Barriers to Stroke Thrombolysis

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ABSTRACT

Introduction: Thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rt-PA) is the cornerstone of acute ischaemic stroke treatment. The number of stroke patients receiving thrombolytic therapy in India has improved over the recent years. However, Warangal despite being the second largest city in Telangana, witnesses stroke thrombolysis infrequently.

Aim: To study the factors which prevent stroke thrombolysis at a tertiary care center in Warangal.

Materials and Methods: The study was undertaken at Kakatiya Medical College (KMC) and its associate Mahatma Gandhi Memorial Hospital (MGMH), from October 2016 to March 2017. The study subjects were recruited from the patients presenting to medical emergency or neurology outpatient department (OPD).We enrolled the consecutive ischaemic stroke patients who presented within three days of the symptoms onset and fulfilled the inclusion and exclusion criteria for thrombolysis as defined by the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA study group. We included the patients arriving after time window for thrombolysis, so as to study the causes associated with pre-hospital delay. Thrombolysis therapy was given within four and a half hours of the stroke onset.

Results: Among a total of 223 study subjects, only 13 (5.8%) arrived within the time window for rt-PA infusion and nine (4%) received thrombolytic therapy. The pre-hospital delay was the single most important constraint for providing timely stroke treatment. 'Lack of awareness of patients and their relatives to recognize stroke as a medical emergency' and 'lack of awareness about thrombolysis' were the most important factors associated with the pre-hospital delay. Non-affordability and in-hospital delays were the barriers for successful stroke treatment among the patients who presented to the medical emergency on time and could not get thrombolytic therapy.

Conclusion: The results of our study suggest the need for a comprehensive stroke care program at our health center to escalate the rate of thrombolytic therapy. Stroke education and awareness modules should be incorporated in the stroke program.

Keywords: Ischaemic stroke, Thrombolytic therapy, Tissue plasminogen activator

INTRODUCTION

Stroke is recognized to be a major cause of death and disability worldwide [1,2]. The burden of stroke related death and disability is even higher in developing countries. A recently conducted large scale study from 17 countries (three high-income, 10 middle-income, and four low-income) reported 'event rates' and 'case fatality rates' of the major cardiovascular events, including stroke to be significantly higher in low and middle-income countries, despite a lower risk-factor burden [1]. Being a developing country, stroke epidemiology is not different in India. The healthcare system of our country which is already riddled with communicable diseases, now faces the challenge of non-communicable diseases, most importantly a recently arrived stroke epidemic [3].

Most of the stroke events are ischaemic strokes which account for more than 80% of all cases [4]. Early thrombolytic therapy with intravenous recombinant tissue rt-PA is of paramount importance for acute ischaemic stroke management. It has proved to be efficacious in improving clinical outcomes if administered within four and a half hours of onset of stroke symptoms [5,6]. In India, the number of patients receiving thrombolytic therapy has increased significantly over the past few years, still however, the rate of thrombolysis remains low. Among the 1944 patients enrolled in the Indo-US stroke registry, 286 patients arrived within four and a half hours and 215 (11%) received thrombolysis [7]. Furthermore, stroke thrombolysis continues to be available mainly in urban corporate hospitals and major academic health institutes [3].

Warangal is the second largest city in Telangana with a population of more than 10 lakh people and being served by a government tertiary referral hospital along with several private hospitals [8]. The healthcare facilities of urban Warangal boasts many trained doctors across all medical specialties and super-specialties. However, stroke thrombolysis in Warangal continues to be an exception rather than a rule. Thus, we aimed to evaluate the reasons for the same in order to take a step ahead for the stroke management in this region. The objective of our study was to scientifically study the various factors which were responsible for the poor rate of thrombolytic therapy at our center.

MATERIALS AND METHODS

This was a cross-sectional study undertaken at Kakatiya Medical College (KMC) and its associate Mahatma Gandhi Memorial Hospital (MGMH) at Warangal. The study was conducted for a period of six months from October 2016 to March 2017. The 'Institutional Ethics Committee' approved the study protocol and a written informed consent was obtained from all the study subjects. We prospectively enrolled acute ischaemic stroke patients presenting within three days of the onset of symptoms who fulfilled the inclusion and exclusion criteria for thrombolysis as defined by the National Institute of Neurological Disorders

and Stroke (NINDS) rt-PA study group [5]. However, we did not limit our inclusion only up to those patients who arrived within the window period for thrombolysis, as we aimed to evaluate the causes of delay in arrival as well. Besides, we planned to perform thrombolysis in those patients who arrived within four and a half hours of the stroke onset, and hence, those who arrived less than or equal to four and a half hours (≤4.5) and more than four and a half hours (>4.5) h were divided into separate subgroups [6].

Selection of Patients

We enrolled the patients with age ≥18 years admitted with a clinical diagnosis of acute stroke with baseline Computed Tomographic (CT) scan showing no evidence of intracranial haemorrhage. Patients were excluded if they had another stroke or serious head injury within past three months, underwent a major surgery in preceding 14 days, had a gastrointestinal haemorrhage or urinary tract haemorrhage within the previous 21 days, had intracranial haemorrhage in the past, had a blood pressure sustained above 180/110 mm Hg despite treatment, had clinical features of subarachnoid haemorrhage, had a seizure at the stroke onset, had arterial puncture at a non-compressible site in the preceding seven days, had rapidly improving symptoms or National Institute of Health Stroke Scale (NIHSS) score less than four (<4). Further, patients on anticoagulants or those who took heparin within the previous 48 hours and had a prolonged partial thromboplastin time were excluded, as were those who had a prothrombin time >15 seconds, platelets <100,000 per cubic millimeter or blood glucose <50 milligrams per decilitre [5].

Selection of the Thrombolytic Agent

Classically, Alteplase is being used as the rt-PA agent for stroke thrombolysis. However, recent randomized controlled trials which demonstrated the efficacy and safety of Tenecteplase at least, comparable to Alteplase have resulted in approval of the former for stroke thrombolysis in India within a period of three hours of the stroke onset [9-11]. Consequently, we planned to thrombolyse with Tenecteplase in cases where the procedure was feasible in less than or equal to three hours (≤3h) time window, owing to its free availability under hospital's government funded indenting scheme. On the other hand, in those cases where thrombolysis has to undergo in the extended time window of three to four and a half hours, we intended to do the same with Alteplase because of extensive evidence based support in favor of the same [6]. However, there was one constraint with Alteplase procurement that it was not available for free and needed to be purchased by the patient, and thus, patient's affordability could be a potential issue.

Subgroups Analysis for Factors Preventing Thrombolysis

Barriers to thrombolysis were separately analyzed in the two subgroups. Those arriving less than or equal to four and a half (≤4.5h) were investigated for the following causes:

1) Non-affordability.

2) Patient's or attendants' refusal to give informed consent.

3) In-hospital delays.

Further, those who arrived after four and a half hours were investigated for the following causes:

1) Failure of patient or family members to recognize stroke symptoms.

2) Lack of awareness of patients and family members to consider stroke as a medical emergency.

3) Lack of awareness about thrombolysis among patients and their relatives.

4) Lack of awareness about thrombolysis among primary care providers (PCPs).

5) Transport delay.

Patient's demographic, clinical and neuroimaging details along with various barriers which prevented thrombolysis, were entered into well-structured questionnaires.

STATISTICAL ANALYSIS

The data entry and analyses were done on software statistical package SPSS version 16.0. Data were summarized as mean±standard deviation (SD) for numerical variables and counts and percentages for categorical variables.

RESULTS

A total of 223 study subjects were enrolled with a mean age of 58.97±8.94 (mean±SD) years. The study group comprised of 143 (64%) males and 80 (36%) females. The study cohort mainly comprised of the rural population, the rural residents being 92.3% of the total enrolled study subjects. Hypertension and Dyslipidemia were observed to be the commonest risk factors, each present in 69.1% of the cases. Most of the study subjects had a large artery stroke subtype (63.7%) and involved anterior cerebral circulation (66.8%). In our study, only 13 (5.8%) patients arrived within four and a half hours window period and out of those nine (4%) could be thrombolysed [Table/Fig-1].

Time of Arrival at our Tertiary Health Care Center

Mean time of the study subjects to arrive at our hospital after the stroke onset was 13.56±12.73 h (mean±SD). Besides 13

	Frequency (N=223)	Percentage(%)
Sex (Male)	143	64.1
Residence (Rural)	206	92.3
Stroke subtype		
Large artery	142	63.7
Lacunar	69	30.9
Cardioembolic	12	5.4
Cerebral circulation		
Anterior circulation	149	66.8
Posterior circulation	74	33.2
Mode of presentation		
Weakness	174	78.0
Aphasia	67	30.0
Dysarthria	138	61.8
Vertigo	39	17.4
Sensory symptoms	19	8.5
Ataxia	18	8.0
Risk factors		
Hypertension	154	69.1
Dyslipidemia	154	69.1
Diabetes	90	40.4
Smoking	65	29.1
Atrial fibrillation	12	5.3
Rheumatic heart disease	7	3.1
Arrival in window period	13	5.8
Thrombolysis with rt-PA	9	4.0

[Table/Fig-1]: Baseline characteristics of the ischemic stroke patients.

patients who reached in the window period of four and a half hours, 169 (75.8%) patients reached between four and a half hours to 24 h, 33 (14.8%) patients reached between 24 and 48 h and eight (3.6%) patients reached between 48 and 72 h.

Time to Reach the First Point of Contact for Medical Assistance

The study subjects took a mean time of 4.35±3.45 h (mean±SD) to reach the first point of contact for medical assistance. The first point of contact for medical assistance was a 'first attending rural doctor' in 183 (82%) cases, a physician or a medical care center not providing stroke thrombolysis facility in 22 (9.8%) cases and our tertiary hospital in 18 (8%) cases.

Barriers to Thrombolysis in Patients Arriving After Four and a Half Hours

Among the patients arriving out of window period, none of the patients or their relatives knew about the thrombolysis as a treatment for stroke, which could have resulted in their delayed arrival. Besides, 66% of the PCPs were unaware of the thrombolytic therapy. Thus, unawareness about thrombolysis appeared to be the most common barrier in late arriving patients. Further, nearly 89% of the patients or their relatives did not consider stroke as a medical emergency, as serious as they would have considered a heart attack to be, thus

Barriers	Frequency (n=210)	Percentage (%)
Failure to recognize stroke symptoms.	88	42
Unawareness about stroke as an emergency.	186	89
Unawareness about thrombolysis among patients or relatives.	210	100
Unawareness about thrombolysis among primary care providers.	139	66
Transport delay.	101	48

[Table/Fig-2]: Barriers to thrombolysis in patients arriving after four and a half hours.

resulting in delayed arrival to the stroke facility. We observed this unawareness as a major hurdle in timely stroke treatment, despite the fact that in almost 58% of the patients, stroke symptoms were recognized promptly. Transport delay played its role as well, in 48% of the late arrivals [Table/Fig-2].

Strength of Association of Various Barriers with Late Arrival

Logistic regression analysis was used to identify the factors most strongly associated with the delay. Binary logistic regression model was used with 'late arrival' as the dependent variable, and the various factors associated with 'late arrival' as the 'covariates'. On univariate analysis, 'unawareness to recognize stroke as a medical emergency' was observed to be the most significant factor associated with the delay (p≤0.001). Additionally, 'lack of awareness about thrombolysis among PCPs and 'transport delay' were also found to have a significant association with 'late arrival' (p=0.003 and p=0.043, respectively). Further, on entering these significant factors into multivariate regression, only 'unawareness to recognize stroke as a medical emergency' and 'lack of awareness about thrombolysis among PCPs were observed to be independently associated with the delay in arrival (p<0.001 and p=0.005, respectively) [Table/Fig-3]. Its noteworthy that 'unawareness about thrombolysis among patients and their relatives' despite being the most common factor for delay on descriptive analysis, was not observed to have a significant association with

Barrier to thrombolysis*	p-value	OR(95% CI)
Unawareness about thrombolysis among primary care providers	0.005	24.10 (2.671-217.556)
Unawareness about stroke as an emergency	<0.001	50 (8.130-250)
Transport delay	0.069	4.64 (0.886-24.352)

[Table/Fig-3]: Multivariate regression analysis showing strength of association of various barriers with pre-hospital delay.
*Barriers having significant association with pre-hospital delay on univariate analysis are shown in the table.
OR: Odds Ratio
CI: Confidence interval

'late arrival' on regression analysis. The reason for the same being that this factor was not group specific for late arrivals and even among the 13 individuals who arrived in window period, nine (69%) were not self-aware about thrombolysis as a treatment modality for stroke. On the other hand, 12 (92%) were advised to reach our hospital fast by their PCPs with a mention of thrombolytic therapy. Thus, PCPs awareness about thrombolysis had an obvious impact on the time of arrival.

Lack of Awareness About Stroke Thrombolysis Among PCPs

Among 183 subjects, for whom the first point of medical assistance was their rural doctor, 130 (71%) were referred to a medical care center not having thrombolysis facility. After visiting the referred center and undergoing some basic management, these cases were thereafter referred to our tertiary health center, in most cases because of poor affordability for private healthcare. Overall, 66% of the late arrivals mentioned that they were not told about the thrombolysis as a treatment option by their first or second attending healthcare provider.

Recognition of Stroke Symptoms and Considering the Same as a Medical Emergency

Among the late arrivals, 122 (58%) subjects recognized their symptoms promptly. Among 44 (21%) cases out of these, stroke symptoms were recognized with confidence, while in remaining 78 (37%) cases, patients or their relatives were partially confident about the same. However, despite 58% recognition rate of the symptoms, only 24 (11%) were rushed for emergent medical care.

Barriers to Thrombolysis in Patients Arriving Less Than or Equal to Four and a Half Hours (≤4.5h)

Among 13 patients who arrived within four and a half hours, four (31%) could not undergo Thrombolytic Therapy. All four of these patients arrived within the extended time window of three to four and a half hours. Among these, two arrived at the medical emergency on time, however, ran out of window period due to hospital delays including shifting to acute medical care unit, assessment by the neurophysician and neuroimaging. We did not thrombolyse other two patients with Tenecteplase as per our study protocol, and Alteplase could not be procured due to non-affordability of the patients.

DISCUSSION

The objective of the present study was to identify the factors which prevent stroke thrombolysis at our center. We performed a separate analysis for the patients who arrived out of the window period and those who arrived on time and yet, could not undergo thrombolytic therapy. The results of the present study showed that stroke thrombolysis rate in Warangal remains drastically low at four percent (4%), despite a significant recent increase

in the overall rate of thrombolysis in our country [3,12,13]. The single broad factor in our study which was responsible for poor thrombolysis rate was patients failure to arrive on time, with as much as 94% of patients arriving out of window period. We observed that 'lack of awareness about stroke thrombolysis' and'unawareness to recognize stroke as a medical emergency' were the most important factors associated with the late arrival of patients. Besides, 'failure to recognize stroke symptoms', and 'transport delay' were also contributory. Though dominant, pre-hospital delay was not the sole reason for failure in receiving thrombolysis, as we could not thrombolyse all patients, who presented to the medical emergency on time. The barriers to thrombolysis in this subgroup of patients were non-affordability and in-hospital delays.

The stroke thrombolysis rate in our study is trivial as compared to other recent studies from India. The Indo-US stroke registry reported a thrombolysis rate of 11% and a recently published study from Chandigarh reported thrombolysis in 189 (21.7%) out of 867 enrolled patients of acute ischaemic stroke [7,14]. This remarkably low rate of thrombolysis in our region can be explained by several factors. Among the previously published stroke literature, 'inability to recognize stroke symptoms' has been reported as the most consistent barrier to stroke thrombolysis. Kwan J et al., reported the same in their meta-analysis, as has been reported in Indian literature as well [15,16]. Among Indian studies, Badachi S et al., reported a 73% failure rate in recognizing the initial stroke symptoms [16]. On similar lines, Gurav SK et al., observed that pre-hospital delay was largely due to unawareness about stroke symptoms in the community [17]. However, our study showed only 6% arrival in window period despite a 58% symptoms recognition rate, thus implying that in most cases, prompt recognition of stroke symptoms did not translate into a prompt arrival of the patient. This observation is in agreement with the results of a prominent study by Giles MF et al., in which they observed that correct recognition of stroke symptoms often do not result in a lesser delay in seeking medical care [18]. Further, we observed that 'lack of awareness to consider stroke as a medical emergency' was one of the most important factors associated with delayed arrival in our patients. In many cases, family members or relatives told that they recognized the onset of stroke, but did not consider it a life-threatening illness, and hence, did not immediately rush to the hospital. Thus, lack of awareness about stroke as a medical emergency translated into significant pre-hospital delays. The other major barrier to the timely arrival of patients was unawareness about stroke thrombolysis as a treatment option among patients or their relatives, as well as the PCPs. Most of the patients in our study were not informed by their rural doctors about the thrombolytic therapy. This unawareness of the 'first attending rural doctors'about thrombolysis resulted in a large number of patients being referred to a health center which did not offer stroke thrombolysis facility. In our study as much as 82% of the cases initially visited a rural doctor, out of which 71% were further referred to a health center where stroke thrombolysis could not be done.This referral chain resulted in patients delayed arrival at our hospital.

Among the four patients who arrived on time and yet could not receive rt-PA, non-affordability and hospital delays in assessment, patient shifting, and neuroimaging were the various barriers which prevented thrombolysis. Although, pre-hospital delay is the major hurdle for successful stroke treatment in our country, in-hospital delays are also vastly contributory. Recently, a study from Kolkata reported that 51 patients out of a total enrollment of 147, could not undergo thrombolytic therapy despite arriving within time due to delay at various steps after emergency entry

[19]. We believe that a team of doctors, paramedics and nurses along with a dedicated neuroimaging facility for stroke patients can help to prioritize and manage patients with acute stroke symptoms. Besides, 'non-affordability' for rt-PA is a nation wide barrier for successful stroke treatment and government hospitals can address the same by providing rt-PA at subsidized rates or free under hospitals medicines indenting schemes.

In a controlled trial, Quain DA et al., observed that stroke education program and stroke protocol implementation improved the proportion of patients receiving rt-PA from 4.7% to 21.4% [20]. The results of the present study also suggest the need for a 'comprehensive stroke care program at our center to escalate the rate of thrombolysis therapy in acute stroke. Stroke education and awareness models should be incorporated as a part of stroke program, with the purpose of educating the community with special emphasis on rural population and rural doctors. Thrombolysis awareness as a modality of stroke treatment should be the part of stroke awareness models. Emergency ambulance services dedicated for acute stroke care may help in preventing transport delays. The results of our study may apply to other peripheral hospitals in India and other developing countries as well and hence, reinforce the importance of dedicated stroke care facilities to combat the epidemic of stroke.

LIMITATION

The main limitation of the study was that we could not analyze well the in-hospital barriers for thrombolysis due to a very small sample size of patients who arrived within the time window for thrombolysis. Thus, we plan to implement the derivations from this study in our stroke program and observe the improvement statistically over the next few years. A future study with an improved rate of on time arrivals will help in a true estimation of the in-hospital hurdles to thrombolysis.

CONCLUSION

We observed that the most common reason for the pre-hospital delay in our patients was unawareness to consider stroke as an emergency condition rather than delay in recognition of stroke symptoms, as reported in earlier studies. We should focus on stroke awareness programs to make people understand the importance of rushing to a stroke facility immediately after the onset. Another important point is to promote awareness for stroke thrombolysis among people as well as first attending rural doctors. It is crucial for the rural doctors to understand that stroke patients must be immediately sent to a hospital offering stroke thrombolysis.

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