

Feasibility study of acute thrombolytic therapy for stroke in a tertiary care center in Nepal

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Abstract

Introduction: Early thrombolysis is the recommended therapy for acute ischemic stroke (AIS). In a developing country like Nepal, many factors contribute to the delay in performing prompt thrombolysis. This was a feasibility study to assess the determinants of pre-hospital delay for patients diagnosed with AIS.

Methods: From 16th July to 16th September 2017, patients diagnosed with AIS in the emergency department (ED) were identified and a structured interview with the patient or next of kin was performed. Various pre-hospital time intervals and possible factors resulting in delay were assessed.

Results: A total of 58 AIS patients were studied. Only 12% of the total patients underwent thrombolysis. The mean delay (+/-sd) from symptom onset to first contact with a medical personnel was 6.74 (+/- 7.84) hours. The mean (+/-sd) total arrival delay to ED was 15.78 (+/-17.48) hours. The mean (+/-sd) delay in dispatch to delivery time was 9.12 (+/-15.57) hours. Ten patients (17%) arrived to our ED within 3 hours of onset of symptoms, and 14 (24%) arrived within 4.5 hours of onset of symptoms. Fifty percent of those who presented on time for thrombolysis underwent the therapy.

Conclusions: This study shows that there are major obstacles before we are able to provide adequate thrombolysis services for AIS. There remain plenty of areas where the government, the hospital and public health services need immediate addressing.

Key words: feasibility, ischaemic stroke, pre-hospital delay, thrombolysis

Introduction

Stroke continues to be a major cause of morbidity and mortality all over the world. According to the latest WHO data published in 2014, stroke deaths in Nepal reached 15,333 or 9.67% of total deaths. The age adjusted death rate is 90.33 per 100,000 of population and ranks Nepal 88 in the world.¹

Until recently, treatment of acute ischaemic stroke has been mainly supportive. There is now evidence that thrombolytic therapy for patients with stroke may improve clinical outcomes. The efficacy of thrombolytic therapy is markedly time-dependent. Current guidelines from the American Heart

Association recommend thrombolytic therapy within 3 hours of onset of symptoms and up to 4.5 hours in selected patients.² Regardless of the type of treatment, the greatest benefit is seen with the shortest delay from onset of symptoms to treatment.³ Unfortunately, several studies have shown that most persons experiencing symptoms of stroke delay a significant amount of time before seeking medical care.^{4,5} Reasons for prolonged delay in response to symptoms have been understudied, making it difficult to develop interventions to reduce the interval from the onset of stroke-like symptoms until receipt of proper medical care.

In a country like Nepal, there are many obstacles in providing prompt thrombolysis to stroke patients. These obstacles include issues related to delay in recognizing the symptoms, delay in accessing healthcare, scarcity of tertiary care centers able to thrombolize, transportation problems, financial cost, as well as inadequacy of the medical team to form a rapid response to stroke management. Thus, despite recommendations for thrombolysis as the current first line management in patients with ischaemic stroke, it has not achieved routine practice in our setup.

The number of research in stroke in Nepal has steadily increased, however this seems to be the first to evaluate the time and factors associated with delay in thrombolysis in Nepal. This study was done to better understand the patient characteristics and environmental circumstances that are associated with inability to thrombolize in our setting. A thorough investigation of these factors will allow us to evaluate strategies that may allow a faster response so that patients for whom thrombolysis is indicated can undergo the appropriate treatment on time.

Methods

This was a retrospective observational study conducted in the emergency department of Tribhuvan University Teaching Hospital (TUTH). TUTH is a tertiary care hospital located in the capital of Nepal and receives one of the most numbers of patients in the country with a large proportion of stroke patients arriving every day. This is also one of the hospitals with adequate staffing and facilities sufficient for rapid thrombolysis. The study was approved by the institutional review board, Institute of Medicine, TUTH.

This was a feasibility study, hence a sample study period of two months was taken and all patients who arrived in the ED and diagnosed with ischemic stroke were included in the study. Interview, with the patient or next of kin was performed, and it consisted of demographic information, place of event, the time of symptom onset, transportation method, urgency, and factors associated with earlier recognition of stroke. Urgency of the situation was scored from 0-10 with 0 meaning least urgent whereas 10 being an extreme emergency. The time intervals to reach the destination were also recorded. The pre-hospital period was divided into various time periods. **Reaction interval** was the time from onset of symptoms to first contact (either by phone or in person) with medical personnel (physician, nurse or paramedic). **Total arrival delay** was the time from onset of symptoms to arrival at the ED. These time

intervals were also recorded. The difference between these time periods would indicate the duration from emergency medical service dispatch to delivery of the patient at the ED. The National Institutes of Health Stroke Scale (NIHSS) was calculated based on examination of the patient and ED records and the CT scan findings were also noted. Data were then entered into Microsoft Excel 2010 spreadsheet and then analyzed using SPSS version 17.

Results

The study was done between 16th July 2017 and 16th September 2017. A total of 58 patients were diagnosed to have ischemic stroke among those who presented to the emergency department (ED) in the 2 months period. There were 56.9 % males and 43.1% females. The mean age of presentation was 61.69 with a range from 29-91 years.

The mean (+/-sd) NIHSS score was 13 (+/- 5.157) and ranged from 2 to 22. Fifty five percent of the cases involved the middle cerebral artery territory, 10% involved the anterior circulation, whereas 15% of the cases were cerebellar strokes. Twenty percent of the time, the CT scan was normal.

Table 1. Age, NIHSS, urgency score and delay intervals

	Minimum	Maximum	Mean	Std. Deviation
Age (in years)	29	91	61.69	15.356
NIHSS ¹	2	22	13.00	5.157
Urgency ²	3	10	7.24	1.380
Total arrival delay (hours) ³	0	96	15.78	17.487
Reaction interval (hours) ⁴	0	36	6.74	7.847
Dispatch to delivery time (hours) ⁵	1	84	9.12	15.571

- 1. National Institutes of Health Stroke Scale
- 2. Urgency was scored from 0 to 10; 0 was considered least urgent and 10 the most urgent
- 3. Time from onset of symptoms to arrival at the ED
- 4. Time from onset of symptoms to first contact (either by phone or in person) with medical personnel (physician, nurse or paramedic)
- 5. Time from first contact with medical personnel to arrival at ED (after excluding those patients whose first medical contact was in the ED itself)

The events occurred mostly at home (96%) and were recognized mainly by their relatives (84.5%). Though most of the events were considered relatively urgent (mean of 7.24 with a range from 3 to 10 in the urgency score), the mean reaction interval was 6.74 hours. Only three of the patients (5.17%) had immediate contact with a medical person, whereas the maximum reaction time was 36 hours. The mean total arrival delay was 15.78 hours. The minimum total arrival delay was 0 hours as one patient had a stroke in ED and the maximum total arrival delay was 96 hours. Ten patients (17%) arrived to our ED within 3 hours of onset of symptoms, and 14 (24%) arrived within 4.5 hours of onset of symptoms. However, a mere 50% of those who presented on time for thrombolysis underwent the therapy, with only one patient having a contraindication to the treatment (use of warfarin). The fastest dispatch to delivery time (after excluding those patients whose first medical contact was ED itself) was 1 hour, the mean was 9.12 hours and the longest was 84 hours (Table 1).

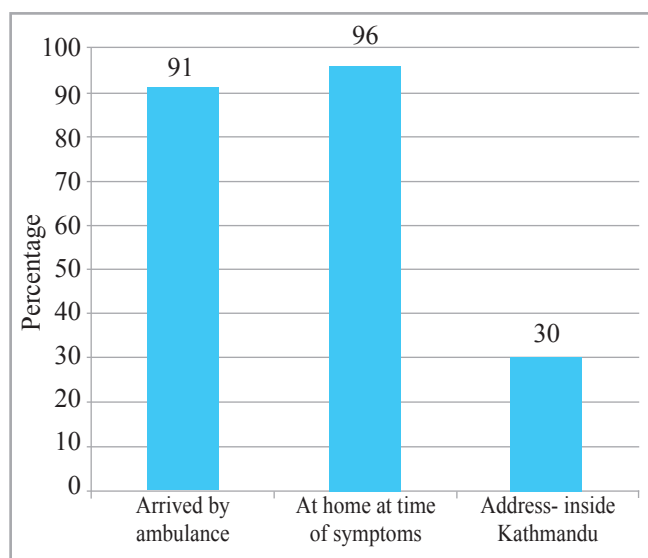


Figure 1. Place of symptom onset, address and transportation methods

1. One patient was transported by air. Two patients were carried for 3-4 hours before using the ambulance
2. One patient had stroke in ED

Thirty percent of the patients were from inside Kathmandu valley. The rest were referred from health centers of various levels outside the valley. The farthest distance travelled to reach our ED was around 688 km, which takes around 18 hours by road. That patient arrived only 3 days after the onset of symptom though the reaction interval was only 3 hours. Five patients arrived to our ED using a public vehicle, whereas 91.3%

of the patients were brought in an ambulance. One patient was transported both using a public vehicle and an ambulance and one patient arrived to our hospital via air transport. There were two patients who needed to be carried from the place of event for 3-4 hours before reaching a place accessible to transportation by road (Figure 1).

Only one patient was aware about stroke symptoms and that was also because she had a past history of stroke. Otherwise none of the patients or their family members had prior information regarding stroke or that they were considered high risk for stroke.

Discussion

This study shows that less than 20% and only one fourth of the patients in our ED with acute ischemic stroke arrive within the time frame and the extended time frame for thrombolysis respectively. The reaction interval and the total arrival delay is significant (mean of 6.74 hours and 15.78 hours). Even for those who arrive on time, only half of them undergo thrombolysis due to various reasons. The thrombolysis rate however has increased. A previous study reported a rate of 11 cases of thrombolysis in 3 years.⁶

Just like the chain of survival in cardiac arrest, there is also a stroke chain of survival and this study shows that there are delays in almost each of these vital steps. The chain of events begins with detection, that is, recognition of stroke signs and symptoms. Our study supports previous studies that reveal that public awareness regarding stroke symptoms is poor and that emergency calls for stroke events are not made as promptly as it should be.^{7,8} People do not know that stroke can lead to long-term disabilities and that the neurological deficits are mostly reversible only when treated promptly.

There is also problem with emergency dispatch and delivery of the patient to a proper center. The system of emergency medical service (EMS) is very rudimentary in Nepal, and non-existent outside the capital. They are responsible for emergency medical response, triage and stabilization, and transportation with a high priority. Most of the patients were referred from outside, some even days later. There is a lack of primary stroke centers or comprehensive stroke centers outside the capital, so there is no possibility of arriving in our ED on time unless they are transported by air. There are people who do use these services for myocardial infarction. However it seems that in case of stroke, none of them

were considered a high priority, suggesting that even the health workers are unaware of thrombolysis or the limited time to thrombolysis in stroke.

Once the patient arrives in ED, a prompt evaluation, stroke team activation and immediate CT scan of the head needs to be performed followed by a decision to undergo thrombolysis or not. The absence of stroke team in our setup also has led to delays in management. For example, one patient, who actually developed stroke in the emergency room itself, was recognized by the attending doctors but thrombolysis was missed.

An extremely concerning issue about thrombolysis is the availability and affordability of the drug. Alteplase, the only FDA approved agent, is scarcely available in only a few centers. Despite fulfilling all the criteria for thrombolysis, one patient in our study did not receive the drug as it was unavailable all throughout the capital. Furthermore, even if it is available, the cost is very expensive. One vial costs around US \$1000⁹ and it takes two vials for most patients, whereas the average per capita income of a Nepalese citizen is only US \$691.7.¹⁰ Without any health insurance, it is hugely unaffordable. For these reasons, on several occasions, tenecteplase, which is used for acute coronary syndromes and is more available and affordable, was administered.

There are solutions that can be considered to address the problems with delay in thrombolysis. An immediate step towards this goal would be to develop a system for activation of a stroke team in our hospital. This would ensure that at least those who do arrive on time for thrombolysis receive the appropriate treatment in the extremely rigid time intervals recommended. Even simply a readymade checklist for indications and contraindications would hasten the preparation time.

On a larger scale, there are plenty of areas that need improvement. It is important to spread awareness about stroke to general public and may be initially target high risk patients such as the elderly, those with hypertension and diabetes, or those with other risk factors. As it is usually the relatives who first identify the event, families should also be educated about how to recognize the symptoms and how to respond appropriately. Even health workers need education and a constant reminder that stroke patients need to be

triaged with the same high priority as serious trauma or acute myocardial infarction.

There is an urgent need for stroke centers outside the capital, or at least acute stroke ready hospitals. These hospitals can treat most ED stroke patients but do not have fully organized inpatient stroke systems of care. The “drip and ship” model may be applicable, where alteplase is administered and the patient transported to a higher center.²

There are various limitations of this study. This was only a feasibility study done in a limited time period and in a single center. Therefore it limits the generalizability of the study. Second, this study could have further evaluated some important factors associated with arrival delay, such as patient or family level of education, occupation and financial status. Third, the study could have analyzed time intervals even after the patient had arrived to the ED. There are time intervals recommended for ED based management. These include door to physician time, door to stroke team time, door to CT initiation time, door to CT interpretation time, door to drug time and door to stroke unit admission time. These time durations are equally important and help in assessing the medical management system in the hospital.² However, our study was only focused on the pre-hospital delays and the data gathered was from interview and ED records. To report these other time durations, the whole of medical staff involved in the management of patients in the ED would need to meticulously record the time at each of these points.

Conclusion

There are major obstacles before we are able to provide adequate thrombolysis services. There remain plenty of areas where the government and public health services need immediate addressing. We need to learn from systems developed to manage acute myocardial infarction, where there has been admirable amount of effort and funding. Though, both of the diseases are equally disabling, there has been an alarming disparity in how we approach them. Reperfusion therapy is being carried out at a steadily increasing rate for myocardial infarction.¹¹ This gives some hope that it can also be achieved for patients with stroke.

Conflict of interest: None declared

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