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How FAST are we? A systematic review and meta-analysis of the effectiveness of intervention done on paramedic services in increasing thrombolysis rate

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Abstract

Objectives: The paramedics' role is pivotal in ensuring eligible stroke patients reach the hospital within 4.5 hours, as this increases the chance of patients being treated with recombinant tissue plasminogen activator (rTPA) and improves their outcome. The lack of reviews on interventions done on paramedic services and the outcomes associated with them necessitates further investigation to enable policymakers to make guided decisions in improving the management of acute ischaemic strokes. Hence, our study aimed to identify interventions done and their impact on thrombolysis rate and onset-to-door (OTD) time. *Methods:* We searched PubMed, Embase, CINAHL and RCN to identify studies published between 1 January 2010 and 30 June 2020. The primary outcome of this study is investigating the impact of interventions done on paramedics services on the rTPA administration rate and OTD timing. Other outcomes include improvement in door-to-needle (DTN), door-to-imaging (DTI) and onset-to-needle (OTN) time. Random effect models were used to analyse the effects of the interventions carried out. *Results:* We gathered 621 papers, of which 11 met the eligibility criteria. The interventions carried out were bypass (n=3), education (n=2), pre-notification (n=4) and telemedicine (n=2). Based on the random effect model, rTPA administration was significantly higher in the intervention arm of ischemic stroke patients (n=7) with an OR of 1.45 (95%CI, 1.01-2.06). The trend was significantly higher with bypass intervention (OR 2.23 95%CI, 1.55-3.2), while the result with pre-notification (OR 0.53 95%CI, 0.09-2.95) and education (OR 1.51 95%CI, 0.87-2.60) were not significant.
Conclusions: Paramedic interventions appear to have considerable effectiveness in improving the rates of rTPA, especially when the interventions used bypass mechanisms. This study provides detailed information on the net and quantitative benefits of the interventions and suggests the use of such interventions to reduce the pre-hospital delay of stroke patients and improve the rates of intravenous thrombolysis.

Keywords: Paramedic, emergency medical service, stroke, onset-to-door, thrombolysis

INTRODUCTION

In acute ischaemic stroke (AIS) patients, rTPA is considered as one of the most evidence-based treatment options from the last two decades.[1,2] It converts plasminogen into plasmin, which lyses the clot and restores the normal perfusion.[3] Despite having a narrow therapeutic window of 4.5 hours and potentially causing post-thrombolysis intracranial haemorrhage (ICH), infusion of rTPA to eligible patients can produce favourable outcomes.[1,4]

Due to the narrow therapeutic time window, the reported rate of thrombolysis globally is quite low.[5-7] Several initiatives have already been tested to change the management of acute stroke practice. Barriers towards utilization of thrombolysis have been identified, and researchers have concluded that pre-hospital and in-hospital management plays a vital role in increasing the chance of eligible patients being thrombolysed, hence determining their fate and outcome.[8] In the late 1990s, it was found that paramedics were not only unable to identify stroke patients, but were also unaware that rTPA has a narrow therapeutic time window.[9] Since then, a lot of effort has been put into changing the practice among paramedics in managing acute strokes.[10-14]

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Three recently published systematic reviews by Huang *et al*.[10], McDermott *et al*.[11] and Hasnain *et al*.[15] evaluated the overall effect of interventions aimed at improving the rates of thrombolysis in AIS and sub-grouped their findings based on study design, intervention type and their components. However, the first step in improving the rates of thrombolysis is to reduce the pre-hospital delay, and paramedics play a pivotal role in pre-hospital acute stroke management. Although several paramedic interventions have already been tested to improve the rates of thrombolysis, a systematic evaluation is needed to understand how pre-hospital mechanisms with paramedics improve thrombolysis rates. So far, no systematic review has been conducted. Therefore, our study aimed to identify the types of paramedic interventions and the improvement in thrombolysis rate and onset-to-door time.

METHOD

This systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[16] The PRISMA statement is demonstrated in Figure 1. This review was registered (PROSPERO registration: CRD42020184936).

Search strategy

Embase, PubMed, CINAHL, and RCN databases were searched for articles published from January 2010 to May 2020. The reason for looking at 2010 onwards was that the extension of Intravenous Thrombolysis (IVT) from 3 hours to 4.5 hours was done in 2008; hence, we wanted to ensure that patients who came in between 3 to 4.5 hours were included in the study and had the chance to be thrombolysed. There were no geographical restrictions, but only articles in English were included. The search strategy included the study population using terms and keywords derived from scoping search and expertise in the subject field such as paramedic, emergency medical service, emergency medical technician,

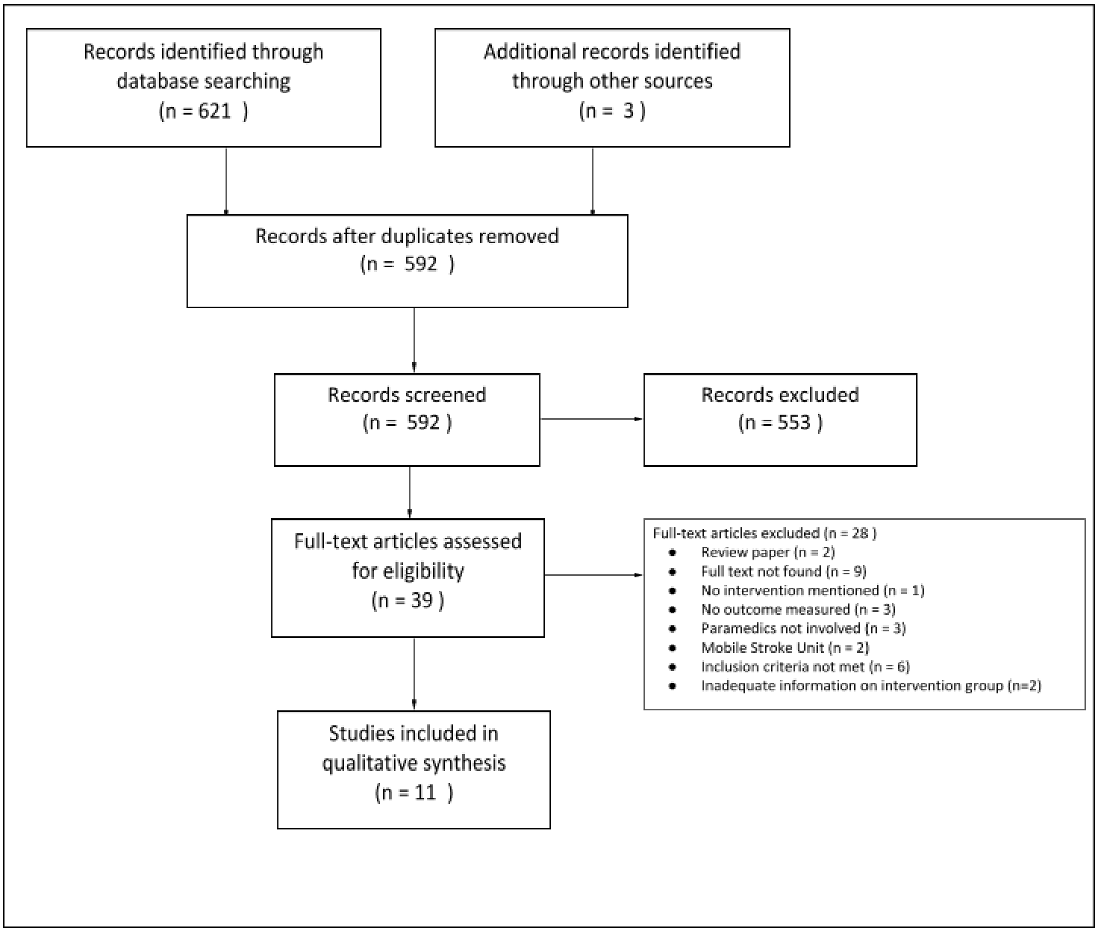

Figure 1: PRISMA flow chart

helicopter, pre-hospital, stroke, cerebrovascular, and cerebrovascular accident. Outcome terms included terms such as onset-to-door, door-to-needle, door-to-imaging, thrombolysis and tissue plasminogen activator.

Inclusion and exclusion criteria

The inclusion criteria were studies that investigated the effect of an intervention aimed at improving the rate of thrombolysis or reducing the OTD time in patients with AIS. The study design included experimental studies covering randomized controlled trials and cluster-randomized trials; non-randomized studies such as uncontrolled before-after studies and parallel group trials; and observational studies including cohort, case-control, and cross-sectional studies. However, non-English publication and study findings solely related to haemorrhagic stroke, transient ischemic attack or stroke mimics were excluded.

Patient and public involvement

Patients or the public were not involved in the design and conduct of this research.

Search processes and data collection

Three reviewers screened records for inclusion and checked and confirmed the publications that were considered in this study (NA, IJ, LC). Initially, abstracts were screened, and full text papers were reviewed and discussed where there was disagreement. Cited references in several articles were also cross-checked to determine studies that were not present in the databases. The papers were then checked for duplicates. To avoid bias, three more reviewers evaluated the extracted data for consistency and clarity (SS, JA, MGH). The data included author and year, study designs, number of participants, intervention, control, outcome measures and main findings (Table 1).

Study quality assessment and control

Three reviewers (NA, IJ and LC) independently assessed the quality of the studies using the QualSyst scoring system.[17] Any disagreements among the reviewers were resolved by the joint discussions among them. Each included study got a summary score based on whether it fully met the criteria (2 points), partially met the criteria (1 point) or did not meet the criteria at all (0 points). Quantitative studies were scored against 14 criteria. Quality control of the inclusion and exclusion process of all studies was performed by three reviewers (NA, IJ and LC) using an independent selection process. All the included studies were then independently assessed by the senior reviewers (SS, JA, MGH). Any disagreement was resolved by joint discussions among the reviewers. However, the agreement rates were always over 90% at all stages of quality control related to inclusion or exclusion of studies and study quality measurement.

Analysis

Narrative synthesis was conducted to demonstrate outcomes for the included studies, including descriptions of the extracted data. Data synthesis involved tabulation of the study findings, for example, describing whether the study intervention found a significant association with the outcome of interest or not. Synthesis of the study findings through meta-analysis was also done where possible. Studies with very similar types of intervention and specifying the rate of thrombolysis with a clear indication of the numerator and denominator were considered for meta-analysis. For the meta-analysis, a pooled odds ratio (OR) with a 95% confidence interval (CI) was calculated using the *metan* command in Stata. In addition, forest plots were used to identify the effect sizes and to measure possible heterogeneity. Statistical heterogeneity was assessed by I^2 statistics. Stata (StataCorp LLC, College Station, Texas, USA) version 14 was used to conduct all analyses.

RESULTS

Study selection

Six hundred and twenty one articles were obtained through three databases: PUBMED (n= 60), EMBASE (n =539) and CINAHL (n = 22). An additional three articles were identified through other sources, giving a total number of 624 articles. After removing the duplicates, 592 articles were included for abstract and title screening. Among the 592 articles, 553 were excluded. The remaining 39 articles were eligible for full-text review, but only 11 articles were used in this research. The 28 articles excluded at this stage were review papers, papers with no full texts available, papers with neither intervention mentioned nor outcome measured, papers involving other healthcare professionals and mobile stroke units, papers not meeting the inclusion criteria and papers with inadequate information on the intervention group (Figure 1).

Description of studies

Table 1 summarises the 11 studies exploring paramedic interventions that were done to improve OTD and rates of tPA. Other outcomes including DTI and DTN were also explored in this research. Three studies explored **bypass** as an approach to improve stroke outcomes.[18-20] Bypass is a system whereby stroke patients are transported directly to a stroke centre, bypassing the nearest district or local hospital without a stroke unit. Two studies implemented **education** among the paramedics around stroke recognition and local protocols.[21,22] Both papers showed improvement in the tPA rate. Four studies looked at **pre-hospital notifications** as an intervention.[23-26] For these, there were significant improvements in DTI and DTN times. Finally, two intervention studies explored the use of **telemedicine** in improving stroke outcomes.[27,28] OTD time was also improved in both papers. Belt *et al*.[27] reported a significant improvement in DTN time.

Meta-analysis

A meta-analysis was done on seven papers which were authored by Sanossian *et al*.[18], Prabhakaran *et al*.[19], O' Brien *et al*.[20], Oostema *et al*.[21], Binning *et al*.[22], Lin *et al*.[23] and Bae *et al*,.[24] Based on the random effect model, a borderline significant effect was found (Figure 2) with a pooled OR of 1.45; 95% CI: 1.01-2.06. Sub-group analysis reveals that only bypass showed significantly higher OR: 2.23; 95% CI: 1.56- 3.20. The pooled OR for the education and pre-notification was non-significant, with OR: 1.51; 95% CI: 0.87-2.60 and OR: 0.53; 95% CI: 0.09-2.95, respectively. High heterogeneity was observed with the overall and pre-notification group; therefore, these pooled estimations should be interpreted with caution.

DISCUSSION

The findings of this systematic review and meta-analysis gathered and summarized together the evidence regarding the paramedic strategies that are potentially effective in improving IVT rates for AIS. This study found significant overall benefits for the studies implemented bypass mechanism as intervention strategy.

The treatment for ischemic stroke is recommended to be initiated within 4.5 hours of symptom onset to improve the level of function.[18] Thus, several paramedic interventions were carried out to identify what interventions improve OTD time and tPA rate, namely bypass (Sanossian *et al*.[18], Prabhakaran *et al*.[19]; O'Brien *et al*.[20]); education (Oostema *et al*.[21], Binning *et al*.[22]); pre-notification (Lin *et al*.[23], Bae *et al*.[24], English *et al*.[25]; Zhang *et al*.[26]), and telemedicine (Belt *et al*.[27]; Bergrath *et al*.[28]).

Bypass involves introducing a protocol to paramedics whereby stroke mimic patients are directed to hospitals with stroke units, bypassing local or district hospitals without one. The FASTER protocol, for example, was used by paramedics in Australia to help with stroke recognition and to evaluate patients' stroke severity, in order to determine the eligibility of stroke mimic patients to be sent directly to a stroke centre, thus bypassing those hospitals closer by without a stroke unit.[20] It can be seen that there is an improvement not only in OTD time (59min vs 76min, $p = 0.18$) but also DTI time (19min vs 49min, $p = 0.004$), DTN time (56min vs 102min, $p = 0.001$) and OTN time (125 min vs 157min, $p = 0.005$). A protocol-based intervention was also implemented in a study by Atsumi *et al*.[30] This protocol focussed on MPSS-based stroke bypass transportation. Unlike other studies, this study looked at the trend throughout the years. It can be seen that there was an improvement in the OTN time and tPA rate between 2009 and 2012.[30] Similar to this study, Prabhakaran *et al*.[19] found that the IV tPA administration increased from 3.8% to 10.1% ($p < 0.001$) and there was an almost 30-minute reduction in OTD time. Therefore, both protocol-based intervention and bypass shows improvement in OTD.

The two studies that implemented education on the paramedics focused on pre-hospital stroke alert in shortening OTD and increasing tPA rate. Binning *et al*.[22] provided education and training to the paramedics and emergency medical technicians of Capital Health. The involved staff members were certified in Advanced Stroke Life Support and the Miami Emergency Neurological Deficit examination. Based on their 'pre-hospital stroke alert' protocol, the paramedics were advised to notify the ED when they identified a stroke patient, and to complete a stroke checklist. Upon arrival at the hospital, the paramedics delivered the patients directly to CT. The result of this study showed that there was an improvement in DTI time (11.8min vs 35min), DTN time (56.5min vs 99min) and tPA rate (18% vs 5%). In another study conducted by Oostema *et al*.[21], 793 paramedics received a web-based training module on the pre-hospital stroke alert protocol. The protocol focuses on the recognition of strokes using the Cincinnati Prehospital Stroke Scale and pre-hospital notification. From the results, an increase

Table 1: Characteristics of the 11 included studies

Author/Year	Country	Journal	Study Design	Study Period	N	Population	Comparison Group	Intervention	Control	Outcome Measures	Main Findings (intervention/control)	Bias Rating
Bypass (n=3)												
Sanossian *et al*. (2015)[18]	US	American Heart Association	Cohort study	2005-2012	1627 patients Intervention: 255 enrolled Control: 215	Patients with likely stroke indicated by a positive Los Angeles Pre-hospital Stroke Screen and paramedic and physician-confirmed LKWT of within 2 hours	Intervention vs Control	EMS routing protocol to approved stroke centre	-	a. On Scene-to-Door Time b. tPA Rate c. Transported to ASC	**OSTD** 33.5 min vs 34.5 min P value = 0.045 (sig) **tPA Rate** 35% vs 33% P value = 0.832 (not sig) **Transported to ASC** 88% vs 17% P value < 0.001 (sig)	81.82 (High)
Prabhakaran *et al*. (2013)[19]	US	Jama neurology	Retrospective multicenter cohort study	2010-2011	2247 patients Pre: 1075 Post: 1172	All admitted patients with stroke and transient ischemic attack.	Pre vs Post	Pre-hospital Stroke Triage	Without pre-hospital stroke triage	a. Onset-to-ED b. tPA Rate c. Onset-to-Treatment d. Door-to-Needle	**OTD** 0-60 min: 108 (13.7%) vs 54 (7.5%) 61-120 min: 58 (7.4%) vs 47 (6.5%) 121-180 min: 18 (2.3) vs 33 (4.6) 181-270 min: 31 (3.9) vs 24 (3.3) 271-360 min: 26 (3.3%) vs 27 (3.8) >360 min: 117 (14.9) vs 108 (15%) P value < 0.001 (sig) **tPA Rate** 64 patients (10.1%) vs 23 patients (3.8%) P value < 0.001 (sig) **OTT** Mean, (SD) 145.7min (55.7) vs 171.1min (46.2) P value = 0.03 (sig) **DTN** Mean, (SD) 89.5min (47.3) vs 102.9min (26) P value = 0.14 (not sig)	100 (High)

O'Brien *et al*. (2012)[20]	Australia	Journal of Clinical	Interrupted time series analysis	2007-2008	Pre: 17 Post: 25		Pre vs Post	FASTER protocol (Face, Arm, Speech, Emergency Response)	Historical controls from the same hospital in the corresponding period 1 year earlier	a. Onset-to-Door b. Door-to-Imaging c. Door-to-Needle d. Onset-to-Treatment	**OTD** Mean tx times for pt receiving tPA 59min vs 76min P value = 0.18 (not sig) **DTI** Mean tx times for pt receiving tPA 19min vs 49min P value = 0.004 (sig) **DTN** Mean tx times for pt receiving tPA 56min vs 102 min P value = 0.001 (sig) **OTT** Mean tx times for pt receiving tPA 125min vs 157min P value = 0.005 (sig)	77.27 (Medium)
Education (n=2)												
Oostema *et*. *al*. (2019)[21]	US	American Heart Association	Interrupted time series analysis	2015-2017	1805 patients Intervention: 793 Control: 1012	Patients with an EMS primary or secondary impression of stroke or transient ischemic attack (TIA) EMS-transported patients with a discharge diagnosis of stroke or TIA following their ED or hospital course who were not recognized by EMS	Pre vs Post	30-minute web-based training module: Pass a post-training test with a score of at least 80 to receive credit for training.	-	a. Door-to-Imaging b. Door-to-Needle c. tPA Rate	**DTI ≤ 25 min** 250/544 patients (46%) vs 297/691 patients (43%) P value = 0.296 (not sig) **DTN** 41/544 patients (8.9%) vs 34/691 patients (5.7%) P value = 0.045 (sig) **tPA Rate** 81/544 patients (17.7%) vs 83/691 patients (13.9%) P value = 0.096 (not sig)	100 (High)
Binning *et*. *al*. (2014)[22]	US	Neuro-surgery	Prospective	2012-2013	141 patients Intervention: N/A Control: N/A	Patients 18 years of age and older identified by EMS as having a possible acute stroke	Intervention vs Control	Education & Training: Pre-hospital stroke alert protocol	-	a. Door-to-Imaging b. Door-to-Needle c. tPA Rate	**DTI** 11.8min vs 35min **DTN** 56.5min vs 99min **tPA Rate** 18% vs 5%	59.09 (Medium)

Pre-notification (n=4)											
Lin *et. al*. (2012)[23]	US	American Heart Association	Retrospective Cohort Study	2003-2011	826656 patients Intervention: 249197 Control: 122791	AIS	Intervention vs Control	EMS pre-notification	No EMS pre-notification	a. Onset-to-Door b. Door-to-Imaging c. Door-to-Needle d. Onset-to-Needle e. tPA Rate	**OTD** 113min vs 150min **DTI** 112580 patients vs 230430 patients Median (IQR) 42min (22-83) vs 55min (28-103) P value < 0.0001 (sig) **DTI ≤ 25min** 22.4% vs 30.9% P value < 0.0001 (sig) **DTN** Median (IQR) 78min (60-100) vs 80min (60-103) P value < 0.0001 (sig) **DTN ≤ 60min** 27.0% vs 25.9% P value = 0.0583 (not sig) **OTN** Median (IQR) 140min (114-168) vs 145min (116-170) P value < 0.0001 (sig) **OTN ≤ 120min** 32.4% vs 29.8% P value < 0.0001 (sig) **tPA Rate** (Arrive by 2h, treat by 3h) 22305/30541 patients vs 7193/11244 patients 73.0% vs 64% P value < 0.0001 (sig)	100 (High)
Bae *et al*. (2010)[24]	South Korea	Journal of Clinical Neurology (Seoul, Korea)	Retrospective observational case study	2008-2009	102 patients Intervention: 18 Control: 33	Central alerting system Hotline system in conjunction with the Korean Emergency Medical Information System (1339) for pre-hospital notification	Intervention vs Control	With pre-hospital notification (1339)	Without pre-hospital notification (1339)	a. Onset-to-Door b. Door-to-Imaging c. Onset-to-Needle d. Door-to-Needle	**OTD** 124.4 min vs 86.5 min P value = 0.02 (sig) **DTI** 17.8 min vs 26.9 min P value = 0.01 (sig) **OTN** 150.8 min vs 128.6 min P value = 0.03 (sig) **DTN** 29.7 min vs 42.1 min P value = 0.01 (sig)	86.36 (High)

English *et al*. (2018)[25]	US	Journal of Stroke and Cerebro-vascular Disease	Retrospective, observational single center cohort study	2014-2015	Intervention: 130 Control: 247	Positive CPSS in field, EMS impression of CVA or TIA, ASP activation in the ED or discharge diagnosis of CVA or TIA	Intervention vs Control	With Acute Stroke pager (ASP)	Without ASP	a. Response Time (EMS dispatch-to-arrival on scene c. Transport Time d. tPA Rate	**Response time** Mean 7.3min vs 7.5min P value = 0.833 (not sig) **Transport time** Mean 9.6min vs 10.2min P value = 0.572 (not sig) **tPA Rate** 23 vs 0	77.27 (Medium)
Zhang *et.al*. (2018)[26]	China	Aging and Disease	Retrospective	2015-2016	Intervention: 41 Control: 36	Patients with acute ishcemic stroke or transient ischemic attack who received IVT between March 2015 and March 2016, have complete follow-up records	Intervention vs Control	Systemized Pre-hospital Notification Procedure (PNP)	Without PNP	a. Onset-to-Door b. Onset-to-Needle c. Door-to-Imaging d. Door-to-needle	**OTD** Mean 133.2min vs 130.3min **OTN** Mean 174.54min vs 182.3min **DTI** Mean 18.1min vs 25.8min P value < 0.05 (sig) **DTN** Mean 41.3min vs 51.9min P value < 0.05 (sig)	95.45 (High)
Telemedicine (n=2)												
Belt *et al*. (2016)[27]	US	American Heart Association	Cohort study	2015-2016	111 patients Intervention: 89 Control: 22	Suspected stroke	Intervention vs Control	In-transit telestroke (ITTS)	Without in-transit telestroke	a. Scene-to-Door b. Door-to-Needle	**STD** 29min vs 34min P value > 0.05 (not sig) **DTN** 28min vs 41min P value = 0.02 (sig)	86.36 (High)
Bergrath *et al*. (2012)[28]	Germany	Plos One	Prospective observational	2010	939 patients Intervention: 18 Control: 46	Patients with suspected stroke	Intervention vs Control	ALS ambulance equipped with telemedical equipped team (ALS: advanced life support)	Regular ALS unit	a. Onset-to-Door b. Door-to-Imaging	**OTD** 37.5min vs 35min P value = 0.9671 (not sig) **DTI** 59.5min vs 57.5min P value = 0.6447 (not sig)	77.27 (Medium)

Abbreviations: OTD= onset-to-door, DTN= door-to-needle, DTI= door-to-imaging, STD= scene-to-door, OTT= onset-to-treatment, tPA= tissue plasminogen activator, OSTD= On scene-to-door time, ASC= approved stroke centres, LKWT= last known well time

Biasness rating cut-off point:
0-50: Low
51-79: Medium
80-100: High

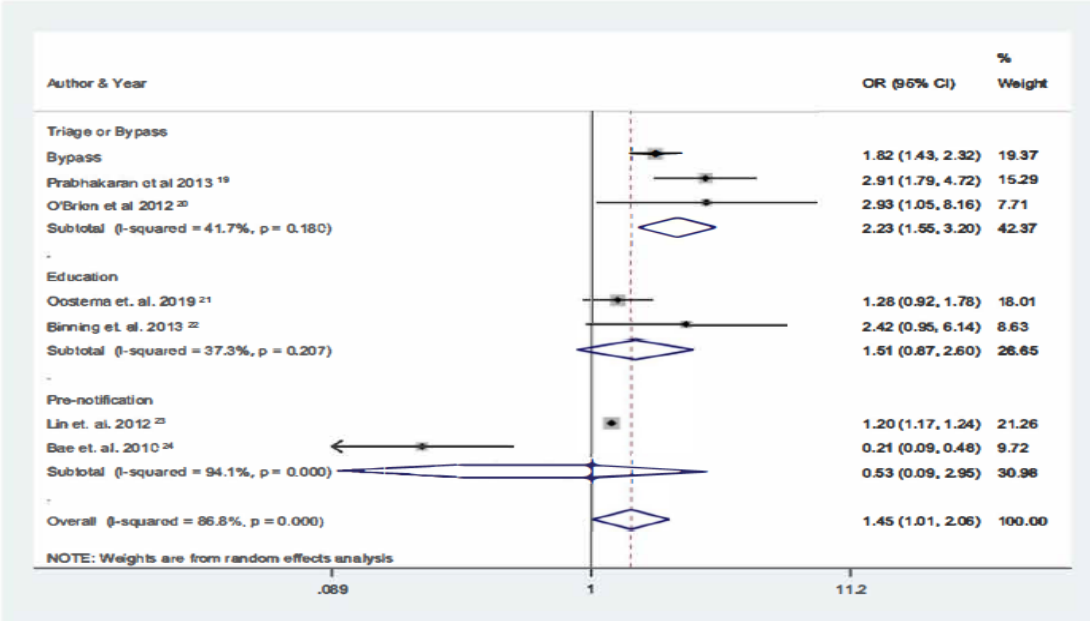

Figure 2. Meta-analysis results showing the effect of intervention on the thrombolysis rate with sub-group results.

in thrombolysis rate can still be seen (from 13.9% to 17.7%, p = 0.096), although not significant. Based on these findings, education intervention has vast potential to improve paramedic services in the future.

EMS pre-notification is one of the most practical interventions that can be done to improve the treatment of stroke patients. It has been shown that pre-notification has a significant impact on in-hospital procedures, especially the time in the ED.[26] A study conducted in the United States by Lin *et al*.[23] showed that the OTD time (113min vs 23 150min), DTI time (42min vs 55min, p < 0.0001), DTN time (78min vs 80min, p < 0.0001) and OTN time (140min vs 145min, p < 0.0001) all improved with the implementation of EMS pre-notification. Furthermore, patients with pre-notification were associated with higher rates of thrombolysis. On the other hand, Bae *et al*.[24] and Zhang *et al*.[26] showed that pre-notification was associated with longer OTD. Bae *et al*.[24] discussed a hotline system in collaboration with the Korean Emergency Medical Information System (1339) which pre-notifies hospitals by providing information about the patient's status, thus allowing more time for the stroke team to make relevant preparations. Similarly, in the study by Zhang *et al*.[26], the systemised pre-hospital notification procedures involve paramedics notifying the ED team. In both of these studies, while having improved DTI, DTN and OTN times, the OTD time is longer in the intervention group compared to the control group. However, the population in both studies was small, so the results may not have been able to capture the impact of pre-notification among the bigger stroke population.

In the studies looking at telemedicine conducted by Belt *et al*.[27] and Bergrath *et al*.[28], cameras, microphones and screens installed in the ambulances serve as a communication bridge between the paramedics and other healthcare professionals such as the ED team or neurologists. In-ambulance assessments and stroke history checklists were done with the devices on board in collaboration with the stroke team in the hospital. This method helped to shorten the onset-to-needle time. However, traffic conditions affected the transportation time. Researchers also suggested that structured training can improve the accuracy of stroke diagnosis.[28] In any case, these technological advancements could be adapted by healthcare systems in developing countries, as they are more affordable, feasible and cost effective. Another method of reducing OTD time is mobile stroke units (MSUs). In Australia, MSUs are utilized to help improve stroke outcomes, especially the tPA rate. MSU ambulances are equipped with computed tomographic scanners and with a neurologist on board, either in person or by telemedicine, to evaluate patients with ischemic stroke symptoms.[31] When a patient with a stroke is identified, treatment is given immediately in the ambulance. According to research, MSUs deliver shorter DTN times.[32] However, an MSU costs more than USD 1 million for the devices and requires other healthcare technicians to be on board, which causes the operating cost to be more than USD 1 million per year.

There are several limitations to this study that need to be noted. Only papers from the past 10 years were included and due to a lack of studies done on this topic, papers with a small sample size were included in this review, which may have reduced the significance of the results. Moreover, most of the studies were conducted in the United States, so the findings cannot be generalised to global health systems as different countries from various continents face different challenges in terms of technology advances, healthcare protocols and financial or economic status. Therefore, bias on efficacy may be present. Besides that, heterogeneous outcome measures, complex interventions and potential uncontrolled confounding factors limit the studies' eligibility for further analysis. Furthermore, many governmental, regional and organizational efforts for improved access to thrombolysis are not published in the journals. Our review possibly fails to capture these interventions. However, despite all these limitations and challenges, the conclusion of this review is considered to be robust and it generates a significant platform for further studies.

In conclusion, overall, these interventions seem to have substantial effectiveness and our findings provide evidence for the pursuit of future interventions and policies in understanding the mechanism of paramedics in reducing the pre-hospital delay and maximizing patient outcomes.

DISCLOSURE

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