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Pre- and In-Hospital Management of Stroke

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Abstract

Background: For acute ischemic stroke (AIS), intravenous thrombolysis (IVT) is an effective but time-dependent therapy. However, patients are usually too late for treatment, mainly because of pre- and in-hospital delays.

Method: Papers were identified through the PubMed search, with keywords such as: 'stroke', 'thrombolysis', 'management', 'prehospital delay', 'in-hospital delay'.

Results: In pre-hospital stroke management, factors related to pre-hospital delays include demographic characteristics, social factors, clinical factors, behavioral factors, and cognitive factors. Great significance should be assigned to the implementation of stroke preparedness interventions, stroke assessment instruments, the use of emergency medical service (EMS), mobile stroke units (MSUs), and the Stroke Emergency Map. With regard to in-hospital stroke management, there are some tasks related to the in-hospital delays, such as registering patients, waiting for the stroke team, CT availability, lab resources, and making a decision for thrombolytic therapy. With good communication between the EMS and the emergency department (ED), delays can be significantly reduced.

Conclusions: With the streamlining of all aspects of pre-hospital and in-hospital thrombolysis processes and the increase of hospital experience, we can achieve a shorter onset-to-treatment time (OTT), and more patients may benefit from timely thrombolytic therapy.

Keywords

Acute ischemic stroke, Thrombolysis, Management, Pre-hospital delay, In-hospital delay, Mobile stroke units

Introduction

Stroke is a leading cause of death and disability [1], which brings a considerable socioeconomic impact as a result of the loss of labor productivity and high health-care costs. Surprisingly, in the United States, someone suffers a stroke every 40 seconds on average, and someone dies of one approximately every four minutes [2].

Intravenous recombinant tissue plasminogen activator (rt-PA), a medical reperfusion therapy [3], is beneficial for stroke patients to reduce irreversible brain damage, prevent death, and improve long-term quality of life [4,5]. However, this treatment has a time window of 4.5 hours, which should be initiated as soon as possible [6]. Better functional outcome is linked to shorter onset-to-treatment time (OTT) [7-10]. Furthermore, the benefit is highly time-dependent within the therapeutic time window [11,12]. As a pooled analysis of randomized trials shows, comparing the patients treated between 3 and 4.5 hours with those treated in the first three hours, the number of people needing treatment to recover without disabilities doubles [11]. Another study indicates that every 15 minutes of expediting rt-PA is advantageous in extending stroke patients' healthy lives by one month [13]. The documented presence of delays increases the odds of symptomatic intracranial hemorrhage and in-hospital mortality, and decreases the odds of independent ambulation at discharge [14]. Therefore, the sooner rt-PA is initiated, the better the outcome for stroke patients.

In AIS thrombolysis, OTT consists of onset-to-door time (ODT) and door-to-needle time (DNT). In this review of stroke management, we stress the need to optimize each link of the stroke rescue chain. With the streamlining of all aspects of pre-hospital and in-hospital thrombolysis processes and the increase of hospital experience, we can achieve a shorter OTT, and more patients may benefit from timely thrombolytic therapy.

Prehospital Stroke Management

Among the factors hindering reperfusion therapy, delayed presentation at the hospital is a significant one [15], especially in non-English speaking and less developed regions and countries [16]. In some comprehensive stroke centers, although the DNT was much lower than 30 minutes, the ODT remained stagnant above 60 minutes over a period of nearly 20 years [17,18].

In 2018, an international symposium was held in China, which focused on the prehospital delays and some novel strategies to effectively address them [16]. The symposium discussed the possibility that long prehospital delay times may be attributable of the poor public awareness, poor usage of EMS, or even lack of EMS.

Table 1: The factors associated with prehospital delay in acute stroke.

Factors	early arrival	Late arrival	References
Demographic	High level of education	Low level of education	[25,27]
	High income	Low income	
		Ethnic minorities	[28]
Medical	Atrial fibrillation		[22]
	Knowing someone who had suffered a stroke		[23]
	Onset location was at outside the home	Onset location was at home	[23,24]
	Onset during daytime	Onset during nighttime	[20,22]
	Greater stroke severity		[21,22,24]
	Coma		[19,20,26]
	By an emergency medical service	By other means of transportation	[22]
Social	Someone else noticed the symptom onset first	Patients noticed the symptom onset first	[20,23]
	Shorter distance from the onset place to the first hospital	Further distance from the onset place to the first hospital	[23]
Cognitive and behavioral	Calling emergency number, going to hospital directly, asking others for help	Doing nothing and waiting	[23]

The factors related to prehospital delays in AIS

Various determinants of prehospital delays have been identified; these include demographic characteristics, social factors, clinical factors, behavioral factors, and cognitive factors [19-28], as shown in Table 1.

Some other factors are unclear, such as age [20], sex [20,29,30], a history of stroke [23,31,32], and transferred from community-based hospitals [23,33,34].

Stroke preparedness

The recognition of stroke-like symptoms by EMS personnel, patients, and their families is the first step in timely workup and treatment of AIS. Furthermore, inappropriate care-seeking behaviors (i.e., visiting a general physician, using a private vehicle, or taking a "wait-and-see" approach), contribute to increased prehospital delay [8]. Timely care-seeking is significantly associated with patients' awareness of AIS [22]. However, in a Greek study, 24% of the study participants surveyed did not know any stroke symptoms [35]; in Spain, 11% did not know any symptoms [36]; in the United States, 32% did not know any symptoms [27], and in Hubei Province in China, around 60% of patients did not recognize initial stroke symptoms [37]. Even in family physicians and non-neurologists, this phenomenon also exists [16,38-41].

With inconclusive and inconsistent results, stroke awareness campaigns have been evaluated in several studies [28,42-48]. Some campaigns indicated that there was no significant reduction in pre-hospital delay after exposure to public education campaigns regarding AIS [28,42,43]. On the other hand, in recent years, some educational campaigns have had a positive effect; among the stroke preparedness campaigns, mass media campaigns may encourage stroke patients to present to the hospital via EMS and bypass their general practitioners, which indicates that these mass media campaigns can not only improve public's recognition and response to stroke, but can also change the behaviors of stroke patients [46]. However, some limitations exist, such as high advertising costs, low penetration of ethnic minority populations [47], lack of cultural customization, and a possible decline in effectiveness once media campaigns end [44]. Besides that, education in schools is attracting more and more attention as an alternative to mass media. Recently, in America, a randomized controlled trial of a school-based stroke education program for minorities who are economically disadvantaged showed that both parents and children have made significant and relatively large advances in stroke preparedness [48].

More endeavors should be made to reach target groups of different ages and backgrounds (i.e., medical students, the neighbors of stroke survivors, the elderly, minorities, children who may be future physicians, patients, and relatives) [16,49,50]. Firstly, to inform the younger generation, who may make decisions to seek medical treatment for elderly family members, education programs could be incorporated into the school system. Secondly, it is critical to educate family doctors and community hospital physicians, which may increase the use of expedited ambulance transportation in the event of a suspected stroke. Thirdly, educating EMS personnel is of great significance, as they could help to identify and prioritize ambulances for potential stroke patients. Since far fewer facilities are available to perform thrombectomies, it is critical for EMS staff on site to identify potential major vessel occlusion according to the stroke scale, which could help them to act quickly in transferring stroke patients to the appropriate hospitals. Fourthly, in-hospital education

aimed at addressing subsequent stroke events should also be developed, because of the higher disability rates and mortality risk associated with recurrence. Such educational work is a long-term task which requires the efforts of several generations.

Stroke assessment instruments

There are several stroke assessment instruments available to help the public and healthcare workers quickly assess and triage patients with acute stroke, such as the Cincinnati Pre-Hospital Stroke Scale (CPSS) and the Los Angeles Prehospital Stroke Screen (LAPSS) in the US, the Face Arm Speech Test (FAST) in the UK, the “Stroke 112” in the Taiwan [38], and the “Stroke 120” in mainland China [51,52].

The CPSS is used to assess whether patients have the following conditions: Facial palsy, asymmetric arm weakness, and speech disturbance (this is measured by having the patient repeat a sentence) [53]. In addition to the analysis of motor weakness, the LAPSS also contains a blood glucose measurement and four historical items [54]. It has a high specificity (97%) and sensitivity (91%) for the diagnosis of prehospital stroke [54]. However, it may exclude some conditions that mimic stroke and consume more time, and it is not useable for public education. The FAST is based on the three elements of the CPSS, but it assesses possible speech disorders during normal conversation [55]. With FAST, 88.9% of patients with TIA or stroke can be identified, and it has the advantage of being easily performed so that it can be used as a public message.

However, for non-English speaking people, it is sometimes difficult to remember “FAST” and the related meaning of each character because of the linguistic barriers. In recent years, Taiwan has developed “Stroke 112”, a national stroke education program designed to penetrate the language barrier [38]. The three numbers can be transformed into three stroke symptoms used in FAST (Face, Arm, Speech, and Time): 1 uneven face (crooked mouth); 1 weak arm (arm weakness); 2 incoherent lips (slurred speech). Similarly, in mainland China, due to language barriers, “Stroke 120” was developed, where “120” is used as an emergency phone number [51,52]. The numbers can be converted into three types of AIS recognition actions, with 1 meaning "First, look for an uneven face", 2 meaning "Second, examine for arm weakness" and 0 meaning "no clear language". Also, the Chinese pronunciation of "zero" is "ling", which means "listening". During the past several years, “Stroke 120” and “Stroke 112” have been well-accepted in mainland China and Taiwan respectively [16]. Therefore, it is more acceptable for non-English speaking countries to remember such novel stroke awareness programs than it is to rely on FAST to recognize the signs of stroke.

The use of EMS

A lot of evidence showed that the use of EMS is a significant factor in increasing the likelihood of early arrival [21,22] and appropriate therapy with rt-PA [56,57]. However, the rate of EMS utilization differed in countries. The EMS utilization rate is 15.4% among stroke patients in Hubei Province in China [37], and in India, less than 15% of people make timely use of EMS [16], which was significantly lower than that in Sweden (53%) [34], the United States (51%) [58], Korea (36%) [59], England (78%) [60] and Germany (72%) [61]. EMS utilization was related to the following factors: Previous use of EMS, early recognition of stroke symptoms, sudden stroke attack, severe stroke, or living in urban communities [37,62]. A study indicated that patients with a history of stroke had a reduced tendency to use EMS [37], while another report showed no relation between EMS utilization and previous stroke [62]. A study showed that patients who recognized initial stroke signs tended to use EMS, which indicates that early identification of stroke signs was a significant factor that influences EMS utilization [37].

Firstly, the poor awareness of when to use EMS is a leading cause of prolonged prehospital delays, so public education plays a significant role in reducing prehospital delays and increasing the utilization of EMS [63-65]. In a study, implementation of the EMS training program successfully reduced the on-scene time (OST) of thrombolysis candidates by 10% [66]. Education programs on stroke risk and the effective use of emergency calls ought to be implemented for patients as well as family members [20]. Therefore, more health education programs should be launched to highlight the need to contact with EMS as soon as a stroke occurs.

Secondly, EMS is not well established in some developing countries, which may account for the low usage of EMS. For instance, India has a very limited number of ambulances, which are operated by different entities, and most of them do not have any necessary medical management equipment [39]. Likewise, in remote areas of many countries, EMS is not well-developed and there are not enough ambulances.

Thirdly, the inconsistent emergency phone numbers are an important cause of pre-hospital delays. In China, some hospitals use their hospital-specific emergency telephone numbers which are too long to remember [52].

A review suggests that the EMS threshold for suspected stroke ought to be lowered to enhance its sensitivity rather than its specificity [67]. Simple stroke evaluations such as FAST or “Stroke 120” should be used as soon as an emergency call has been made and the EMS alerted [68]. Similar to trauma or myocardial infarction, every potential stroke patient ought to be evaluated as

an emergency; meanwhile, ambulances should be sent first. In many cases, EMS staff do not know which hospitals are capable of stroke management, causing some patients to be re-transferred to hospitals with stroke management facilities. Due to referral procedures and extra travel, access to thrombolytic treatment is further delayed. Therefore, EMS personnel should be clearly aware of the hospitals with stroke centers, which is significant for appropriate dispatch, especially in areas where there are many hospitals [22]. Meanwhile, EMS personnel ought to contact stroke centers in advance, which can not only ensure that a particular hospital is equipped to perform thrombolysis treatment, but also prepare the hospital for the arrival of patients.

Prehospital mobile stroke units

As we know, specialized mobile stroke units (MSUs) are presently deployed in Berlin, Germany; Houston, Texas; and Cleveland, Ohio. Equipped with a point-of-care laboratory, an imaging system, proper medications, and a telemedicine connection to the hospital [69,70], MSUs aim to pre-hospital diagnosis and treatment and to divert diagnosis-based patients to the most fitting target hospital [71].

By issuing the diagnosis at the emergency site, MSUs can prevent additional hospitalization delays in inspection, transfer, and secondary (inter-hospital) transport, reducing the transport time during the prehospital and in-hospital phase. In Homburg, Germany, a randomized single-center controlled trial was conducted to compare the time from alarm to therapy decision between MSU and hospital intervention [72]. With an MSU trial, the median time from symptom onset to treatment decision was 56 minutes (IQR 43-103) and the median time of OTT was 72 minutes (53-108), far lower than that of the hospital intervention group (104 minutes (IQR 80-156) and 153 minutes (IQR 136-198) respectively) [72]. Similar trends in time savings were seen in an observational study in Houston, TX, USA [73], as well as in the PHANTOM-S (Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke) study [74].

"The golden hour" is a term attributed to a trauma surgeon who found that the earlier patients are treated within the first hour after a trauma, the better their chances of survival. This term is also used in AIS management to emphasize the time sensitivity. However, very few stroke patients received treatment within 60 minutes, which indicates that there may be a ceiling effect of the timing of conventional stroke management [75,76]. With the first MSU trial, the treatment decision rate within 60 minutes was much higher than that of the hospital intervention group (57% vs. 4%), breaking the "golden hour" limit [72]. Further studies such as the PHANTOM-S trial [77] and the Houston MSU program [78] also increased the rate of treatment within 60 minutes, supporting this conclusion.

However, significant questions remain about clinical efficacy, safety, cost-effectiveness, and best setting for interventions [71]. In the future, MSUs may allow new diagnostics (eg., automated imaging evaluation and biomarkers) and treatments (eg., neuroprotective drugs and treatments for hemorrhagic stroke) to be developed in a pre-hospital setting. With such functions, MSUs may serve as valuable research tools for the pre-hospital management of AIS [71].

The stroke emergency map

As we know, the Stroke Emergency Map unites all the qualified centers and local hospitals capable of providing intravenous thrombolysis and/or endovascular thrombectomy, which could guide the EMS to send stroke patients to nearby hospitals with appropriate stroke care. The first Stroke Emergency Map of China was established in Shenzhen by Dr. Ren in 2016 [16]. Subsequently, the Stroke Emergency Map was established in many regions of China, and the rate of thrombolysis was improved.

The Thrombolysis Map is supported by local health administrations and it consists of EMS staff training, ambulance dispatch and triage guidelines, as well as stroke center standards. Besides that, it can not only direct policymakers to establish new stroke centers in under-served areas, but can also promote improvement in the quality of stroke centers, reducing both pre-hospital and in-hospital delays [16].

In-Hospital Stroke Management

In-hospital delays are another major barrier to the availability of thrombolysis. The American Heart Association and American Stroke Association has recommended that DNT be no more than 60 minutes [79]. However, less than half of stroke patients in the United States [18] and even fewer in China [80,81] receive rt-PA treatment within this time frame. Lots of time is often consumed in trivial non-medical processes (i.e., registering patients, excessive patient transfers, filling out request forms, or waiting for the stroke team, CT availability, or lab resources).

Taking the history

It usually takes a lot of time to take a patient history, particularly for aphasic patients, and information can be distorted or lost in the communication process. The initial history relayed by the EMS, may not always be accurate, and reaching eyewitnesses or next of kin afterward for treatment decisions is often time-consuming and difficult.

Therefore, the treating stroke team can communicate with the original information provider over a phone

already at prenotification, during EMS contact on-scene. It is also preferable to have the next of kin transported by EMS with the patient to allow for additional history to be communicated rapidly if needed.

Laboratory tests and CT scans

Of all the potential in-hospital delays, waiting for the laboratory tests is an essential element, and blood biochemistry tests play a significant role [82]. One study suggests that door-to-laboratory time (DTL) has an independent relationship with in-hospital delays [81], and relevant testing can be conducted during patient transportation. In particular, blood glucose and the international normalized ratio (INR) are the two indices which directly affect treatment decisions; fortunately, glucose can be measured by the EMS and point-of-care (POC) INR samples can be taken immediately upon admission and reported within a minute.

CT scans sometimes also hinder acute thrombolysis treatment. Door-to-imaging time (DTI) was considered to be a factor related to in-hospital delay [81,83,84]. It is time-consuming to write a patient into a computer system as well as to order CT scans. To address these issues, such clerical and administrative duties can be completed before the patient arrives while transferring the patient straight from the ambulance onto the CT table, which can save a lot of time.

Physicians delay thrombolysis

A study indicated that physicians may have a tendency to delay thrombolysis treatment if they believe that thrombolysis would be less beneficial or if they have more time before the end of the thrombolytic treatment window [85].

In consequence, it is of great significance to improve adherence to guidelines and treat patients as soon as possible after arrival at the hospital, no matter how much time is left to the end of the thrombolytic treatment window.

Decision-making for IVT

Before thrombolytic treatment, all patients and family members present are informed of the benefits and risks of stroke treatment, which usually takes less than a minute. In a few countries, informed consent for thrombolytic therapy is not even required. However, in some countries, such as China, the decision-making process for thrombolytic treatment can be a factor in increasing in-hospital delay [81]. Because of the threat of violence from patients or their proxies [86-88], as well as situations wherein doctors are not fully understood by the public [89], doctor-patient relations in China are strained, and the benefits and risks of treatment are often biased by the physicians.

The difference between the healthcare system of western countries and that of China may account for such a phenomenon [90]. Firstly, patients in China usually have so many offspring that it is often difficult for physicians to know which of the patient's relatives is the primary decision-maker. Secondly, clinicians are inclined to exaggerate the risk of increased hemorrhagic complications. Thirdly, the high cost of thrombolysis may also be an obstacle to a smooth decision-making process.

Measures to Reduce Treatment Delays

Before a patient's arrival, prompt reactions based on prenotification play key roles in reducing treatment delays; efficient, coordinated reactions involve seamless collaboration between the prehospital and inpatient

Table 2: Measures to reduce treatment delays [17,67,91-94].

Measure	Description
Pre-hospital phase	
EMS involvement	Education of EMS staff to recognize and prioritise acute stroke. And the ambulance personnel ensuring vital functions, measuring blood glucose, and inserting an intravenous line.
Hospital prenotification	Ambulance calls stroke consultant on mobile phone, who accepts patients, takes history, checking additional medical history from patient records.
Registration and preorder of tests	Patient registration, CT request electronically and pre-order of laboratory tests before patient arrival.
Stroke team	Gathering the stroke team, including a stroke neurologist, an ER nurse, and a lab nurse, at the CT
Medications preparation	Having the medications and infusion pumps ready for the patient at the CT.
In-hospital phase	
Transfer onto CT-table	Direct transfer onto CT-table upon hospital arrival. The CT is performed and immediately interpreted by a stroke neurologist.
Neurologic evaluation and blood withdrawal	Simultaneously EMS briefing, neurological evaluation, and blood withdrawal on CT-table. POC INR if needed.
Decision	Treatment decision before laboratory results are available.
rt-PA on CT table	rt-PA can be initiated on CT table, but usually in adjacent room where the drug is kept.

Table 3: Studies of effects of stroke management.

	Site	Year	OTT (min) with and without intervention	OTD (min) with and without intervention	DTN (min) with and without intervention	DTI (min) with and without intervention	Thrombolysis rates (%) with and without intervention	The rate of DTN ≤ 60 min (%) or DNT ≤ 30 min (%)
Meretoj, et al. [67,93]	Helsinki, Finland	1998-2011	119 (80-176) vs. 195 (164-250)	89 (62-138) vs. 75 (45-145)	20 (14-32) vs. 105 (65-120)	-	31% in 2011, no earlier rates specified	94% in 2011, no earlier rates Specified (DTN ≤ 60 min)
Sanne M. Zinkstok, et al. [94]	Amsterdam, Netherlands	2000-2012	105 (75-160) vs. 158 (135 - 177), p < 0.001	71 (48-120) vs. 65 (50-90), P = 0.156	28 (20-37) vs. 75 (60-105), P < 0.001	6 (4-10) vs. 35 (27-47), P < 0.001	-	62.7% vs. 0.0% (DNT ≤ 30 min)
Meretoja, et al. [17]	Australia	2011-2012	115 vs. 140	73 (50-108) vs. 77 (53-113)	46 (24-79) vs. 61 (43-75), P = 0.040	-	-	-
Qiang Huang, et al. [91]	Beijing, China	2011-2015	173 (130-225) vs. 229 (185-270), P < 0.001	106 (67-140) vs. 110 (67-164), P = 0.510	53 (43-86) vs. 116 (93-135), P < 0.001	24 (16-29) vs. 28 (15-40), P = 0.002	-	60.3% vs. 9.9%; P < 0.001 (DTN ≤ 60 min)
Sang-Beom Jeon, et al. [92]	Seoul, Korea	2014-2016	102.5 (49.0-153.5) vs. 129.0 (84.3-183.3), p = 0.024	91.0 (36.0-199.0) vs. 107.0 (45.5-218.5), P = 0.144	20.5 (15.8-32.5) vs. 46.0 (36.0-57.0), p < 0.001	13.0 (8.0-19.0) vs. 18.0 (15.0-23.0), P < 0.001	15.8% vs. 9.8%, P = 0.002	-

*Data are presented as median (IQR).

OTT: onset to thrombolysis; OTD, onset-to-door time; DTN, door-to-needle time; DTI, door-to-imaging time.

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components of stroke treatment [17,67,91-94] as shown in Table 2.

Some studies have examined the effect of stroke management in thrombolytic treatment [17,67,91-94] as shown in Table 3. Surprisingly, the Helsinki model had a median DNT of only 20 minutes [93] and the Acute Brain Care (ABC) intervention study showed the median DNT decreased from 75 to 28 minutes [94].

A study in China showed that the intervention improved all parameters (all $P < 0.05$) including door-to-examination, door-to-laboratory, door-to-imaging, final-test-to-needle times, and DTN with net reductions of 2, 28, 4, 23 and 63 minutes, respectively [91]. Another study in Korea showed that after SAT implementation, the median door-to-laboratory, door-to-CT and door-to-MRI time decreased to 8 minutes, 13 minutes, and 37.5 minutes respectively ($P < 0.001$) [92]. The median DNT time was reduced from 46 minutes to 20.5 minutes. The thrombolysis rate increased from 9.8% to 15.8%, and the post-thrombolysis intracranial hemorrhage rate decreased from 12.6% to 2.1%.

In view of the mixed results of several studies, it may be of significant benefit to optimize management protocols.

Conclusions

This review clearly demonstrates that each part in the pre- and in-hospital stroke rescue chain is significant; further studies are needed to assess the efficacy of other potential improvements.

Since these delays depend on many factors, improved public awareness, pre- and in-hospital management, education of ambulance teams, increased information for the public, and the optimization of acute management strategies at hospitals should all enable more stroke patients to get timely treatment of rt-PA as well as to attain functional recovery. Additional research is required in order to develop the most effective public awareness programs to affect the behavior of patients, relatives, and bystanders in an actual emergency situation. EMS is a key factor in reducing prehospital delays, and it is important to make good use of MSUs and the Stroke Emergency Maps. Furthermore, the in-hospital portion of stroke treatment is another significant challenge to manage. Seamless collaboration between prehospital and inpatient care is an integral part of stroke treatment, which is necessary to reduce overall delays and thus improve patient outcomes.

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