as three times the per capita GDP, per WHO-CHOICE standards.

Sensitivity analysis

Three types of sensitivity analyses will be performed to account for uncertainty and determine which parameters affect outcomes to the greatest degree.

One-way sensitivity analysis will be used to identify the thresholds of the primary and secondary outcomes. By holding all but one variable constant while adjusting the input of the remaining variable (for example, the percentage of MSU patients receiving tPA), the thresholds for cost-effectiveness and cost savings can be determined.

Two scenario analyses can then be run. First, an analysis of the cost-effectiveness of MSU transport and treatment can be compared with standard ambulance transport. Next, a second scenario can vary the cost of tPA for a range of potential healthcare payer reimbursements and correlate the corresponding ICER for each against standard ambulance transport without tPA use.

Last, probabilistic sensitivity analysis can be utilized to test a random distribution of each parameter to attain ICER values. Computer models can run thousands of iterations upon a beta distribution of each parameter, following the current ISPOR guidelines for parameters from sparse sources.[17]

CONCLUSION

Discussion

MSU operations differ widely by research group and the cost structuring is often opaque due to their individualized construction methods and undetermined reimbursement mechanisms. Additionally, most findings from existing research are not generalizable across the United States, as studies tended to be clustered in metropolitan areas. In order for the MSU model to be translated to other settings (particularly rural regions of the country), additional research needs to be conducted with lower population densities.

Our cost-effectiveness analysis proposal is challenged by variability and uncertainty of cost structuring MSU operations. In order to mitigate the differences in construction, personnel, and equipment used by different MSU projects, our study design relies on threshold analysis. This differs from existing MSU cost accounting by structuring an adaptable model capable of determining the parameter ranges through which an MSU reaches cost-effectiveness and/or cost-savings.

Summary

Stroke is a major contributor to death and disability in the United States.[1,2] Patients who experience AIS benefit from early definitive treatment when that treatment is indicated.[5] However, when AIS occurs in the community, timely intervention is often barred in part by the time it takes to reach the proper healthcare setting where that management is available. In several studies, the MSU model has demonstrated efficacy in reducing time-to-treatment in cases of AIS.[8,10,14]

Still, questions persist around the feasibility of implementing the model on a larger scale due to large upfront expense of outfitting an MSU, as well as continuous operational and personnel costs. One potential answer raised by Parker et. al. was to use a telemedically linked VN to conduct the neurological assessment and interpret the results of the CT scan.[8] Although the connection quality was satisfactory in a high percentage of cases, it remains a point of concern outside of metropolitan areas where connection quality can be variable.

As demonstrated by recovery data presented by Kunz et. al., some of the greatest potential benefits of the MSU model are long term cost-savings from aversion of chronic disability.[9] Unfortunately, this is difficult to quantify for stakeholders in charge of funding the expensive startup, although an ongoing trial by Yamal et. al. has methods in place to more specifically measure them.[16]

In addition to discussion of direct treatment benefits, there remains uncertainty surrounding the triaging efficacy of the MSU model. Currently, there is little data investigating the rate at which patients are being triaged by an MSU to a CSC due to CT scan demonstrating ICH. Presumably, under standard ambulance management many of these patients are being transported to the nearest receiving PSC, while triage by a CT-equipped MSU may save a hospital transfer and time to definitive treatment.

The proposal in this paper seeks to offer a flexible tool for determining when an MSU becomes cost-effective, or even cost-saving. The goal is to allow for inputs from past, current, and future studies when more data becomes available regarding long term cost avoidance, healthcare payer reimbursement models, and up-scaled production costs.

Clinical and/or public health significance

By reducing time-to-treatment and producing better long-term recovery for community-based cases of AIS, MSUs have the potential to diminish acute and chronic stroke-related healthcare needs. This poses a direct benefit to the public whose insurance costs are associated with expenditures of healthcare payers. It is in the additional interest of hospital providers who benefit from earlier diagnostic imaging, more informed triage, and earlier intervention when indicated.

The proposed threshold CEA is aimed at providing a financial frame of reference to help inform public policy makers considering future MSU projects. By establishing a lens through which costs and benefits of MSUs can be compared to the current standard of prehospital AIS management, this research proposal can be utilized in tandem with the current efficacy data to better inform public health policy.

LIST OF JOURNAL ABBREVIATIONS

Cerebrovasc Dis Basel	Cerebrovascular Diseases (Basel, Switzerland)
Contin Minneap Minn	Continuum (Minneapolis, Minn.)
Int J Stroke	International Journal of Stroke
Med Decis Mak	Medical Decision Making
Lancet Neurol	The Lancet. Neurology
Rev Neurol (Paris)	Revue Neurologique
Scott Med J	Scottish Medical Journal

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CURRICULUM VITAE

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