APPRAISALS IN META-JOURNAL HOUR 9

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The paper:

PROSPECTIVE, MULTICENTER, CONTROLLED TRIAL OF MOBILE STROKE UNITS

https://pubmed.ncbi.nlm.nih.gov/34496173/

Why was this study conducted?

A potential way to reduce the time from stroke onset to treatment is with mobile stroke units (MSUs), which are ambulances equipped with a CT scanner, point-of-care laboratory testing, and personnel trained (paramedics, CT technologist and critical care nurse) to diagnose and treat patients with stroke in the ambulance, including administration of tissue plasminogen activator (t-PA) and triage for endovascular thrombectomy (EVT). Outcomes with t-PA and EVT are best with treatment as soon as possible especially within the first hour after the stroke onset. MSUs have the potential to increase the frequency and speed of the delivery of t-PA treatment, but whether and how much t-PA treatment in an MSU alters outcomes has not been extensively studied. Thus, this study aimed to compare clinical outcomes in patients eligible for t-PA who received care from MSU as compared with standard care by emergency medical services (EMS).

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How was it done?

Trial design and interventions

The study was a prospective, multicenter, alternating-week, cluster-controlled trial that compared outcomes in t-PA eligible patients with acute stroke who received MSU or standard emergency medical services (EMS) care. Patients who met the screening criteria for t-PA treatment on MSU or EMS arrival at the scene were considered for enrollment (regardless of the eligibility for primary outcome analysis). All sites collaborated with local EMS to treat patients according to the trial protocol. Enrollment of patients into the two trial groups was based on the prospective designation of alternating MSU or EMS weeks. As blinded enrollment of individual patients was not possible, several measures were taken to reduce the potential for ascertainment bias including enrollment of patients on both MSU and EMS weeks on the basis of assessment of the same clinical and laboratory criteria carried out on arrival of the MSU or EMS on the scene, later adjudication of eligibility for t-PA by a vascular neurologist who was unaware of the trial group assignments and treatment, and blinded assessment of 90-day outcomes by a trained site investigator. Patients with potential stroke within 4.5 hours after the onset of symptoms were identified by a 911 dispatch center. The MSU and EMS teams were both alerted on MSU and EMS weeks. The patient's history, blood glucose level, neurologic and general physical condition, and NIHSS score were obtained from the patients. All the enrolled patients were followed up for 12 months.

Power and sample size calculations

There were several changes made to the original trial protocol including sample size estimation. The number of t-PA eligible patients to be enrolled was increased from 541 to 1038 based on newly available data from the previous study. This sample size re-estimation was blinded to study outcomes and considered the numerical imbalance between the MSU and EMS groups observed during the run-in phase and first part of the trial. The sample size was calculated using a two-sample t-test. By assuming numerical imbalance in MSU as compared to EMS enrollment (1.8) in the previous trial, a potential loss to follow up of 5%, pooled standard deviation for the primary outcome (0.385), and at least 80% power to detect a between-group difference of 0.07 points in the score on the utility-weighted modified Rankin Scale, a total of 1038 patients were required for analysis.

Outcomes

PRIMARY OUTCOME	SECONDARY OUTCOMES	SAFETY OUTCOMES
The score on the utility-weighted modified Rankin scale (uw-mRS) at 90 days in patients who were adjudicated to be eligible to receive t-PA based on subsequent blinded review. ▪ The score on the utility-weighted modified Rankin scale (uw-mRS) is range from 0 to 1 (higher scores indicate a better outcome). A score on the utility-weighted modified Rankin scale (uw-mRS) of at least 0.91 is approximately equivalent to a score on the modified Rankin scale (mRS) of 0 or 1, denoting no or minimal disability. ▪ All modified Rankin scale (mRS) assessments at 90 days involved the use of a standardized questionnaire (Rankin Focused Assessment) and were obtained by a trained investigator at each site who was unaware of the trial-group assignments.	▪ Changes across the modified Rankin scale (mRS) for all patients who received t-PA. ▪ A 30% reduction (improvement) from baseline to 24 hours in the NIHSS score. ▪ Time metrics related to treatment times from stroke onset. ▪ The percentage of eligible patients treated with t-PA and EVT.	▪ Symptomatic intracerebral hemorrhage. ▪ Death. ▪ The number of patients with symptoms that mimic stroke (stroke mimics) who were treated with t-PA in each trial group based on final diagnosis after hospital evaluation.

Statistical Analysis

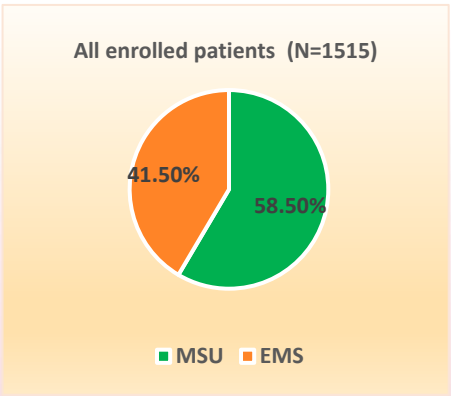
The primary analysis was of the score on the utility-weighted modified Rankin scale (uw-mRS) in the subgroup of patients adjudicated to be eligible for t-PA, whether or not they received t-PA. Because the assumptions of the linear regression model and proportional-odds assumptions were not met, the prespecified statistical plan was defaulted to use a prespecified binary logistic regression for dichotomized scores on the uw-mRS of at least 0.91 or less than 0.91 (equivalent to a score on the mRS of ≤1 or >1). Logistic
regression was used for the secondary outcome of a 30% reduction in the NIHSS score. Because trial-group assignments to MSU or EMS were not truly randomized, in a post hoc analysis, propensity scores were used to estimate the MSU group effect on all outcomes regarding scores on the uw-mRS, the mRS, and the NIHSS. Subgroup analyses were conducted as in the primary models. However, the trial was not powered to analyze these subgroups, and no definite conclusions can be drawn from these data. The interim analysis of the dichotomized scores on the utility-weighted modified Rankin scale at 90 days was conducted by means of a two-sample, two-sided test of proportions with the use of a Haybittle–Peto boundary (alpha spent, 0.001).

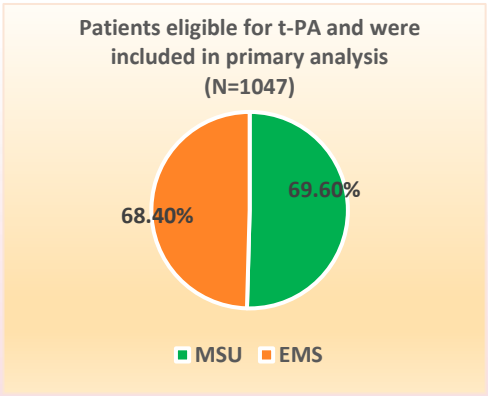
What was the finding?

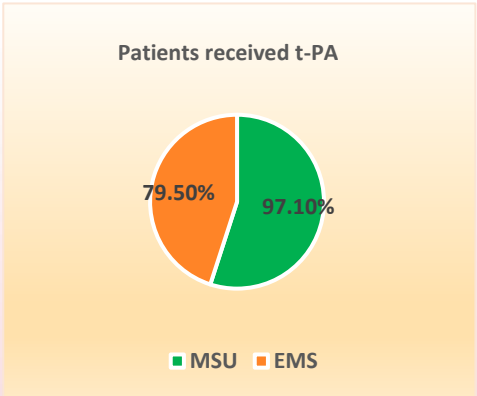
Patients Enrolled

Of the 1515 enrolled patients, a total of 1047 patients [MSU: N= 617 (69.6%); EMS: N= 430 (68.4%)] were adjudicated to be eligible for t-PA and included in the primary analysis. Of the patients who were eligible to receive t-PA, 97.1% who were assigned to MSU received t-PA, compared with 79.5% in the EMS group. About 14% (N=218) of all the patients enrolled were not eligible for t-PA because intracranial blood was detected on CT. Baseline characteristics were similar in the MSU and EMS groups for the patients eligible for t-PA, including stroke severity.

Outcomes







Primary Outcome

OUTCOME	MSU	EMS
The mean score on the uw-mRS at 90 days in patients eligible for t-PA.	0.72 ± 0.35	0.66 ± 0.36
The mean score on the uw-mRS at discharge for all enrolled (N=1515) patients.	0.57 ± 0.37	0.51 ± 0.36
The percentage of patients who were eligible for t-PA who had a score on the mRS of 0 or 1 at 90 days.	55%	44.4%

EFFICACY:

Patients who received MSU care were more likely than those who received EMS care to have a utility weighted disability score of ≥0.91.

Secondary Outcomes

OUTCOME	MSU	EMS
30% reduction in the NIHSS score from baseline to 24 hours occurred in patients eligible for t-PA.	75%	67.8%
Improvement to an NIHSS score of 0 by arrival at the emergency department.	5.5%	3.3%
The median time from stroke onset to t-PA treatment.	72 minutes	108 minutes
Percentage of patients were treated within 60 minutes after onset.	32.9%	2.6%
The median time from alerting of emergency services to EVT start.	141 minutes	132 minutes
The percentage of patients ultimately treated with EVT.	23.7%	27.0%
Safety outcomes	**MSU**	**EMS**
Symptomatic intracerebral hemorrhages among patients who received t-PA.	Approximately 2.0%	
Mortality at 90 days.	8.9%	11.9%

How much can we take out from this research/ paper?

A very well done study despite the many and real challenges as faced by clinical research such as disproportional sample size achieved from the 8 different sites with Houston contributed about 80%, different level of emergency response and services at different sites, MSU experienced a down service during the study period, maintaining blinding throughout and for all outcomes were an almost impossible task in a real-world clinical research, and encountering non-normal but not unexpected data distribution that complicated the statistical analysis. On top of all these was the choice of a cohort and controlled instead of a randomised controlled study design. This has undoubtedly made the study to have another challenge of between-group comparison to determine the effect of MSU versus EMS. Despite all these challenges, it was a well-planned and conducted study with good power, comparability between the 2 groups was achieved, blinding on primary outcome evaluation was done, adjudication was imposed on study decisions where needed, statistical analyses were properly and meticulously done supplemented with sensitivity analysis that confirm ITT and as treated analysis showed consistent with expected lower effect sizes in the former.

There is a growing interest in using utility weight as a measurement of disease burdens and cost-effective analysis of disease and treatment. Uw-MRS has been proposed to be used as a primary outcome for stroke trials. However, no consensus on the best way to apply the utility weight which hinders many people, and standardization is difficult to do. Uw- MRS combines the value from clinician through MRS score and utility base via EQ-5D-3L from patient and derives a score through regression analysis (linear or logistic). So far, there is no publication for Uw-MRS for the Malaysian population, however, we already developed the utility value for EQ-5D-3L in 2019 [2].

To bear in mind the mainly US urban setting, healthcare system and likely to be locally and culturally related UW-mRS measure in this study, then the results could be safely interpreted and generalised. Indeed, the results showed that MSU performed significantly better (remember the clinically significant different of the UW-mRS was 0.03) across all investigated outcomes with some expected and now quantified effects such as the percentage of patients who were treated with t-PA within 60 minutes after onset was almost 33% in MSU compared to 3% in EMS!

Naturally, the obvious questions followed from this study are why not MSU service be studied in other setting, and be established? True enough, many studies have also been replicated in other countries and MSU is available elsewhere beside US[3,4]. There are systematic reviews and meta-analyses, one of the recent one shows that MSU is indeed better than EMS[5]. Remaining questions are the same that face the health system and services when a change is required. These conceived challenges can be overcome one-by-one with high-quality research that involved public and community assessment and involvement, healthcare professionals training and availability, political will and government support.

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