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Mobile stroke unit versus standard medical care in the management of patients with acute stroke: A systematic review and meta-analysis

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Abstract

Introduction: Mobile stroke units have recently been introduced in the care of patients suspected of having an acute stroke, leading to shortening in the time to thrombolytics. We aimed to compare the clinical effectiveness in terms of functional outcome and survival among patients treated in mobile stroke unit and/or conventional care.

Methods: A systematic search of electronic databases, comparing the clinical outcomes among patients with acute stroke in the same study was conducted from 1990 to 2019. Pooled and subgroup analysis were performed using the random- and fixed-effect model based upon the I^2 heterogeneity.

Results: A total of 21,297 patients from 11 publications (seven randomized controlled trials and four non-randomized controlled trials including prospective cohort studies) were retrieved. This included 6065 ($n = 28.4\%$) of the patients treated in the mobile stroke unit and 71.6% ($n = 15{,}232$) of the patients managed in the conventional care. The mean age at clinical presentation (70.1 ± 14.5 vs. 71.05 ± 15.8) and National Institute Health Stroke Scale (9.8 ± 1.7 vs. 8.4 ± 1.5) was comparable ($p > 0.05$) in patients treated with mobile stroke unit and conventional care, respectively. The mean time-to-treatment window was significantly shorter among the patients treated in mobile stroke unit compared to conventional care (62.0 min vs. 75.0 min; $p = 0.03$, respectively). The pooled analysis of clinical outcome at day 7 indicated that patients treated in mobile stroke unit had 1.46-folds higher likelihood of better clinical outcome (modified Rankin scale 0–2) than those in the hospital (odds ratio: 1.46, 95% confidence interval: 1.306–2.03, $p = 0.02$). However, there was no significant difference in terms of mortality (odds ratio: 0.98, 95% confidence interval: 0.81–1.18, $p = 0.80$), stroke-related neurological deficits (odds ratio: 1.37, 95% confidence interval: 0.81–2.32, $p = 0.24$), and other serious adverse events (odds ratio: 0.69, 95% confidence interval: 0.39–1.20, $p = 0.19$) among patients treated in mobile stroke unit versus conventional care.

Conclusion: Our results corroborate that patients treated in mobile stroke unit lead to short-term recovery following acute stroke without influencing the mortality rate. Further prospective studies are needed to validate our results.

Keywords

Acute stroke, mobile stroke unit, conventional care, thrombolytics

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Introduction

Stroke care has significantly improved due to recent technological innovations in the form of imaging (CT- and MRI) and high-speed wireless data transmission, resulting in better outcomes as reflected by reduced mortality and morbidity.[1] Perhaps the most important factor in determination of clinical outcome following stroke is the "time to reperfusion,"[2] which has been significantly reduced due to management of patients in the mobile stroke unit (MSU).[3] Since these

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MSUs are equipped with necessary imaging technique and laboratory testing equipments along with a well-trained designated MSU staff, thus early access and management to eligible stroke patients have been made.[4,5] Several studies have reported on better time to treatment and improved outcome with MSUs.[6–8] Furthermore, MSU also provides "accurate triage decision"[9] to stroke patients. This prehospital management involves transport to comprehensive stroke center (CSC) for patients with large vessel occlusion or intracranial hemorrhage (ICH) and to a noncomprehensive stroke center for patients with other stroke syndromes. The resulting hospital transfers considerably reduce costs and detrimental delays before treatment.[9]

To date, no one of the meta-analysis has been conducted to evaluate the difference in terms of time gains and clinical outcome among patients treated in the MSU versus standard conventional care. Hence, we aimed to do meta-analysis to determine the safety and efficacy of the treatment given to the patients in MSU versus standard conventional care. Our a priori hypothesis is that the patients treated in MSU exhibit better short- and long-term clinical outcome and better survival rate.

Methods

Data search strategy: We followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)[10] for literature search. Two reviewers (NF and MS) conducted a detailed systematic review on electronic databases using PubMed, Google Scholar, EMBASE, Medline, Scopus, and Cochrane library for the articles published between 1 January 1970 and 15 November 2019. MeSH terms (using the Boolean operators "and" and "or") which included "mobile stroke unit," "stroke," ambulance," "tissue plasminogen activator," and "thrombolysis" were searched. All articles irrespective of the language were included in our study. Consensus was made in the presence of discrepancy between the two reviewers.

Inclusion and exclusion criteria: We included randomized controlled trials (RCTs), retrospective or prospective studies that compared the clinical outcomes among patients treated in either MSU or conventional care/standard medical care for the acute stroke. We excluded case–control studies, case series, and case reports from our analysis.

Data extraction and outcome measures: The data were extracted by two authors (NF and MS) using a structured template form based on the Cochrane Consumers and Communication Group. Any disagreement between the two authors was resolved by discussion. The following data were extracted from each article: (i) demographic characteristics (type of study, location, number of patients, age, National Institute of Health Stroke Scale (NIHSS)), (ii) clinical condition, (iii) alarm to therapy decision (intravenous (IV) thrombolysis or intra-arterial recanalization), (iv) alarm to end of CT, (v) NIHSS at immediate and last follow-up, (vi) clinical outcomes (modified Rankin scale (mRS), mortality, stroke-related neurological death, and other serious adverse events).

Clinical outcomes included: (i) mRS dichotomized as good outcome (0–2) and poor outcome (3–6) at day 1 and day 7 of treatment, (ii) all-cause mortality at day 7, (iii) stroke-related or neurological death, and (iv) other adverse events which include, intracerebral hemorrhage (ICH) and seizures, etc.

Primary outcome analysis includes determination of clinical outcome as defined by modified Rankin scale at day 7 and day 1 post treatment. Secondary analysis included mortality, stroke related-neurological death, other adverse events, and mean time gains. The stroke-related or neurological death was described as mentioned by the included studies as cumulative events of fatal–ischemic stroke, fatal reinfarction, fatal primary ICH, or fatal secondary ICH. While other adverse events as cumulative events of nonfatal reinfarction, secondary ICH (change in NIHSS < 4), myocardial infarction, pneumoniae, and other infection.

Statistical analysis: Rev Manager (Rev Man 5.3) was used for comparing data from included studies. Pooled weighted mean difference (MD) was used to analyze the continuous data, while we analyzed the dichotomous data using the odds ratio (OR). The results were reported as either MD or OR with 95% confidence interval (CI). The heterogeneity among the studies was evaluated using the I^2 statistics. The fixed effect model was used for I^2 was $< 50\%$, while for $I^2 \geq 50\%$ a random-effect model was employed. All tests were two-tailed, and p value < 0.05 was considered as statistically significant.

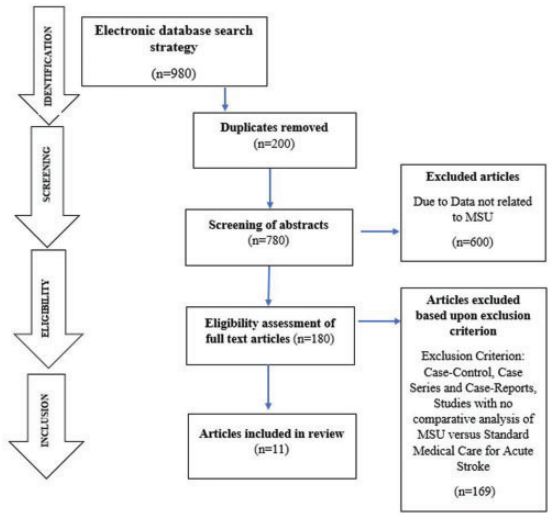
Risk of bias across studies: We included RCTs in our study; however, no RCTs were designed as double-blind trials. The high heterogeneity was analyzed using the funnel plot, which showed asymmetrical distribution, which could be attributed to a small sample size as the removal of small sized cohort significantly decreased the heterogeneity.

Results

Study selection

A total of 980 articles were retrieved from electronic databases (PubMed, Google Scholar, Scopus, Medline, EMBASE, and clinical trials.gov) and reviewed according to PRISMA guidelines[11] (Figure 1). After screening

Figure 1. Database search strategy of the included studies according to PRISMA guidelines.



of the abstracts, 200 articles were excluded due to data not related to MSU. A total of 180 full text articles were assessed for eligibility of which, 169 articles were excluded based upon the inclusion and exclusion criterion. Hence, 11 articles were included in our review, including 7 RCTs[3,8,9,12–15] and 4 non-RCTs.[6,7,16,17] These studies were conducted in different centers in Germany ($n=7$) and USA ($n=4$).

Overall characteristics of the study

A total of 21,297 patients were included in our analysis, with 71.6% ($n=15{,}232$) in the control group and 6065 ($n=28.4\%$) in the intervention group as treated in MSU. Baseline characteristics of included studies are illustrated in Table 1.

The mean age was 70.1 ± 14.5 years and 71.05 ± 15.8 years in the intervention and control group, respectively. The mean NIHSS of the intervention and control group was 9.8 ± 1.7 and 8.4 ± 1.5, respectively. The clinical presentation included acute ischemic stroke, transient ischemic attack, intracerebral hemorrhage, seizures, subarachnoid hemorrhage, subdural hematoma, and neurological noncerebral vascular pathology.

The characteristics of therapy decisions are shown in Table 2. The mean symptom onset to therapy decision was 59.3 min (32–96.3 min) versus 75 min (48–153 min) in patients treated in MSU and conventional treatment in the hospital, which was statistically significant $p=0.03$. The mean duration of alarm to IV thrombolysis and/or intra-arterial recanalization was 62.0 min (38–75 min) versus 75.0 min (61–110 min) in patients treated in MSU and conventional treatment in the hospital, with a statistically significant difference ($p=0.03$). The mean alarm to end of CT scan was 28.6 min (12.0–37.7 min) and 37.5 min (14.0–71.0 min) in patients treated in MSU and conventional treatment in the hospital with a statistically significant difference ($p=0.04$). The mean time from symptom onset to IV thrombolysis in patients in conventional treatment group was 110.5 ± 15.8 min compared to 62.02 ± 16.7 min among patients treated in MSU group. However, we could not compare it with the patients who received IAT due to lack of data pertaining to it in the included studies. Only one study[18] reported data on alarm-to recanalization (IAT) as 93 min (75–116.5 min) in the MSU compared to 200 min (185–223 min) in the patients with standard medical care. The alarm to IV thrombolysis or IAT was reported as a single entity[12] as 38 min (34–42 min) in the MSU compared to 78 min (61–110 min) ($p<0.0001$), respectively.

The MD from symptom onset to IV thrombolysis was significantly longer among patients treated in the conventional standard care than MSU (MD: 47.50, 95% CI: 28.28–66.72, $p<0.00001$) (Figure 2). The symptom onset to therapy decision was significantly longer in patients presented to the hospital compared to those presented in the MSU (MD: 23.91, 95% CI: 6.24–41.57, $p=0.008$) (Figure 3). The mean time from alarm onset to end of CT scan was significantly longer among patients treated in the hospital compared to MSU (MD:13.25, 95% CI: 2.60–23.89, $p=0.01$) (Figure 4).

Outcome characteristics

The clinical outcome characteristics are described in Table 3. The pooled analysis of clinical outcome at day 7 indicated that patients treated in MSU had 1.46-folds higher likelihood of better clinical outcome (mRS 0–2) than those treated in the emergency department (OR: 1.46, 95% CI: 1.306–2.03, $p=0.02$) (Figure 5). Only two studies[12,17] reported mRS at day 1 which demonstrated that patients treated in MSU had 1.1-folds higher likelihood of good clinical outcome (mRS 0–2) compared to conventional treatment, though statistically insignificant (OR: 1.18, 95% CI: 0.88–1.57, $p=0.26$) (Figure 6).

Furthermore, there was no significant difference in terms of mortality among patients treated in MSU or conventional treatment modality (OR: 0.98, 95% CI: 0.81–1.18, $p=0.80$) (Figure 7). There was no significant difference in terms of stroke-related or neurological death (OR: 1.37, 95% CI: 0.81–2.32, $p=0.24$) (Figure 8). Similarly, there was no significant difference in terms of other adverse events between the two groups (OR: 0.69, 95% CI: 0.39–1.20, $p=0.19$) (Figure 9).

Table 1. Baseline characteristics of all included studies

Name of the study	Type of study	Location	Number of patients	No. of patients in each group	Age (years) Mean (range)	NIHSS Mean (range)	Diagnosis, *n* (%)	Inclusion criteria	Exclusion criteria
Walter et al. (2012)	RCT	Germany	100	Group1: (MSU): 53 Group 2: Conventional pathway: 47	Group 1: 72 (59–76) Group 2: 71 (55–75)	Group 1: 5 (3–11), Group 2: 6 (3–12)	Group 1: Ischemic stroke: 29 (55), TIA: 8 (15), ICH: 4 (6), Stroke mimics: 12 (23); Group 2: 25 (53), TIA: 9 (19), ICH: 7 (15), Stroke mimic: 6 (13)	1. Patient aged 18–80 years 2. One or more stoke symptoms according to the modified recognition of stroke in the emergency room (ROSIER) scale that started within previous 2–5 h	1. Uncertain symptom onset 2. No focal-stroke like symptoms 3. Pregnancy
Weber et al. (2013)	Prospective	Germany	127	Group 1: 77 Group 2:50	Group 1: 75 Group 2: 70	Group 1:8 (5–12) Group 2: 8 (5–16)	Group 1: TIA 7 (5.7) ischemic stroke 45 (35.4) ICH 1 (0.1) Other 8 (6.2) SAH 1 (0.1)[a]	NA	NA
Edinger et al. (2014)	RCT	Germany	7713	Group 1 (MSU): 1804 Group 2: 5909	Group 1: 73.9 Group 2: 73.9	Group 1: 10.5 Group 2 10	Group 1: TIA 182 (21), Ischemic stroke 614 (70.9) ICH 45 (5.2) SAH 3 (0.3) others 22 (2.5) Group 2: TIA 643 (10.2) Ischemic stroke 2111 (35.4) ICH 145 (2.4) SAH 11 (0.1) Others 66 (0.7)	All stroke patients	NA
Bowry et al. (2015)	RCT	USA	26	Group1: (MSU): 26 Group 2: Conventional pathway: 2	Group 1: 64	Group 1: 11	Group 1: ICH:4 Seizures:4 TIA: 1 Ischemic Stroke: 11 others 6[a]	NA	NA
Wendt et al. (2015)	RCT	Germany	5833	Group 1(MSU): 1804 Group 2: Conventional: 4378	Group 1: 73.9 Group2: 74.2	NA	Group 1: Cerebrovascular: 866 (48): TIA 185 (10.3) Ischemic Stroke 610 (33.8) ICH 4.5(2.5) SAH 3(0.2) Other 23(1.3) Neurological	All patients with Stroke	Less than 18-year-old

(continued)

Table 1. Continued

Name of the study	Type of study	Location	Number of patients	No. of patients in each group	Age (years) Mean (range)	NIHSS Mean (range)	Diagnosis, *n* (%)	Inclusion criteria	Exclusion criteria
							noncerebral vascular:418 Non-neurological :520 (35) Group 2: Cerebrovascular: 2110 (48.2) TIA 461(10.5) Ischemic Stroke 1497 (34.2) ICH 100 (2.3) SAH 8 (0.2) Other 44 (1.0) Neurological noncerebrovascular 1058 (24.2) Non-neurological 120 (27.6)		
Parker et al. (2015)	RCT	USA	24	Group 1: 24	NA	NA	Group 1: ICH:4 (16.7) Seizures:3 (12.5) TIA:2 (8.3) Subdural Hematoma:1 (4.2) Time no specify:1 (4.1) Ischemic Stroke:13 (54.2)[a]	Stroke patients with r-tPA criteria	NA
Ebinger et al. (2015)	RCT	Germany	6182	Group 1 (MSU): 1804 Group 2: 4378	Group 1: 73 ± 15 mean	Group 1: 10 (3–19)	Group 1: Ischemic stroke 614(70.9) TIA 182 (21) ICH 45 (5.2)[a]	NA	NA
Cerejo et al. (2015)	Retrospective	USA	11	Group 1 (MSU):5 Group 2: 6	Group 1:75 (51.5–81) Group2:71 (51.25–79.25)	Group 1:19 (18.5–21.5) Group 2: 9.5 (7–20)	NA	Ischemic stroke due to emergent large vessel occlusion	NA
Itrat et al. (2016)	Prospective	USA	156	Group 1: 100 Group 2: 56	Group 1: 62 (53–76) mean Group 2: 64 (57–79) mean	Group 1: 6 (2–12)	Group 1: Ischemic stroke 33(33) TIA 4(4) ICH 5(5)[a]	NA	NA
Kunz et al. (2016)	Observational	Germany	608	Group 1: (MSU) 305 Group 2: 353	Group 1: 70.7 (72–79) Group 2: 70.2 (72–79)	Group 1 and 2: 8.9 (7.4–13)	Acute Ischemic stroke and thrombolysis	All patients with Stroke	Patients who doesńt have private or professional assistance

(continued)

Table 1. Continued

Name of the study	Type of study	Location	Number of patients	No. of patients in each group	Age (years) Mean (range)	NIHSS Mean (range)	Diagnosis, *n* (%)	Inclusion criteria	Exclusion criteria
Helwig et al. (2019)	RCT	Germany	116	Group 1: 63, Group 2: 53	Group 1: 75 ± 11 Group 2: 74 ± 11	Group 1: 5 (3–11), Group 2: 8 (4–15)	Group 1: Ischemic stroke 32 (50.8), ICH 8 (12.7), TIA 17 (27.0) and stroke mimics 6 (9.5). Group 2: Ischemic stroke 39 (73.6), ICH 8 (15.1), TIA 4 (7.5) and stroke mimics 2 (3.8)	Age at least 18 years with the presence of 1 or more stroke symptoms on the FAST scale, as reported to the EMS dispatch office and confirmed by study physician either in the hospital or in the MSU; reported time from symptom onset to call of 8 hours or less; the occurrence of a "wake-up" stroke; and written consent by the patient or the patient's legal representative.	Unavailability of vascular imaging, renal dysfunction, pregnancy, allergy or contraindication to the use of contrast agents, preexisting severe or terminal disease, unstable cardiopulmonary medical conditions requiring immediate intensive care unit treatment

NIHSS: National Institute of Health Stroke Scale; ICH: intracranial hemorrhage; RCT: randomized controlled trial; MSU: mobile stroke unit; SAH: subarachnoid hemorrhage; TIA: transient ischemic attack; tPA: tissue plasminogen activator; NA: not applicable.

[a]Diagnosis in the Group 2 is missing in the included studies.

Table 2. Difference in time to treatment strategies among patients treated in mobile stroke unit versus conventional care

Name of the study	Alarm to therapy decision (min) Mean (IQR)	Alarm to IV thrombolysis or intra-arterial recanalization (min) Mean (IQR)	Alarm to end of CT (min) Mean (IQR)	Symptom onset to therapy decision (min) Mean (IQR)	Symptom onset to IV bolus thrombolysis (min) Mean (IQR)
Walter et al. (2012)	Group 1: 35 (31–39) Group 2: 76 (63–94)	Group 1: 38 (32–42) Group 2: 78 (61–110)	Group 1: 34 (30–38) Group 2: 71 (62–87)	Group 1: 56 (43–103) Group 2: 104 (80–156)	Group 1: 72 (53–108) Group 2: 153 (136–198)
Weber et al. (2013)	Group 1: 13 (10–16) Group 2: 44 min (37–48)	NA	NA	NA	Group 1: 58 (50–63) Group 2: 146 (103–176)
Edinger et al. (2014)	NA	NA	Group 1: 37.7 (35.6–39.7) Group 2: 52.4 (50.3–54.4)	NA	Group 1: 51.8 (49–54.6) Group 2: 76.3 (73.2–79.3)
Bowry et al. (2015)	Group 1: 25 (17–42)	Group 1: 175 min (140–224)	NA	Group 1: 98 (47–265) min	Group 1: 4 (33%) 0–60 min 4 (33%) 61–80 4 (33%) 81–270
Wendt et al. (2015)	NA	NA	NA	NA	NA
Parker et al. (2015)	NA	NA	Group 1: 25 (20–29) Group 2: 25 (19–35)	NA	Group 1: 4 (31%) 0–60 min 4 (31%) 61–80 min 5 (38%) 81–270 min
Ebinger et al. (2015)	NA	NA	Group 1: 37.7 (35.6-39.7)	Group 1:80.5 (54–126) Group 2:105 (82–146)	Group 1: 62 < 60 min 138 > 60 min Group 2: 16 < 60 min 313 > 60 min
Cerejo et al. (2015)				NA	NA

(continued)

Table 2. Continued

Name of the study	Alarm to therapy decision (min) Mean (IQR)	Alarm to IV thrombolysis or intra-arterial recanalization (min) Mean (IQR)	Alarm to end of CT (min) Mean (IQR)	Symptom onset to therapy decision (min) Mean (IQR)	Symptom onset to IV bolus thrombolysis (min) Mean (IQR)
	Group 1: 19 (16–24) Group 2: N/A	Group 1:52 (39.5–63) Group 2:75 (49–88)	Group1: 12 (9–13.5) Group 2: 14 (12–17)		
Itrat et al. (2016)	Group 1: 12 (8–14) Group 2: NA	NA	Group 1:25 (20–29) Group 2:25 (19–35)	Group 1: 13 (7–18) Group 2:44 (36–61)	Group 1: 32 (24–47) Group 2: 48 (53–68)
Kunz et al. (2016)	Group 1: 48 (46–53) Group 2: 82 (76–93)	NA	NA	Group 1: 49 (22.8–64) Group 2: 47 (28.9–71)	Group 1: 96.3 (46.4–53) Group 2: 129.3 (85–175)
Helwig et al. (2019)	Group 1: 10.3 ± 3.6, Group 2: 41.5 ± 12.8	Group 1: 50.1 ± 10.1, Group 2: 84.9 ± 30.2	Group 1: 39.3 ± 7.8, Group 2: 80.0 ± 39.6	Group 1: 83 ± 99, Group 2: 63 ± 89	NA

NA: not available; NIHSS: National Institute of Health Stroke Scale; IQR: interquartile range.

Figure 2. Forest plot showing mean difference from symptom onset to IV thrombolysis.

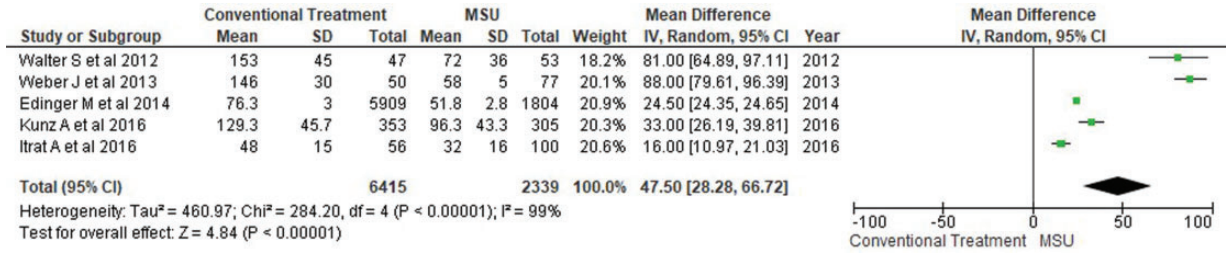


Figure 3. Forest plot showing mean difference from symptom onset to therapy decision.

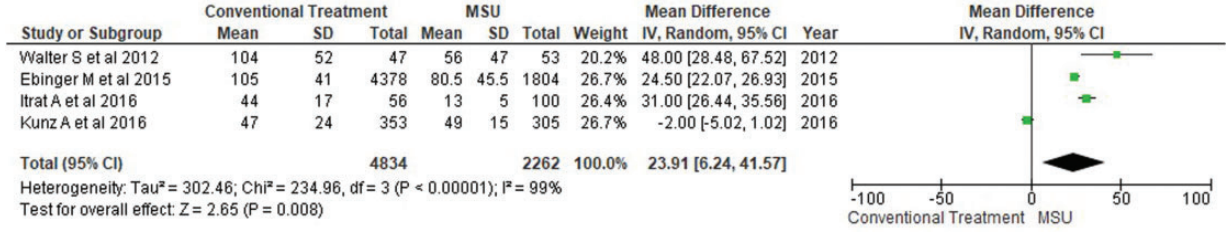
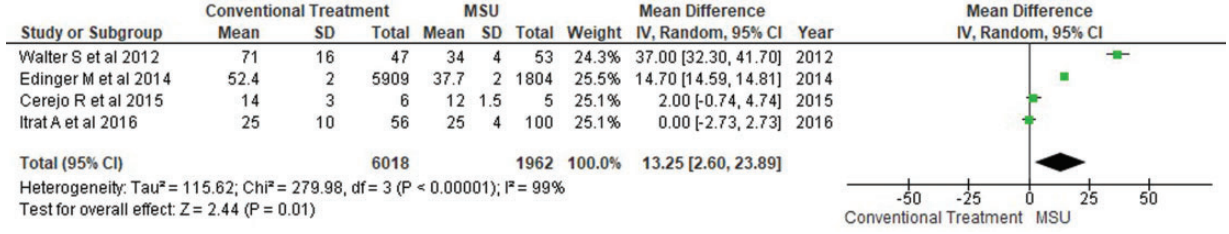


Figure 4. Forest plot showing mean difference from alarm onset to end of CT scan.



The definition of stroke and conventional or standard medical care is illustrated in Table 4.

Discussion

Our meta-analysis aims to determine the safety and efficacy of the treatment delivered to the patients in the MSU compared to the conventional standard medical care. Our results corroborate that patients treated in MSU had better short-term recovery but had no stastically significant impact on mortality, stroke-related or neurological death, and other adverse events ($p > 0.05$). Furthermore, the patients managed in the conventional standard care group seek longer time from symptom onset to therapy decision ($p = 0.008$), symptom onset to IV thrombolysis ($p < 0.00001$) and alarm onset to end of CT scan ($p = 0.01$) than MSU. Currently, there are two clinical trials that include B_PROUD (Berlin Prehospital or Usual Delivery of Acute Stroke Care) (2.0)[18] and BEST-MSU[19] (BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit) conducted at Berlin, Germany, and Texas, USA respectively; both of which are related to determination of clinical outcomes (mRS) as a primary end point in patients treated in MSU versus standard medical care. These large trials will further add information to the safety and efficacy of treatment of the patients in the MSU compared to conventional care.

Our meta-analysis included 21,297 patients with 28.4% of the patients treated in the MSU. The mean age at clinical presentation (70.1 ± 14.5 vs. 71.05 ± 15.8)

Table 3. Outcome characteristics, including modified Rankin scale, mortality, and neurological-related death among patients treated in two cohorts

Name of the study	mRS at day 1 (0–2)	mRS at day 1 (3–6)	mRS at day 7 (0–2)	mRS at day 7 (3–6)	Mortality at day 7	Stroke-related neurological death	Other serious adverse events
Walter et al. (2012)	20/53 (37.7) vs. 21/47 (44.6)	21/53 (39.6) vs. 20/47 (42.5)	20/53 (37.7) vs. 21/47 (44.6)	21/53 (39.6) vs. 20/47 (42.5)	6/53 (11.3) vs. 2/47 (4.3)	5/53 (9.4) vs. 2/47 (4.3)	0/53 (0.0) vs. 2/47 (4.3)
Weber et al. (2013)	NA	NA	9/77 (11.7) vs. 5/50 (10.0)	68/77 (88.3) vs. 45/50 (90.0)	4/77 (5.2) vs. 1/50 (2.0)	0/77 (0.0) vs. 0/50 (0.0)	2/77 (2.6) vs. 3/50 (6.0)
Edinger et al. (2014)	NA	NA	NA	NA	73/1804 (4.0) vs. 237/5909 (4.0)	9/1804 (0.4) vs. 15/5909 (0.2)	7/1804 (0.3) vs. 22/5909 (0.3)
Bowry et al. (2015)	NA	NA	NA	NA	NA	NA	NA
Wendt et al. (2015)	NA	NA	NA	NA	62/1804 (3.4) vs. 173/4378 (3.9)	NA	NA
Parker et al. (2015)	NA	NA	NA	NA	NA	NA	NA
Ebinger et al. (2015)	NA	NA	NA	NA	9/1804 (0.5) vs. 15/5909 (0.2)	7/1804 (0.3) vs. 22/5909 (0.3)	NA
Cerejo et al. (2015)	NA	NA	NA	NA	NA	NA	0/5 (0.0) vs. 2/6 (33.3)
Itrat et al. (2016)	NA	NA	NA	NA	NA	NA	NA
Kunz et al. (2016)	161/305 (52.7) vs. 166/353 (47.0)	144/305 (47.2) vs. 187/353 (52.9)	253/305 (82.9) vs. 260/353 (73.6)	52/305 (17.0) vs. 93/353 (26.3)	7/305 (2.3) vs. 14/353 (3.9)	NA	9/305 (2.9) vs. 17/353 (4.8)
Helwig et al. (2019)	NA	NA	NA	NA	NA	3/63 (4.8) vs. 4/53 (7.5)	NA

mRS: modified Rankin scale.

Figure 5. Pooled analysis of clinical outcome in terms of modified Rankin scale (0–2) at day 7.

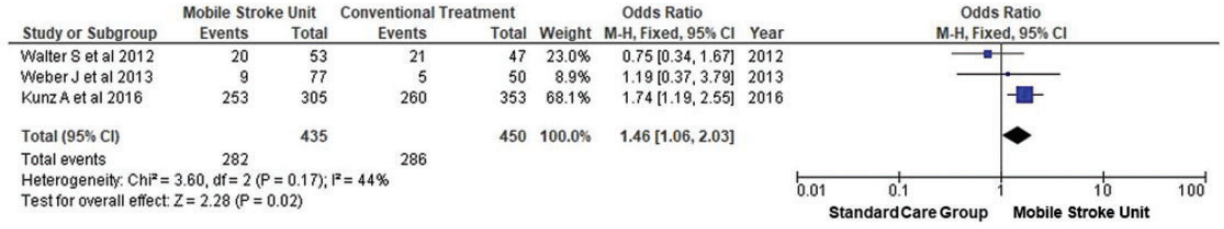


Figure 6. Pooled analysis of clinical outcome in terms of modified Rankin scale (0–2) at day 1.

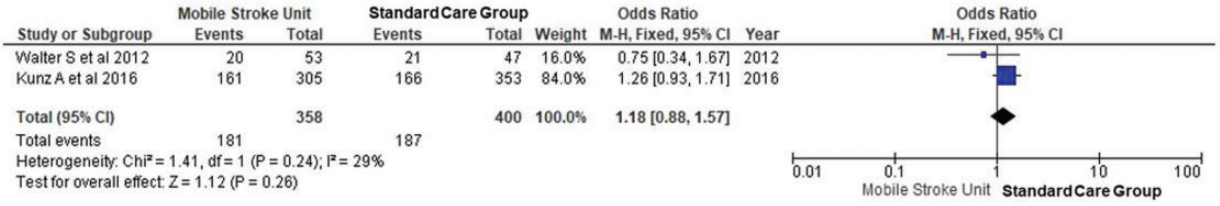


Figure 7. Pooled analysis of in-hospital mortality.

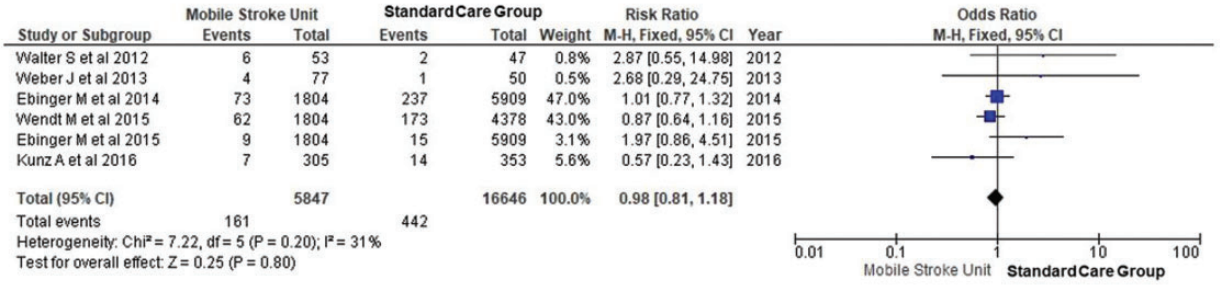
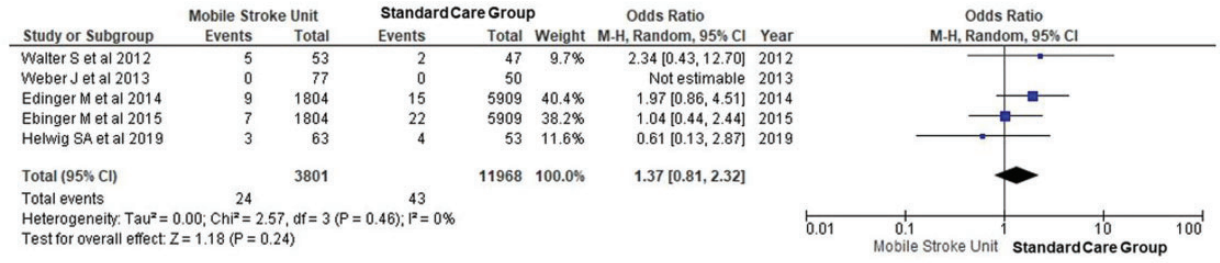


Figure 8. Pooled analysis of stroke-related or neurological death.



and NIHSS (9.8 ± 1.7 vs. 8.4 ± 1.5) was comparable in patients treated with MSU and emergency department, respectively. This is comparable to the previously published literature[20]; however, recent studies have shown increased proportion of patients with stroke under age 55 from 12.9% to 18.6%.[21] This is a public health concern since the younger stroke patients hold a greater potential for lifetime burden of disability. The mean

Figure 9. Pooled analysis of other adverse events.

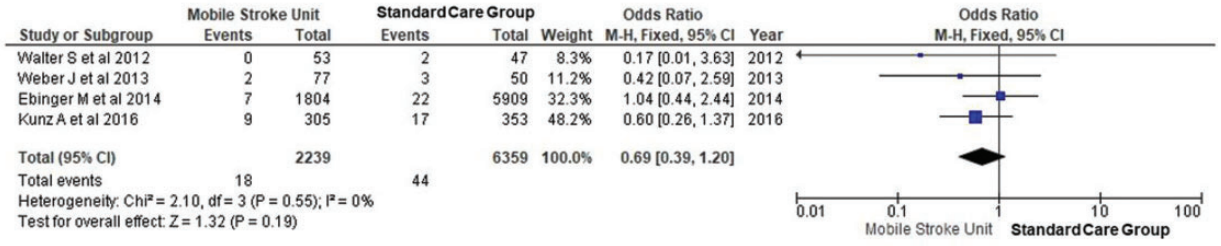


Table 4. Descriptions of mobile stroke unit and standard/conventional medical care

	Definition
Mobile stroke unit	MSU consists of prehospital thrombolysis. The MSU vehicle is a specialized ambulance equipped with a CT-scanner and point-of-care laboratory, and staffed by a paramedic, a radiology technician and physician who is specialized in neurology and emergency medicine. When an acute stroke is suspected during an emergency call, this vehicle is sent out in response. Depending upon the clinical symptoms such as disabling stroke symptoms, head CT scan and blood tests are done at the site. CT-scan interpretation is done by tele radiologists and thrombolysis is started immediately within the MSU vehicle.
Conventional care or standard medical care	Conventional care consists of in-hospital thrombolysis. The stroke patients are taken to the hospital through emergency medical series either in the specialized stroke centers or emergency department and given thrombolysis according to the imaging report.

thrombolysis time of 75 min was achieved in majority of the included studies[6,9,12] among patients treated in the standard care. All these studies were carried out in Germany. However, one of the other study[17] included which was also carried out in Germany had a mean time of alarm to IV thrombolysis of 82 min (76–93 min). The alarm to therapy decision and alarm to IV thrombolysis or IAT was calculated from the mean of the included studies; however, did not correspond to each other due to lack of available data in respective studies. However, in a study by Helwig S et al. 2019,[5] the alarm to therapy decision was 10.3 ± 3.6 min in the MSU group compared to 41.5 ± 12.8 min in the Standard Medical Care group. This was quite different from the alarm to IV thrombolysis or IAT which was 50.1 ± 10.1 min in the MSU group versus 84.9 ± 30.2 min in the standard medical care group.

Our study further demonstrates that patients treated in MSU had much faster opportunity to thrombolytics from the onset of acute stroke symptoms. The clinical evaluation and high-quality imaging provided in the MSU prompts the accurate diagnosis and appropriate treatment. Our results suggested that patients treated in MSU achieved significantly better clinical outcome. Three of the included studies[6,12,17] reported mRS at day 1 and 7 post treatment. However, only one included study[17] reported mRS at day 30 with mRS of 0–3 in 253 (83%) patients in the MSU group compared to 260 (74%) patients in the standard or conventional care group ($p = 0.004$). Another study[9] reported mRS at day 90 with a median mRS of 1 (0–3) in MSU group and 3 (1–5) in the conventional care group. The faster onset to thrombolysis treatment allowed better opportunity for prevention of the neuronal injury.[1] Our study showed that ambulance-based management of the stroke patients reduced alarm-to-treatment time, increased thrombolysis rates, and was effective in terms of clinical outcomes. Whereas, we did not show an improvement in long-term morbidity and mortality, further experience with larger number of patients will hopefully allow for definitive analysis. Although we do not have complete data pertaining to it, but it has been reported in the included studies that there were no higher reports of secondary hemorrhage when tissue plasminogen activator (tPA) was started in smaller hospitals and transferal to a referral stroke center was initiated immediately (drip and ship).[15] Furthermore, compared with the direct referral to CSCs (mothership paradigm), the patients with large-vessel occlusion are

often transferred to hospitals that cannot offer thrombectomy and then after eventually undergoing IV thrombolysis are secondarily transferred to a thrombectomy-capable CSC (drip-and-ship paradigm).[9]

Stroke is a medical emergency, for which "time is considered as brain"[1]; therefore, reduction in time by providing treatment in the MSU compared to that in the hospital should translate into improved outcome as evident by our study (mRS 0–2 at day 7; $p = 0.02$). Although in-hospital mortality and stroke-related neurological deficits were lower among patients treated in MSU compared to conventional standard care, but it did not reach statistical significance ($p > 0.05$). This could be due to the confounders predictive of mortality and stroke-related neurological deficits which were not considered while doing the analysis due to lack of reported data, which include: age, altered level of consciousness, risk factors, and comorbidities.[2] Thus, further studies are needed which consider these predictive factors into account while managing the patient either in MSU or hospital. Furthermore, there is a possibility that non-MSU patients traveled shorter distances to accepting facilities, thus have comparable outcome. However, further in-depth data are needed to evaluate for these differences.

Although duplication of studies is a critical issue but according to previously published literature[22] choosing one study and discarding the others could cause loss of information, which could be severe. However, we do not have reported data of number of patients that were included or excluded from the repeated studies[8,14,15] from the same institution included in our review. However, even after removing the studies[8,15] and keeping Ebinger et al.[14] (latest study with maximum number of patients) for the assessment of differences between mortality and stroke-related neurological deficits, the results were statistically insignificant ($p > 0.05$) between the two groups. There are several limitations of our study which include (i) data acquisition might vary between different care takers, hence we cannot rule out information bias, (ii) enough data regarding the time to stroke alarm and arrival at the scene were not documented adequately by the studies, therefore, we can potentially overestimate the time savings in the patients treated in the MSU, (iii) long-term clinical outcomes at six to nine months after treatment were not reported, (iv) patients with loss-to-follow up might have introduced an additional bias in our analysis, (v) confounding variables like diabetes mellitus and hypertension were not adjusted in our analysis due to lack of data, and (vi) the discharge diagnosis of ICH and stroke mimics differed among patients treated in MSU compared to those in conventional care among included studies. However, the OR calculated for the primary and secondary end point included total number of patients recruited in two groups at the time of initial clinical presentation due to lack of data.

However, a large sample size and strong statistical analysis strengthen our meta-analysis. Further prospective studies are needed which can compare the treatment in both groups with the clinical assessment on both short- and long-term basis.

Conclusion

Our study suggests that reducing the treatment time by starting thrombolytics in the MSU in patients with acute ischemic stroke improve the functional outcome without an increase in the mortality or adverse event rate. However, further studies with long-term clinical outcome are necessary to validate our results.

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