Original Article

Predictors of Intracerebral Hemorrhage in Acute Stroke Patients Receiving Intravenous Recombinant Tissue Plasminogen Activator

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Abstract

Background: Symptomatic Intracerebral hemorrhage (sICH) is a serious complication of recombinant tissue-plasminogen activator (rt-PA) therapy for acute ischemic stroke (AIS). **Objective:** To estimate the prevalence and predictors of sICH in patients after receiving IV rt-PA for AIS. **Material and Methods:** Consecutive patients of AIS thrombolysed between January 2010 and June 2016 in a University hospital in Hyderabad (India) were studied prospectively for sICH and it's various variables compared with the control group without sICH to determine any sigificantant difference. **Results:** Out of 113 patients , sICH was detected in 12 (10.61%) whose mean age(58±12.0 years) and gender ratio (2:1) was not statistically significant from controls. In s ICH group mean NIHSS score was 16.53± 5.81 vs 10.19± 5.06 in controls (p<0.001), gap between stroke onset and thrombolysis was 227.50±46.15 min vs 178.50± 69.20 min in controls(p=0.018).At presentation mean blood sugar was 208.75±90.97 mg/dl in sICH group vs 146.83±70.21 mg/dl in controls (p=0.002). Prior diabetes was in 7(53.30%) vs 23 (22.8%) in controls (p= 0.014)and hypertension in 11 (91.7%) vs (56(55.4%) in controls (p= 0.026) The mortality in sICH was 7 (58.30%) vs 4 (4.94%) in controls (p<.0.001). At 3 months mean mRS ofsICH patients was 5.57± 0.54 vs 2.17± 1.69 in controls (p<.05).**Conclusion:** High NIHSS score, increased stroke onset to thrombolysis time , high blood sugar at presentation ,prior diabetes and hypertension increase the chances of sICH. None of these contraindicate thrombolysing strokes but should caution the physician.

Keywords: India, intracerebral hemorrhage, stroke, thrombolysis

Introduction

Intracerebral hemorrhage (ICH) is the most serious complication of recombinant tissue-plasminogen activator (rt-PA) therapy for acute ischemic stroke (AIS) with high mortality and morbidity.[1] Fear of ICH after rt-PA partly limits more widespread use of rt-PA.[1] Identifying predictors of ICH may improve the selection of patients and the safety of thrombolysis.[2]

In the NINDS trial, where rt-PA was given within 3 h, 6.4% patients developed symptomatic ICH within 36 h of treatment, compared with 0.6% in the placebo group.[3,4] Risk factors for symptomatic ICH in the NINDS rt-PA stroke trial were the severity of neurological deficit at baseline and the presence of ischemic changes on pretreatment computed tomography (CT) scan.[5]

Previous pooled analysis of six IV rt-PA stroke trials showed 5.9% of rt-PA-treated patients compared to 1.1% of placebo cases had ICH associated with neurologic deterioration. Multiple studies of patients with AIS receiving rt-PA have identified several risk factors for ICH after thrombolysis. These include stroke severity as assessed by baseline National Institutes of Health Stroke Scale (NIHSS), older age, history of diabetes, presence and extent of ischemic changes on CT or diffusion-weighted imaging, presence of small vessel disease on CT scan, high baseline serum glucose, admission fibrinolytic profile, statin use, and current smoking. However, none has explored the ability to predict the risk of ICH at the

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individual level. There are limited published studies from India which have shown marked variation in the incidence of ICH complications of thrombolysis.[6,7]

Objective of study

This study was aimed to estimate the prevalence and predictors of symptomatic ICH in patients who had received IV thrombolysis for ischemic stroke.

Materials and Methods

The present study was a prospective observational study performed between January 2010 and June 2016 at Nizam's Institute of Medical Sciences, a tertiary care health center and a university hospital located in Hyderabad, the capital city of Andhra Pradesh and Telangana. The study protocol was approved by the ethics committee of the university and shown by flowchart in Figure 1. Informed written consent was obtained from all the participants or next of their kin. In this observational study, all patients who were thrombolysed with IV rt-PA for AIS within the window period of 4.5 h were included. Thrombolysis was done according to the American Heart Association/American Stroke Association guidelines.[8] Demographic variables, vascular risk factors, mean arterial blood pressure at presentation, blood glucose at presentation, NIHSS scores at presentation and 24-hours after thrombolysis and the time gap between stroke onset to thrombolysis were recorded. Risk factors were identified based on history and laboratory evaluation. For all patients, time of symptom onset was defined by the time when they were "last seen to be well." A comprehensive workup of all the patients was done to determine the stroke mechanism and subtype. Mechanism of stroke was classified according to Trial of ORG 10172 in Acute Stroke Treatment criteria as five categories which includes cardioembolism, large artery atherosclerosis, small artery occlusion (lacunae), stroke of other determined etiology, and stroke of undetermined etiology.[9] Imaging findings including at baseline, at 24 h after thrombolysis or when there was clinical deterioration were noted. Follow-up was done on OP check-up or telephonic interview with patient/patient attenders at 1 and 3 months.

Post-rt-PA ICH was defined as any hemorrhage in the brain within 36 h after thrombolysis which was detected on imaging.[4] ICH was classified as symptomatic ICH and asymptomatic ICH. Symptomatic ICH was defined as a CT or magnetic resonance imaging documented hemorrhage associated with clinical deterioration in the form of a decline in NIHSS score of ≥4 points or death.[4] Different variables (age, sex, vascular risk factors, gap between stroke onset and thrombolysis, mean arterial blood pressure at presentation, blood glucose at presentation, and admission NIHSS scores) were evaluated as predictors of symptomatic ICH and were compared between symptomatic ICH group and without symptomatic ICH group. The outcome of patients with symptomatic ICH and patients without symptomatic ICH was evaluated by measuring intrahospital mortality and modified Rankin Scale (mRS) at 3 months. Good outcome was defined as a mRS of ≤2 at 3 months.

Statistical analysis

All the analysis was done using SPSS version 16 (SPSS Inc, Ill, Chicago, USA). $P < 0.05$ was considered statistically significant. Comparison of categorical values was done using Fischer's exact test/Chi-square test and continuous variables were done using Mann–Whitney U-test.

Results

During study from January 2010 to June 2016, a total of 113 patients of ischemic stroke were thrombolysed whose mean age was 54 ± 15.0 years (range: 20–94 years). The demographics and baseline characteristics of all thrombolysed patients are enlisted in Table 1.

In this study, 18 (15.92%) out of 113 patients had ICH among whom12 (10.61%) had symptomatic ICH and 6 (0.05%) had asymptomatic ICH. Among these, 8 patients had bleed within the region of infarct [Figure 2], one patient had subarachnoid region bleed [Figure 3], and three patients had a bleed in a region away from the infarct [Figure 4].

The mean age of patients (58 ± 12.0 vs. 54 ± 16.0 years), patients aged more than 60 years (50% vs. 31.7%), mean arterial blood pressure at presentation (114.53 ± 16.92 vs. 107.11 ± 15.62 mm of Hg) in symptomatic and without symptomatic ICH groups did not attain statistical significance. The gap between stroke onset and thrombolysis, mean blood sugar at presentation was significantly higher in symptomatic ICH group compared to without symptomatic ICH group with statistically significant difference ($P = 0.018$, $P = 0.002$), respectively. In symptomatic ICH group, mean NIHSS score was 16.53 ± 5.81 and in without symptomatic ICH group it was 10.19 ± 5.06 with statistically significant difference ($P < 0.001$).

Regarding the prior history of risk factors, the incidence of diabetes mellitus (58.3% vs. 22.8%) and hypertension (91.7% vs. 55.4%) showed a marked difference between the symptomatic and without symptomatic ICH groups. There was no significant difference in the incidence of previous strokes, cardiac diseases, hyperlipidemia, hyperhomocystinemia, smoking and alcoholism in between these 2 groups.

Large artery atherosclerosis was found to be the most common mechanism of stroke in both groups (66.7% vs. 44.55% in symptomatic and without symptomatic ICH, respectively). Small artery occlusion was not seen in symptomatic ICH group and was seen in 15 (14.9%) patients in asymptomatic ICH group. In this study group, only one patient with Takayasu arteritis had stroke of other determined etiology. In symptomatic ICH group, 3 (25.0%) patients had stroke of undetermined etiology whereas in without symptomatic ICH group 25 (25.25%) patients had undetermined etiology.

Outcome was analyzed by measuring intrahospital mortality and mRS at 3 months. The mortality rate was significantly

Table 1: Demographics and baseline characteristics of all thrombolysed patients and comparison of characteristics of patients in symptomatic intracerebral hemorrhage and without symptomatic intracerebral hemorrhage groups

	Demographics (%)	Symptomatic ICH (%)	Without symptomatic ICH (%)	*P*
Number of patients	113	12 (10.61)	101 (89.38)	
Age (years)	54.11±16.4	58.0±12	54±16.0	0.332
Age >60 years	30 (33.9)	3 (25.0)	27 (26.73)	0.61
Male:female	2.26:1	1:1	2.15:1	
Female	81 (71.70)	6 (50.0)	29 (28.71)	0.99
Time to thrombolysis (min)	183.71±68.66	227.50±46.15	178.50±69.20	0.018
Blood glucose at presentation in mg/dl	153.41±74.71	208.75±90.97	146.83±70.21	<0.002
Mean arterial pressure at presentation (mmHg)	107.90±15.85	114.53±16.92	107.11±15.62	0.12
NIHSS at presentation	10.86±5.48	16.50±5.81	10.19±5.06	<0.001
Hypertension	67 (59.30)	11 (91.69)	56 (55.44)	0.026
Diabetes	30 (26.50)	7 (58.33)	23 (22.81)	0.014
Previous stroke	12 (10.60)	1 (8.34)	11 (10.92)	0.99
Previous TIA	6 (5.30)	2 (16.71)	4 (3.96)	0.122
Coronary artery disease	23 (20.40)	3 (25.0)	20 (19.86)	0.707
Atrial fibrillation	5 (5.65)	1 (8.3)	4 (4.0)	>0.99
CRHD	7 (6.20)	0	7 (6.87)	>0.99
Congenital heart disease	3 (2.70)	0	3 (2.97)	>0.99
Dilated cardiomyopathy	4 (3.50)	0	4 (3.96)	>0.99
Hyperlipidemia	19 (16.80)	2 (16.67)	17 (16.83)	>0.99
Hyperhomocysteinemia	25 (22.10)	1 (8.33)	24 (23.76)	0.296
Smoking	30 (26.50)	5 (41.67)	25 (24.75)	0.297
Alcoholism	17 (15.20)	3 (25.0)	14 (13.86)	0.388
Mechanism of stroke				
Cardioembolism	16 (14.15)	1 (8.33)	15 (14.85)	0.337
Large artery atherosclerosis	53 (46.90)	8 (66.7)	45 (44.61)	
Small artery occlusion	15 (13.27)	0	15 (14.85)	
Stroke of other determined etiology	1 (1.13)	0	1 (1.24)	
Stroke of undetermined etiology	28 (24.78)	3 (25.04)	25 (25.24)	
Intrahospital mortality	11 (12.43)	7 (58.33)	4 (3.96)	<0.001

NIHSS=National Institutes of Health Stroke Scale, CRHD=Chronic rheumatic heart disease, ICH=Intracerebral hemorrhage, TIA=Transient ischemic attack

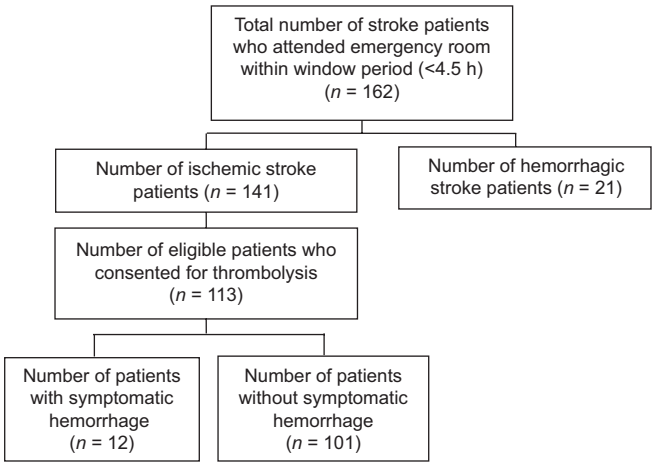

Figure 1: Flowchart depicting study protocol

high in patients who had symptomatic ICH ($P < 0.001$). Out of 12 patients of symptomatic ICH, 4 patients underwent decompressive craniectomy and 2 of them survived. Remaining 8 patients did not undergo decompressive craniectomy as 7 of them were unfit for surgery and one died within 2 h. In patients without symptomatic ICH, intrahospital mortality was seen in only 4 (0.04%) patients which was due to varied reasons such as cardiac arrest ($n = 2$), cardiac failure due to Duchenne muscular dystrophy with cardiomyopathy ($n = 1$), and cerebral edema with sepsis ($n = 1$). The two patients without symptomatic ICH underwent decompressive craniectomy due to cerebral edema with mass effect, and they survived after decompressive craniectomy. At 3 months, mean mRS of symptomatic ICH patients was 5.57 ± 0.54 and of patients without symptomatic ICH was 2.17 ± 1.69 ($P < 0.05$).

Discussion

In our study group, symptomatic ICH was seen in 10.6% of thrombolysed patients which was higher than that reported in NINDS (6.4%) and ECASS III (7.9%) trials. This could be because of late thrombolysis in our patients due to the delayed arrival and also because of the inclusion of post-rt-PA ICHs referred from other hospitals to our tertiary center. We found no significant difference in mean age of patients

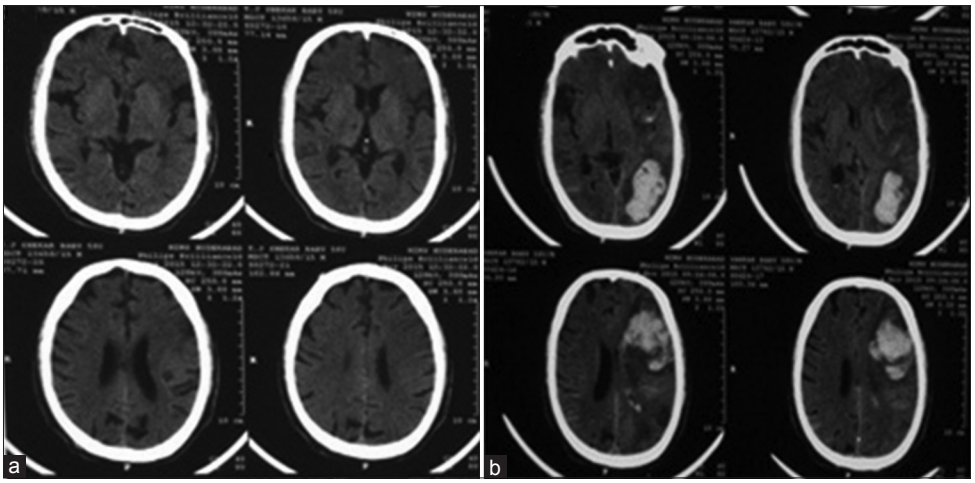

Figure 2: Computed tomography scan brain of 58-year-old patient showing left middle cerebral artery territory infarct (a) with postthrombolysis hemorrhage in the same region (b)

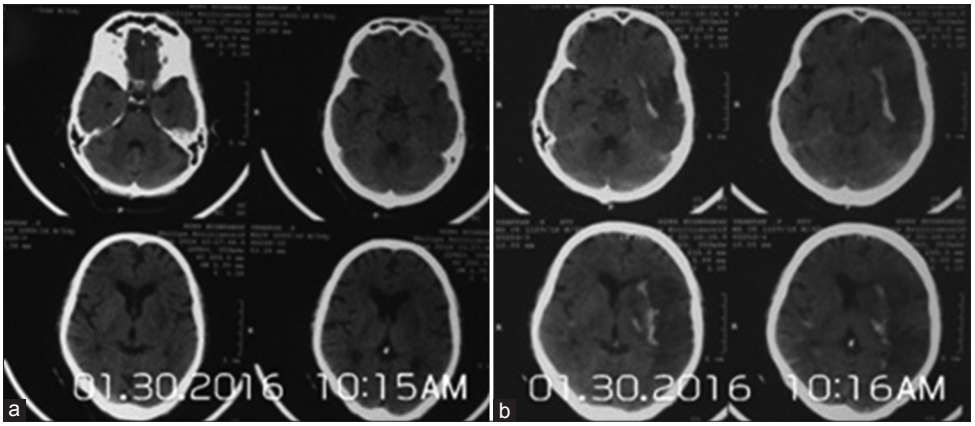

Figure 3: Computed tomography scan brain of 63-year-old patient showing left middle cerebral artery territory infarct (a) with postthrombolysis hemorrhage in subarachnoid space (b)

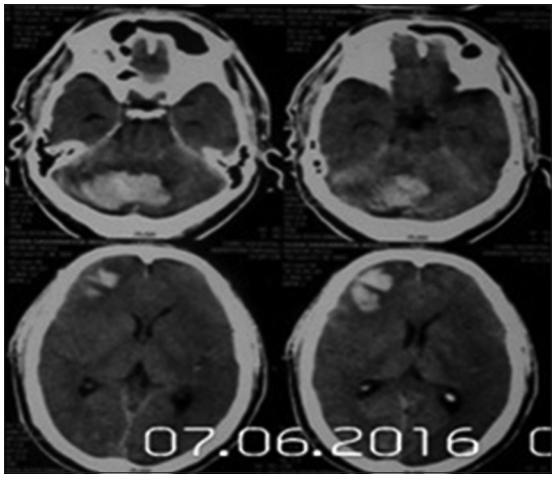

Figure 4: Computed tomography scan brain of 69-year-old patient showing left middle cerebral artery territory infarct with postthrombolysis hemorrhage in bilateral cerebellum and right frontal area

with and without symptomatic ICH (58.06 ± 12 years vs. 54 ± 16.0 years), but a higher proportion of those over 60 years of age had ICH in our study. Our study has shown that time to thrombolysis was significantly higher in symptomatic ICH group (227.5 ± 46.15) compared to without symptomatic ICH group (178.5 ± 69.20 min) which is consistent with several previous studies. In NINDS trial[4, 10-12] where rt-PA was given within 3 h of stroke onset incidence of symptomatic ICH was 6.4% but in ECASS III trial where rt-PA was given within 3–4.5 h the incidence of symptomatic ICH rose to 7.9%.[12] The Alteplase Thrombolysis for Acute Noninterventional Therapy in Acute Ischemic Stroke trial investigated the efficacy of rt-PA used within 3–5 h of onset of stroke which showed high rates of spontaneous ICH in the rt-PA group (7%) compared to the controls (1.1%).[13] The Canadian Alteplase for Stroke Effectiveness Study results showed that time to thrombolysis was an independent predictor of symptomatic ICH and trend toward a higher rate of symptomatic ICH in the 3–4.5-h group compared to the 0–3 h group (7.8 vs. 3.8%, $P = 0.06$).[14] The results of these trials including the present study clearly showed that time to thrombolysis has a significant impact in developing ICH after thrombolysis.

We did not find any significant association between symptomatic ICH group and mean arterial blood pressure at presentation, probably because there were not enough patients with severe hypertension either before or after thrombolysis in our study. The mean blood sugar at admission in our study was 208.75 ± 90.97 mg/dl in symptomatic ICH group compared to146.83 ± 70.21 mg/dl in without symptomatic ICH group, and this difference was statistically significant. Hyperglycemia has been found to exaggerate blood–brain barrier injury, enhancement of intracellular acidosis in the ischemic penumbra, leading to loss of ion homeostasis, mitochondrial dysfunction, and bioenergetic failure resulting in hemorrhagic transformation of the cerebral infarct.[15,16] The present study showed statistically significant ($P < 0.001$) differences in NIHSS scores at presentation between symptomatic ICH group and without symptomatic ICH group (16.5 ± 5.81 vs. 10.19 ± 5.06). NIHSS represents baseline stroke severity which mainly depends on infarct size. Most of the previous studies including ECASS and NINDS trials have also showed that baseline stroke severity was one of the most important predictor of ICH after thrombolysis.

Regarding the preexisting risk factors, diabetes was seen in 7 (58.3%) patients in symptomatic ICH group and 23 (22.8%) patients in without symptomatic ICH group. Diabetes is known to produce damaging effects on microvasculature which results in increased bleeding risk after thrombolysis.[17] History of hypertension was present in 11 (91.7%) patients in symptomatic ICH group and 56 (55.4%) patients without symptomatic ICH group.[18]

Regarding stroke mechanism, there was the similar prevalence of cardioembolism and large artery atherosclerosis in patients with and without symptomatic ICH.[19,20] However, no one in symptomatic ICH group had underlying small artery occlusion, as reported in earlier studies.[21] Most patients who were categorised under large artery atherosclerosis had intracranial large artery disease, which has previously been reported as the most common stroke mechanism in our patients.[22] As expected patients with symptomatic ICH group had a significant higher mortality and significant disability in comparison to those without symptomatic ICH. To conclude, identifying predictors of ICH at individual level may help to refine the selection of patients before thrombolysis.

Limitations

The main limitation of the present study was the small sample size because of being a single-center study, but several other larger studies have identified same predictors.

Conclusion

The present study showed that time to thrombolysis, baseline NIHSS, prior history of hypertension and diabetes were the most important predictors of symptomatic ICH after thrombolysis. Patients with symptomatic ICH had high mortality and morbidity. Although none of the predictors of symptomatic ICH constitute a contraindication to stroke thrombolysis, yet having this information may help a clinician to be cautious and achieve the optimum outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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