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A RETROSPECTIVE STUDY ON IN-HOSPITAL DELAY FACTORS INFLUENCING INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHEMIC STROKE PATIENTS FROM A TERTIARY CARE HOSPITAL IN NORTH EAST INDIA.

Neurology

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ABSTRACT

Objective: Reports on the inverse relation between onset-to-door (OTD) and door-to-needle (DTN) in stroke thrombolysis have been repeatedly reported. The current study aimed to explore the association between DTN with the outcome and multi-component interventions influencing DTN to understand better why some patients get IVT in >60 mins DTN time. **Methods**: Twenty-five consecutive AIS patients treated with rt-PA in the Department of Neurology from January 2019 to December 2022 admitted to our tertiary care hospital were included in this analysis. The patients were grouped into a delay group (door-to-needle time (DTN) > 60 minutes; n=11) or a non-delay group (DTN time< 60 minutes; n= 14). The baseline data, laboratory tests, onset-to-door (OTD) time, door-to-imaging time (DTI), and decision-making time in both groups were retrieved. Multivariate logistic analysis was performed to analyze the data. **Results**: There were significant differences in hypertension, coronary artery disease, admission National Institutes of Health Stroke Scale (NIHSS), the Door to Imaging (DCT), Door to Needle (DTN), and decision-making time (DMT) between the two groups (all P<0.05). Multivariate logistic regression analysis revealed that the in-hospital delay was closely related to mRS score, OTD time, DCT time, DMT, and hypertension (p<0.001). **Conclusion**: The study reflects that the lesser the door-to-needle time and the sooner the treatment of thrombolysis to stroke patients, the better the clinical outcomes and recovery of the patients.

KEYWORDS

acute ischemic stroke, in-hospital delay, intravenous thrombolysis, door-to-needle time.

INTRODUCTION

Acute Ischemic stroke corresponds to a loss in neurologic function in an area of the brain due to sudden loss of blood circulation in that area. (1) It is the major cause and most common type of adult disability. (2) In the near future, it is projected to increase mostly in developing countries compared to developed ones. (3) The treatment of both hemorrhagic and ischemic strokes is time-dependent, the lesser the time the better the patients' outcome be it symptomatic intracranial hemorrhage, lower mortality rates, and better discharge destinations. (4) Despite the time-dependent factor, significant delays in the treatment process are observed which can be attributed to many limiting factors. (3,5) These delays can be categorized as prehospital and in-hospital delays, the latter is the one which the hospitals should/can take care of. Intravenous tissue-type plasminogen activator(tPA) thrombolysis within 4.5 hrs of symptom onset is the most proven effective pharma-logical treatment of AIS patients.(6)

The odds of achieving a modified Rankin Scale score of 0 to 1 decrease from 2.6 in patients treated 0 to 90 minutes after symptom onset to 1.2 in patients treated 271 to 360 minutes after symptom onset indicating the time-dependent efficacy of IVT.(7) Hence, shortened time periods of onset-to-door (OTD) and door-to-needle (DTN) both play crucial roles in improving IVT's efficacy. The study was conducted to get a deeper insight into the window period story with special emphasis on the relation between different limiting factors of in-hospital delays and that of onset-to-door time (OTD)

2. MATERIALS AND METHODS

2.1. Participants' Enrollment and Groups

Twenty-Five consecutive AIS patients treated with rt-PA in the Department of Neurology of GNRC Hospitals from January 2019 to December 2022 admitted to our tertiary care hospital in Guwahati were included in this analysis.

The study group was divided into two groups namely the Delay group (DTN>60 minutes; n=11) and non -delay group (DTN< 60 minutes; n=14) as per the DTN time. A retrospective retrieval of data was done which included -the arrival and imaging time of the patients (tracked from the electronic database system of the hospital) and tPA bolus and infusion time (from the nurses' chart). Onset time was specified as the time when the patient was last seen normal on the basis of information collected from the attendant. Age, gender, weight, National Institutes of Health Stroke Scale (NIHSS), systolic blood pressure, CT manifestations and typing of responsible vessels, occlusion site, serum glucose, hospital arrival time, onset-to-door time (OTD), door-to-imaging time (DCT), decision-making time (DMT), door-to-needle time (DTN), were collected from the electronic medical record system. CT documented hemorrhage with deterioration in NIHSS of ≥4 within 36 h of thrombolysis was reported as Intracranial hemorrhage (ICH). The study was approved by the institutional ethical committee with the informed consent of the participant patients/ family members.

2.2. Performance of IVT

As described previously, the method of IVT using rt-PA (Boehringer Ingelheim) was performed (8). 0.5 to 0.9mg/Kg with a maximum of ≤ 90mg were the selected doses of rt-PA with 10% of rt-PA injected within one minute and the remaining 90% intravenously within 1 hour. Specialist physicians evaluated and recorded the admission NIHSS scores. Within the next 24 hrs, antiplatelets or anticoagulants administration was prohibited with strict monitoring of BP within the required limits.

2.3 Post -thrombolysis assessment

Post IVT, the patient's vitals were continuously monitored for the next 24 hrs and in case of any worsening neurologic status, the patient was moved urgently for NCCT brain to rule out ICH. If not, post 24 hr all thrombolysed patients were subjected to another NCCT brain. Post

IVT, at 24 and 48 hrs NIHSS scores were reassessed. On the 7th day or at the time of discharge (whichever was later) and 90 days post thrombolysis Modified Rankin scale (mRS) score was assessed.

Statistical analysis

All data were entered into MS Excel and analyzed using SPSS version 17.0 Chicago, SPSS Inc, IL, USA, with $p<0.05$ as statistically significant. Pearson chi-squared test was used for categorical variables and ANOVA test for continuous variables. Multivariable linear regression analysis was used to indentify independent factors of in-hospital delay.

RESULTS

The number of stroke patients admitted to our stroke center was 1045 during the study period. Of them, only 30 (3.87%) eligible patients were treated with intravenous thrombolysis after overcoming many exclusion criteria and constraints. 25 cases are included in the study as 5 cases lost follow-up.

As shown in Table 1, there were 11 cases in the delay group and 14 cases in the non-delay group respectively. The mean ages were 60.54 years in the delay group and 60.63 years in the non-delay group respectively with no statistical significance. There were significant differences in hypertension, and coronary artery disease, between the groups (all $P<0.05$). Other demographics such as gender, age, and medical history showed no statistical significance.

Table1: Demographic comparison between the two groups

Items		Delay Group, n=11	Non-Delay Group, n=14	P-value
Age (yrs)	(Mean±SD)	60.54±12.01	60±13.53	0.92
Gender				
	Male n,(%)	8, (72.72%)	11, (78.57%)	0.734
	Female n,(%)	3,(27.27%)	3((21.42%)	
Weight (kg)	(Mean±SD)	66.09±5.07	61.5±9.06	0.162
Comorbidities				
	Hypertension,n, (%)	11,(100%)	10,(71.42%)	0.053
	Dyslipidemia, n, (%)	7,(63%)	8,(57.1%)	0.742
	Diabetes, n, (%)	4,(36.36%)	8,(57.14%)	0.301
	Coronary Artery Disease (CAD), n, (%)	1,(9.09%)	8,(57.14%)	0.012
	Non valvular atrial fibrillation (NVAF), n, (%)	2,(18.18%)	2, (14.28%)	0.791
	Rheumatic Heart Disease(RHD), n, (%)	3,(27.27%)	3,(21.42%)	0.734
	Prior Ischemic Stroke n, (%)	1,(9.09%)	0, (0.00%)	0.249
	Prior hemorrhagic Stroke n, (%)	0,(0.00%)	0,(0.00%)	

SD= Standard Deviation

Comparison of clinical features and time intervals between 2 groups

The results revealed that the delay group had lower scores of NIHSS (P=0.037) than the non-delay group. Modified Rankin scale (mRS) of the non-delay group after 90 days showed a statistically better outcome (p=0.038). Again, the Door to imaging (DCT), Door to needle (DTN), and decision-making time (DMT) were found to contribute significantly to in-hospital delay factors.

Table 2: Comparison of clinical features and time intervals between the two groups

Items		Delay Group, (n=11)	Non-Delay Group, (n=14)	P-value
GCS On Admission	(Mean±SD)	12±3.516	13.78±1.42	0.11
NIHSS On Admission	(Mean±SD)	9.18±3.53	12.71±4.02	0.037
NIHSS after 24 hrs	(Mean±SD)	9.63±2.18	6.5±3.7	0.027
mRS on 90 days	(Mean±SD)	2.27±2.00	0.928±0.79	0.038
SBP(mmHg)	(Mean±SD)	155.71± 21.28	146.36±17.72	0.272
DBP(mmHg)	(Mean±SD)	91.81±9.35	92.14±11.45	0.942
Blood glucose (mmol/L)	(Mean±SD)	157.27± 52.23	147.42± 52.811	0.667
Responsible vessels				
	MCA,n,(%)	10,(90.90%)	10,(71.42%)	0.22
	PCA,n,(%)	5,(45.45%)	4,(28.57%)	0.382
	ACA,n,(%)	4,(36.36%)	3(21.42%)	0.409
Hospital arrival time	8.00am - 6.00pm	8	12	0.42
	6.00pm-8.00 am (+1 day)	3	2	
OTD (mins)	(Mean±SD)	68.18±17.15	100.14±45.33	0.044
DCT (mins)	(Mean±SD)	21.63±13.13	9.64±6.49	0.008
DTN (mins)	(Mean±SD)	99.27±27.68	41.35±13.82	0.000
DMT (mins)	(Mean±SD)	48.72±30.55	22.85±9.24	0.008
OTN (mins)	(Mean±SD)	200.18±27.92	111.21±53.65	0.000

GCS= Glasgow coma scale, NIHSS= National Institutes of Health Stroke Scale, SBP= systolic blood pressure, DBP= diastolic blood pressure, mRS= modified Rankin scale, OTD= onset to door time, DCT= Door to CT time, DTN= door to needle time, DMT=decision making time, OTN= onset to needle time

Multivariate linear regression analysis to identify independent variables that affect in-hospital delay

Results of the multiple linear regression (Model 1) indicated that there was a very strong collective significant effect between the age, mRS, ODT, DCT, DMT, HTN, weight, gender, and DTN, ($F(5), 19) = 67.58$, $p < .001$, $R^2 = 0.95$, $R^2_{adj} = 0.93$). When analyzed further the results suggested that mRS, OTD, DCT and DMT, Hypertension were the independent risk factors of in-hospital delay of IVT for AIS patients indicating no multicollinearity concern as all the VIF (variance inflation factor) values were smaller than 2.5. Hence, Multivariate Regression (Model 2) including six variables (gender, mRS, ODT, DCT, DMT, HTN) was found to fit more and the risk factors affecting the in-hospital delay were analyzed. The results revealed that the in-hospital delay was closely related to mRS score (OR=0.14, P=.04), OTD time (OR=0.12, P=.05) DCT (OR=0.51, P<0.001), and decision-making time (DMT) (OR= 0.63, P<0.001), Hypertension (OR=0.31, p<0.001).

Table 3: Multivariate linear regression analysis to identify independent variables that affect in-hospital delay

Variables	Standard Coefficient	P-value
Gender	0.04	0.49
mRS	0.14	0.04
OTD	0.12	0.05
DCT	0.51	0.00
DMT	0.63	0.00
HTN	0.31	0.00

mRS= modified Rankin Scale, OTD= onset to door, DCT= door to CT, DMT=Decision making time, HTN= Hypertension

DISCUSSION

IVT with rt-PA though being the most effective treatment for AIS patients has the disadvantages of a strict time window, a large number of contraindications, low awareness, and high cost, resulting in non-using widely in low-income countries. Globally, 26.6% to 47.0% (approximately) of IVT-treated patients are thrombolysed with DTN< 60 mins.[9]. More efforts to improve upon treatment delays are the need of the hour.

In the present study, we investigated the factors associated with in-hospital delay in a tertiary care hospital in North East India, revealing that mRS, OTD, DCT, hypertension, and decision-making time were the independent risk factors of in-hospital delay. Out of all these

variables, the factors that need to be worked upon mainly for reducing in-hospital delays are DCT, DMT, and DTN.

The Modified Rankin Scale (mRS), the most widely used clinical outcome measure for stroke clinical trials, is used to measure the degree of disability in patients who have had a stroke.(10) The level of mRS score can reflect the clinical situation of the patient more intuitively. This study showed that patients with higher admission mRS scores have a lower risk of in-hospital delays, which might be explicated by the fact that severe clinical symptoms easily attracted family members' attention which in turn influences the attention of emergency specialists and physicians. Namely, the patients who had higher mRS scores underwent quick inspections after they arrived at the hospital. Again, OTD time being an independent risk factor of in-hospital delay projects that a long time of the symptom progression makes the DTN time shorter. Our results are consistent with the reports in other studies. (11) The risk of the independent factor DCT time can be attributed to the arrival of patients during the rush or odds hours of the hospitals, and pre-occupancy. Patients approaching the hospital with less time left in the window period of IVT treatment are dealt more promptly. This is the "3-hour effect", the negative correlation between OTD and DTN time. (6) At times, urgency is based on the fact that a shorter time of symptom progression has more time for IVT. This should be given a second thought as it's a well-known fact that the effect of IVT is significantly reduced with an increase in time. A better prognosis can be seen in patients with early IVT treatment.

The decision-making process for IVT was again found to be a prominent factor contributing to the in-hospital delay. After a definite diagnosis is made, medical professionals' communication with the patient or his/her family members stating the risk of IVT and letting them sign the consent; which is absolutely necessary in developing countries needs to be done quickly. This promptness may contribute to lessening the impact of decision-making time. In India, AIS patients or their family members have much more concerns about IVT risks and the expensive cost of rt-PA, leading to a longer time to make a decision, and subsequently increasing DTN time. Hypertension was also found to be one of the prominent risk factors contributing to in-hospital delays in IVT treatment. Antihypertensive drugs are to be given to AIS patients with hypertension to have a prescribed range of blood pressure prior to IVT treatment. This necessary step also adds a few minutes to get the treatment delayed.

For the first time from North East India, our study supported that in-hospital delay is mainly due to door-to-imaging, decision-making time, hypertension, as well as lack of proper communication between physicians and patients.

Limitations

Our study had several limitations. First, one single-center experience may not depict the full picture of the whole country. Secondly, the sample size of the study is quite less. Thirdly, we did not divide the degrees of severity for the delay situation. Finally, our experience on reducing in-hospital delay might be only successfully applied in specific local conditions. However, given the extreme homogeneity of the IVT process, attempts to shorten in-hospital delays are more likely to succeed.

CONCLUSION

In brief, this study suggested that mRS score, OTD time, DCT time, decision-making time and hypertension are the independent factors affecting the in-hospital delay of thrombolysis for AIS patients.

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