Original Research Article

A study of short term and long term risk of ischemic stroke and other vascular events following early treatment of tia and minor stroke in a tertiary centre in North India

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ABSTRACT

Introduction: Transient ischemic attack and minor ischemic stroke are associated with early recurrence and deterioration respectively. There is a high risk of stroke after TIA ranging between 10-20% in the ensuing 90 days in the various studies. There are various clinical and imaging factors which predict the early risk of stroke after a TIA.

Aim of the study: To evaluate the short term and long term risk of ischemic stroke following early treatment of TIA and minor stroke.

Materials and Methods: TIA is defined as sudden focal neurologic deficit of presumed vascular origin lasting less than 24 hours. Minor ischemic stroke is defined as National institute of Health Stroke scale score of ≤5. TIA mimics were excluded from the study. The patients were followed up till 1 year. In patients with minor ischemic stroke, a 2-point worsening in the NIHSS was considered as an event. Modified Rankin score at 3 months was assessed.

Results: Total 320 patients were analysed with a mean age of 60.6 ± 13.6 years. Out of the them 20.7% were females, 78% of patients had minor stroke. There is significant association of lacunar stroke in minor stroke patients ($p<0.01$), whereas most TIA patients, etiology remained undetermined. In multiple regression analysis, both diabetes [$p<0.05$] and significant vessel stenosis (>50%) [$p<0.05$] were found to be an independent predictor of recurrent stroke in TIA and minor stroke patients.

Conclusion: Urgent treatment after TIA and minor ischemic stroke is associated with reduced risk of ischemic stroke recurrence. Both diabetes mellitus and significant vessel stenosis are independent predictor of stroke recurrence.

1. Introduction

Transient ischemic attack and minor ischemic stroke are associated with early recurrence and deterioration respectively. There is a high risk of stroke after TIA ranging between 10—20% in the ensuing 90 days in the various studies. But recent studies have found urgent interventions to be associated with substantial reductions in stroke risk within the first 90 days following TIA (0.6% to 3.1%). There are various clinical and imaging factors which predict the early risk of stroke after a TIA. Identifying the stroke subtype also help in estimating the risk of stroke recurrence and also the risk of deterioration after a minor stroke. Large artery atherosclerosis has been found to be associated with a high risk of stroke after a TIA. A metanalysis of four population based studies of stroke showed that the risk of recurrent stroke was 4 % (95% CI: 0.2—7.8) at 7 days and 12.6% (95% CI: 5.9—19.3) at 30 days in patients with large artery atherosclerotic aetiology compared to 0 and 2 % (95% CI 0—4.2) respectively in patients with lacunar stroke. In addition to the short-term risk of stroke, these patients are at increased long-term risk of ischemic vascular events. We

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know that urgent evaluation and treatment of these patients is associated with significant reduction of the short-term risk of stroke, but there was not much literature available about the effect of early treatment and long-term outcome. The purpose of the study is to evaluate short term and long-term outcome and their predictors in patients with TIA or minor ischemic stroke who receive urgent intervention.

2. Aim of the study

1. To evaluate the short term and long term risk of ischemic stroke following early treatment of TIA and minor stroke
2. To evaluate the occurrence of non stroke vascular events following early treatment of TIA and minor stroke.

3. Methods and Materials

Patients with TIA and minor ischemic stroke admitted in stroke unit of Geetanjali Medical College, Udaipur within 48 hours of onset and patients seen as outpatient within 48 hours of symptom onset from November 2016 to October 2020. TIA mimics were excluded from the study. The patients were followed up till 1 year.

3.1. Study design

The proposed study is a retrospective cohort study of patients with TIA and minor ischemic stroke admitted in stroke unit of Geetanjali Medical College, Udaipur. within 48 hours of onset and patients seen as outpatient within 48 hours of symptom onset from November 2016 to October 2020. TIA is defined as sudden focal neurologic deficit of presumed vascular origin lasting less than 24 hours. Minor ischemic stroke is defined as National institute of Health Stroke scale score of ≤5. TIA mimics were excluded from the study. The patients were followed up till 1 year.

The primary outcome is stroke or TIA at 3 months and at one year. In patients with minor ischemic stroke, a 2-point worsening in the NIHSS will be considered as an event. The Modified Rankin score at 3 months is assessed. The secondary outcome will be any non stroke vascular events or vascular deaths at 3 months and at one year. Non-stroke vascular event will include any Myocardial infarction, unstable angina and peripheral vascular disease leading to amputation of that limb occurring during follow up.

Clinical and socio demographical data, National Institutes of Health Stroke Scale scores and Modified Rankin Scale scores, as well as data on vascular risk factors were collected from patients. The vascular risk factors include
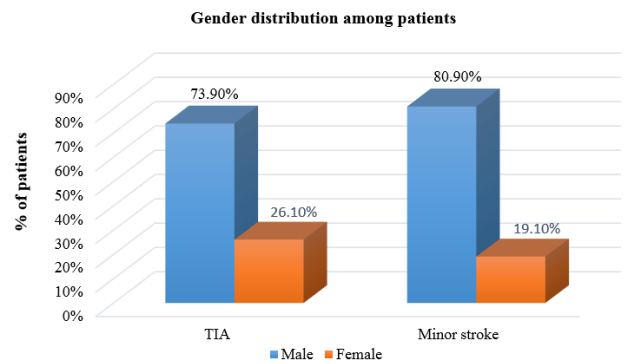
1. Diabetes
2. Hypertension
3. Age
4. Smoking
5. Renal dysfunction
6. Dyslipidemia
7. Peripheral vascular disease
8. Coronary artery disease

Statistical analysis

All statistical analysis was performed using SPSS software. Continuous variables are reported as mean ± SD. Categorical variables were reported as proportions. Baseline characteristics were compared between the 2 groups. Differences in continuous variables were assessed by 1-way analysis of variance and differences between proportions were assessed by the X^2 test. Univariate and multivariate analysis was done to identify predictors of new vascular events. Multiple logistic regression model was used to identify independent predictors of new vascular events.

4. Results

Total 320 patients were analysed with a mean age of 60.6 ± 13.6 years. Out of the them 20.7% were females.

Fig. 1: Sex distribution of the study group

Table 1 Out of 320 patients, 78% of patients had minor stroke.

Table 2 Among the study group, 198 patients (61.9%) had Hypertension, 138 patients (43.1%) had Diabetes, 137 patients (42.8%) had dyslipidaemia and 34 (10.6%) had atrial fibrillation.

4.1. Comparison of baseline characteristic between TIA and Minor stroke patients

There is no significant difference between demographic characteristic, risk factor association and clinical characteristic between TIA and minor stroke patients. Limb weakness (63.4%) was the most common in both groups of patients followed by speech impairment (dysarthria in 46.3% and aphasia in 12.8% patients). There is significant association of DWI positivity and minor stroke patients compared to TIA patients (p<0.01).

Table 1: Risk factors associated with TIA and Minor stroke patients

Risk Factor	TIA	Minor stroke	Total
Hypertension	43(62.3%)	155(61.8%)	198(61.9%)
DM	23(33.3%)	115(45.8%)	138(43.1%)
Smoking	19(27.5%)	66(26.3%)	85(26.6%)
CAD	9(13%)	41(16.3%)	50(15.6%)
Atrial Fibrillation	4(5.8%)	30(12%)	34(10.6%)
Valvular heart disease	5(7.2%)	30(12%)	35(10.9%)
Dyslipidaemia	28(40.6%)	109(43.4%)	137(42.8%)
Peripheral Vascular Disease (PVD)	0	10(4.1%)	4(3.1%)

Table 2: Comparison between baseline characteristic between TIA and Minor stroke patients

	TIA	Minor stroke	Total	P value
No. of patients	69(21%)	251(79%)	320	
Age	62.6 ± 13.8	59.4 ± 13.5	60.6± 13.6	0.13
Sex (M: F)	51:18	203:48	254:66	0.2
Hypertension	43(62.3%)	155(61.8%)	198(61.9%)	0.9
DM	23(33.3%)	115(45.8%)	138(43%)	0.05
Smoking	19(27.5%)	66(26.3%)	85(26.6%)	0.83
CAD	9(13%)	41(16.3%)	50(15.6%)	0.5
Atrial Fibrillation	4(5.8%)	30(12%)	34(10.6%)	0.14
Valvular heart disease	5(7.2%)	30(12%)	35(10.9%)	0.26
Dyslipidaemia	28(40.6%)	109(43.4%)	137(42.8%)	0.6
Peripheral Vascular Disease (PVD)	0	10(4.1%)	4(3.1%)	0.09
Limb weakness	45(65.2%)	158(62.98%)	203(63.4%)	0.7
Dysarthria	31(44.9%)	117(46.6%)	148(46.3%)	0.8
Aphasia	7(10.1%)	34(13.5%)	41(12.8%)	0.4
MRI DWI positive	29(48.3%)	169(92.3%)	198(61.8%)	<0.01
MRI DWI multiple positive	11(18.3%)	53(29.0%)	64(26.3%)	0.1
Significant vessel stenosis (>50%)	12(15.4%)	66(26.3%)	78(24.4%)	0.12

Table 3: Distribution of etiologic subtypes of TIA and Minor stroke patients

Etiologic subtypes	TIA	Minor stroke	Total	P value
LAA	9(13%)	38(15.1%)	47(15%)	0.6
Lacunar	6(8.7%)	81(32.6%)	87(27.2%)	<0.01
Cardioembolism	7(10.1%)	51(20.3%)	58(18.1%)	0.05
Undetermined	47(68.1%)	72(28.6%)	119(37.2%)	<0.01
Other determined	0	9(3.6%)	9(2.8%)	0.11

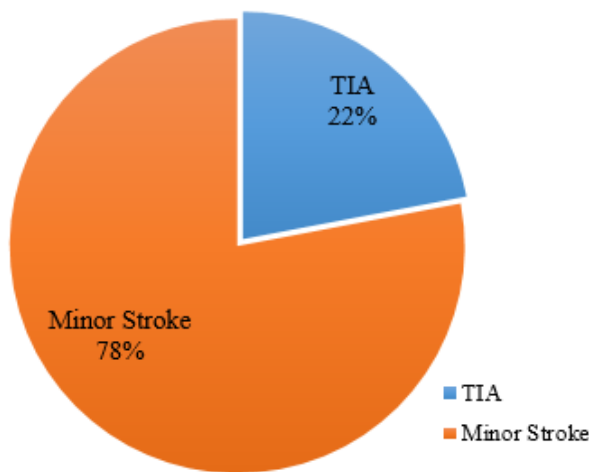## 4.2. Etiologic subtypes of TIA and Minor stroke patients

Table 2 According to TOAST classification, in 47(15%) patients, the cause of stroke was large artery atherosclerosis, in 58 (18.1%) cardioembolism, in 87 (27.2%) lacunar, in 9(2.8%) other determined etiology and in 119 (37.2%) undetermined cause. There is significant association of lacunar stroke in minor stroke patients(p<0.01), whereas most TIA patients, etiology remained undetermined. In the large artery atherosclerosis group, 32(68%) of patients had intracranial atherosclerosis. Carotid endarterectomy was performed in 8 patients.

4.3. New events in TIA and stroke patients at 3 months and 1 year

Table 3 New cerebrovascular event occurred in 23 (7.7%) and 25 patients (8.5%) at 3 months and 1 year respectively. 14 out of 23 events (60%) occurred within 3 days of occurrence of stroke. There is no significant difference between TIA and minor stroke patients regarding association of new events. In case of cardiovascular event, 7 and 13 patients (2.2% and 4.4%) respectively, had new events at 3 months and 1 year. There were 5 deaths in 3 months of stroke, out of which 2 were vascular death and one patient died due to intracranial hemorrhage who was

Table 4: New cerebrovascular and cardiovascular events in TIA and Minor stroke patients

	TIA	Minor stroke	Total	P value
No. of patients	69(21%)	251(79%)	320	
Cerebrovascular event at 3 months	2(2.9%)	21(8.4%)	23(7.2%)	0.11
Cerebrovascular event at 1 year	3(4.9%)	22(9.4%)	25(8.5%)	0.26
Cardiovascular event at 3 months	2(2.9%)	5(2%)	7(2.2%)	0.65
Cardiovascular event at 1 year	4(6.6%)	9(3.8%)	13(4.4%)	0.35

Fig. 2: Proportion of patients with TIA and minor stroke

Table 5: Predictors of recurrence of stroke

Factors	Stroke recurrence	P value
Age (>60 years)	9(5.3%)	0.16
Sex	20:3	0.35
Hypertension	17(8.6%)	0.22
DM	15(10.9%)	0.01
Smoking	5(5.9%)	0.59
CAD	4(8.1%)	0.8
Valvular heart disease	4(11.4%)	0.31
Atrial Fibrillation	3(8.8%)	0.7
Peripheral Vascular Disease	2(20%)	0.11
Dyslipidemia	10(7.3%)	0.96
ABCD (≥ 4)	23(100%)	0.11
Multiple DWI lesion	4(6.3%)	0.7
Significant vessel stenosis (>50%)	11(14.1%)	0.01
LAA	6(12.8%)	0.1
Lacunar	8(9.2%)	0.4
CE	7(12.1%)	0.11

on anticoagulant. 2 other patient died due to non-vascular causes.

4.4. Predictors of recurrence of stroke at 3 months

Table 4 In univariate analysis both diabetes mellitus and significant vessel stenosis (>50%) were significantly associated with recurrence of stroke. All patients who had recurrent event had ABCD2 score ≥4.

Table 5 In multiple regression analysis, both diabetes [OR- 2.6 CI (1.1—6.6), p<0.05] and significant vessel stenosis (>50%) [OR- 3.1 CI (1.3—7.6), p<0.05] were found to be an independent predictor of recurrent stroke in TIA and minor stroke patients.

4.5. Outcome of stroke at 3 months

14 out of 23 patients (60%) who had recurrence of stroke had significant disability (mRS ≥2), whereas 53 patients (17.8%) who do not have recurrence of stroke had significant disability at 3 months. During these periods only 6 patients received IV thrombolysis, out of which one patient had significant disability (mRS 3), whereas other patient had good outcome (mRS 0 or 1). No patient had symptomatic intracranial hemorrhage.

5. Discussion

Our study investigated the short term and long-term recurrence of ischemic stroke in TIA and minor stroke patients in a tertiary care centre in north India, where round the clock stroke service is available. The study population consisted of 320 patients out of which 21% of patient had TIA.

Patients were classified according to TOAST classification. In our study in TIA group, 13%, 8.7% and 10.1% of patients were having large vessel atherosclerosis, lacunar and cardioembolism as etiology whereas in 68% of patient's etiology remained undetermined. Levelle et al[1] in their study showed comparable frequencies [26%, 4.1% and 10.5% patients were having large artery atherosclerosis, lacunar and cardioembolism as etiology, whereas in 51% of patient's etiology remained undetermined]. Similarly, in the minor stroke group, 15.1%, 32.6% and 20.3% of patients were having large vessel atherosclerosis, lacunar and cardioembolism as etiology. In 28.6% of patients the etiology was undetermined. Previous study done by Wu et al[2] reported 41.8%, 22.4% and 2.8% patients were having large artery atherosclerosis, lacunar and cardioembolism as etiology of stroke. In the study, 28.8% of patients the etiology remained undetermined. Overall in our study,

14.7%, 27.2% and 18.1% of patient had large vessel atherosclerosis, lacunar and cardioembolism as etiology of stroke. These differences can be explained by regional differences in risk factors and different study population.

Hypertension (62.3% in TIA and 61.8% in minor stroke, overall 61.9% of patients), diabetes mellitus (33.3% in TIA and 45.8% in minor stroke, overall 42.2% of patients) and dyslipidemia (40.6% in TIA and 43.4% in minor stroke, overall 42.8% of patients) were the vascular risk factors most commonly associated with study population. Levelle et al[1] in their study also reported similar association of risk factors with study population.

In our study limb weakness (63.4%) and speech impairment (55%) were the predominant clinical symptoms presented by the patient which were same as reported by Levelle et al[1] in their study.

The study showed a recurrence of ischemic stroke in 2.9% and 8.4% of patients with TIA and minor stroke at 3 months. Overall, recurrence rate of cerebrovascular event at 3 months is 7.2% which was similar to the rate of stroke recurrence reported in a recent metanalysis (6.7% (CI—5.2—8.7%)).[3] The recurrence rate is higher for minor stroke patients compared to TIA patients. Most of the stroke recurrence (60%) occurred within 3 days, suggesting the importance of urgent evaluation and treatment of these patients. In our study, stroke recurrence rate at one year is 8.5% which was lower compared to a metanalysis which reported risk of recurrent of stroke at > 90 days to be 11.3% (CI 7.5—16.6%).[3] But a study by Amarenco et al, showed that the 3 months and 1 year stroke recurrence rate was 3.7 and 5.1%, which was lower compared to our study.[4] This may be related to geographic variation, resource availability and health seeking behaviour of peoples of developing countries.

In our study 2.2% and 4.4 % of patients had new cardiovascular event at 3 months and 1-year suggestive high risk of association of cardiovascular event with TIA and minor stroke patients. Previous studies also found similar rate of occurrence of cardiovascular event in TIA and minor stroke patients.[5–7]

All our patients with TIA and minor stroke, who had stroke recurrence had ABCD2 score of 4 or more, suggesting a high sensitivity but poor specificity for prediction of new vascular event. Wardlaw et al in a recent metanalysis reported similar findings (sensitivity 86.7% and specificity 35.4%).[8]

In our study, increasing age was not associated with increased risk of stroke in TIA and minor stroke patients. This contrasts with earlier study by Jhonston et al[9] where they reported age as a predictor of stroke recurrence. But Ois et al in their study had found age was not significantly associated with further stroke recurrence in both TIA and minor stroke patients.[10]

Among vascular risk factor, diabetes mellitus was found to be an independent predictor of stroke recurrence in our patient. Similar findings had been reported by Chen et al in their study as both diabetes and metabolic syndrome independently associated with increased stroke risk in TIA and minor stroke patient.[11] However, in our study we have not evaluated the association of metabolic syndrome with stroke recurrence.

In our study, both intracranial and extracranial significant vessel stenosis (>50%) found to be an independent predictor of stroke recurrence at 3 months, irrespective of the stroke subtype. Coutts et al in their study also reported similar findings as significant vessel stenosis as a strong predictor of stroke recurrence.[12]

Our study reported stroke recurrence rate as 12.8%, 12.1% and 9.2% in large artery atherosclerosis, cardioembolism and lacunar stroke subtype respectively. We do not find any significant association between stroke recurrence and individual stroke subtype. This contrasts with findings reported by most of the previous studies where a strong association was found with large artery atherosclerosis and early recurrence of stroke.[4,10] But Ay et al in their study did not find large artery atherosclerosis as independent predictor of recurrent stroke in TIA patients.[13] Previous study done by Lovett et al reported as 19.2%, 11.9% and 3.4% recurrence rate of stroke in LAA, cardioembolism and lacunar etiology.[14] Ohara et al have reported high risk of recurrent stroke (mostly lacunar) in TIA patients without LAA or AF which may be specific to Asian populations compared to western population.[15] In our study also there is higher recurrence of stroke in lacunar group compared to western data. The low risk of recurrent stroke in large artery atherosclerosis in our population may be explained by geographic variation, early intervention in the form of early revascularization surgery and optimum medical management and lower prevalence of intracranial (32%) than extracranial stenosis.

In our study, 60% of patient who had recurrence of stroke had significant disability (mRS ≥2), whereas 17.8% who do not have recurrence of stroke had bad outcome at 3 months. This is in accordance with the study done by Coutts et al, suggesting that a substantial portion of patients remained disabled after TIA and minor stroke.[12] During these periods only 6 patients received IV thrombolysis, out of which one patient had significant disability (mRS 3), whereas rest of the patient had good outcome (mRS 0 or 1). No patients had symptomatic intracranial hemorrhage.

5.1. Strength of the study

The strength of the study is early inclusion of the patient within 48 h of the index event. Acute stroke patients were selected because these are the patients who are likely evaluated in detail in the stoke care unit. This is one of the largest studies from north India which focuses on

the outcome of early treatment of TIA and minor stroke. Patients were evaluated by stroke neurologist, mimics were excluded from study as far as possible.

5.2. Limitation of the study

It was a retrospective study so chances of bias are high. Moreover, the record for compliance of treatment were not available. Only those patients presented within 48 hours of index event were included in the study, hence patient present late were not studied.

6. Conclusion

Our study showed that urgent treatment after TIA and minor ischemic stroke is associated with reduced risk of ischemic stroke recurrence. They are also having increased risk of both short term and long term cardiovascular events subsequently. Both diabetes mellitus and significant vessel stenosis are independent predictor of stroke recurrence. We have also found that a substantial portion of patient remained disabled at 3 months.

The role of IV thrombolysis in decreasing disability needs to be validated with further study. Patients, who have significant vessel stenosis being at highest risk of disability in view of recurrent event, early intervention will be most beneficial in this group of patients.

7. Source of Funding

8. Conflicts of Interest

There are no conflicts of interest.

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