Original Research Article

Trial of ORG 10172 in acute stroke treatment classification and associated risk factors of ischemic stroke: a prospective study from a tertiary care center in South India

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ABSTRACT

Background: Stroke is the leading cause of acquired disability worldwide. Better understanding of risk factors helps to reduce the community burden of stroke. Aim of the study was to determine pattern of ischemic stroke subtype and associated risk factors.

Methods: Of 220 patients with first ever stroke, 168 patients of ischemic stroke were enrolled prospectively from January 2016 to May 2016 at ESIC Superspeciality hospital, Hyderabad. Patients were categorized in accordance with the Trial of Org 10172 in Acute Stroke treatment (TOAST) criteria.

Results: Of 168 patients, 110 (65.4%) were males; male to female ratio was 1.8:1. The mean age was $53.9 \square 12.3$ years. Small vessel occlusion (SVO) occurred in younger age group as compared to other stroke subtypes. Frequency of large-artery atherosclerosis (LAA) (46.4%) was highest (Extracranial: 41.1%, intracranial: 36.9%), followed by SVO (32.4%), cardio embolism (15.4%), undetermined (4.7%) and other determined causes (1.1%). Risk factors included dyslipidemia (79%), hypertension (67.8%), smoking (58.3%), alcohol use (54.7%), diabetes (40.4%) and physical inactivity (27.3%). Common association observed was smoking (P - 0.004) and alcohol (P - 0.003) with LAA and SVO, and dilated cardiomyopathy with cardio embolism.

Conclusions: LAA was observed frequently than SVO. Frequency of SVO was lower than Asian but higher than western, while cardio embolism was lower than Western and similar to Asian stroke studies. Dyslipidemia was the predominant risk factor than hypertension reported from Asian and Western stroke registry. This unique pattern can be attributed to differences in demographic and risk factor profiles. The study confirms the need for vigorous primary and secondary prevention measures targeting modifiable risk factors of stroke.

Keywords: TOAST subtypes, Risk factors

INTRODUCTION

Stroke is the second leading cause of death and leading cause of adult disability worldwide.[1] Almost two-thirds of the global burden of stroke is borne by those in developing countries.[2] The primary etiology of stroke differs according to race and ethnicity: emboli originating from the heart or extra cranial large arteries are common in Western populations, whereas small-vessel occlusion or intracranial atherosclerosis is more prevalent in Asians.[3] There are limited studies on stroke subtypes in India because most health centers lack facilities for magnetic resonance imaging (MRI) and neck vessel Doppler scan. Often, where the facilities are available, they are unaffordable.[4] Knowledge derived from clinical studies can prevent the burden of stroke by risk factor modification. Hence, the current study was conducted to identify ischemic stroke risk factors and subtypes based on TOAST criteria and to compare with previous similar studies done in India.

TOAST classification was introduced in 1993 to improve the sub classification of ischemic stroke.[5] TOAST classification categorizes patients with ischemic stroke into five subgroups according to the presumed etiological mechanism (Table 1).[5] This classification has been found to be valid and reliable.[6]

Table 1: TOAST Classification 5 of subtypes of acute ischemic stroke.

Subtypes of acute ischemic stroke.
Large-artery atherosclerosis (embolus/thrombosis)*
Small-vessel occlusion (lacune)*
Cardioembolism (high-risk/medium-risk)*
Stroke of other determined etiology*
Stroke of undetermined etiology   a. Two or more causes identified   b. Negative evaluation   c. Incomplete evaluation
TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Possible or probable depending on results of ancillary studies.

METHODS

It was a prospective study which was conducted at ESIC Superspeciality hospital, Hyderabad from January 2016 to May 2016. Total of 220 patients were identified out of which 168 were enrolled who had first ever-ischemic stroke.

Information regarding the relevant variables in the study was collected with the help of structured proforma comprising age, gender, risk factors, clinical features, imaging findings, and pattern of stroke. Modifiable risk factors like hypertension, diabetes mellitus, smoking, alcohol use, coronary artery disease (CAD), and transient ischemic attack were enquired.

All patients underwent hematological and biochemical tests (complete blood count, erythrocyte sedimentation rate, fasting plasma glucose, lipid profile, serum creatinine and screening for human immunodeficiency viruses).

Chest x-ray, electro cardiography, echocardiogram and brain imaging including computed tomography (CT) and magnetic resonance imaging (MRI) with angiographies brain was performed. Additionally a majority of patients underwent neck vessel Doppler scan. Patients were categorized to one of the five major ischemic stroke subtype in accordance to TOAST classification and associated risk factors were evaluated. Study protocol was approved by Institutional ethical committee.

Statistical analysis

The recorded data were statistically analyzed by Statistical package for social science version 17.

Percentages, mean, median, standard deviation, Chi Square, p value and odd's ratio were calculated for study variables. P<0.05 was considered as statistically significant. Multivariate analysis was performed using logistic regression for the risk factors

Stroke

Stroke defined according to WHO criteria as "rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[7]

Young onset stroke

Patients having acquired stroke at less than or equal to 50 years of age.[7,8]

Old onset stroke

Patients having acquired stroke above 50 years of age.[8,9]

Hypertension

Patient taking either antihypertensive drugs or if the blood pressure is >140 mm of Hg systolic and >90 mmHg diastolic in two measurements.[7]

Diabetes mellitus

Patient is already diagnosed as diabetic or has fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l) or 2-hour plasma glucose ≥ 140 mg/dl (7.8 mmol/l) or glycosylated hemoglobin of $\geq 6.5\%$.[10]

Dyslipidemia

Dyslipidemia is defined according to the National Cholesterol Education Program-Adult Treatment Panel III criteria as abnormality in one or more lipid fractions, total cholesterol ≥ 240 mg/dL, or low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL, or High-density lipoprotein cholesterol (HDL-C) <40 mg/dL, and Triglyceride ≥ 200 mg/dL.[11]

Physical inactivity

Physical activity is defined as any bodily movement produced by skeletal muscles that require energy expenditure. Physical inactivity is the lack of physical activity.[12]

Large-artery atherosclerosis

These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or Branch cortical artery, presumably due to atherosclerosis.[5]

Cardio embolism

This category includes patients with arterial occlusions presumably due to an embolus arising in the heart.[5]

Small-artery occlusion (lacunae)

This category includes patients whose strokes are often labeled as lacunar infarcts where CT/MRI examination shows relevant brain stem or sub cortical hemispheric lesion with a diameter of less than 1.5 cm.[5]

Acute stroke of other determined etiology

This category includes patients with rare causes of stroke, such as Non -atherosclerotic vasculopathies, hyper-coagulable states, or hematological disorders.[5]

## Stroke of undetermined etiology

This category includes patients in whom the cause of a stroke cannot be determined with any degree of confidence.[5]

- Two or more causes identified
- Negative evaluation
- Incomplete evaluation.

RESULTS

Demographic characteristics

Of 220 acute stroke patients admitted, 168 (76.3%) were acute ischemic stroke who were enrolled in the study. Age range of study sample was 18-85 years. Mean age was 53.9±12.3 years. Those with age range of 18-50years were considered as young, and 51-85 years as older onset stroke. Ischemic stroke was frequent in older age in all TOAST subtypes except small vessel occlusion (Figure 1). Of the 168 patients 110 (65.4%) were males. The male to female ratio was 1.8: 1.
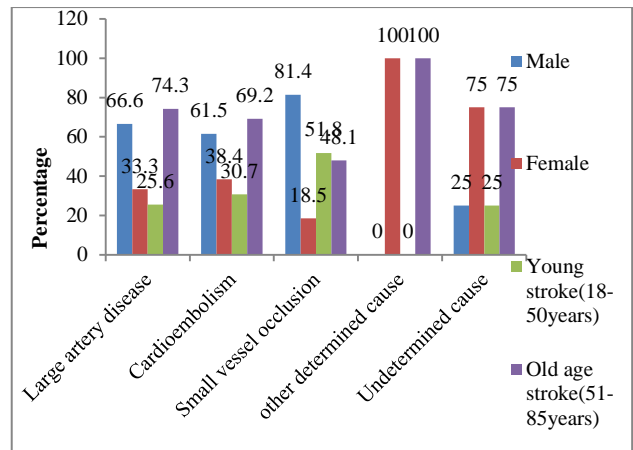
Figure 1: Age and sex distribution of TOAST subtypes.

TOAST classification subtypes

Frequency of LAA (46.4%) was the highest followed by SVO (32.4%), cardio embolism (15.4%), undetermined (4.7%), and other determined causes (1.1%).
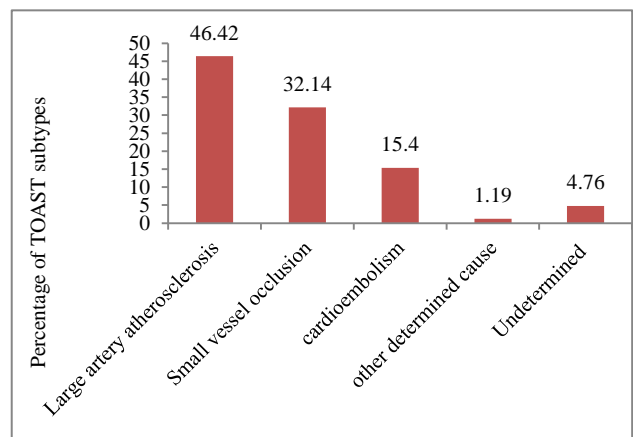
Figure 2: Frequency of stroke subtype.

Table 2: TOAST classification according to gender.

Subtypes	Male(n=110)	Female(n=58)	P value	Odd ratio(95%CI)
Large artery disease	52 (47.2%)	26 (44.8%)	0.76	1.10 (0.58 to 2.08)
Small vessel occlusion	44 (40%)	10 (17.2%)	0.003	3.20 (1.46 to 6.98)
Cardioembolism	16 (14.54%)	10 (17.2%)	0.64	0.81 (0.34 to 1.93)
Other determined causes	0	2 (3.4%)	0.05	0.10 (0.004 to 2.166)
Undetermined cause	2 (1.81%)	6 (10.3%)	0.01	0.16 (0.03 to 0.82)

TOAST classification according to gender

When data were analyzed according to gender, there was significant association between SVO and gender (P value of 0.003 with odds ratio of 3.20). Men were more likely than women to have SVO, LAA and cardio embolism (Table 2).

TOAST classification according to age

Analysis of TOAST subtype according to age group (Young versus old), showed significant association of SVO subtype with younger age (P value of 0.001 with odds ratio 3.01). LAA was frequently observed in older age group, which was statistically significant (P value of 0.02 with odds ratio of 0.47) (Table 3).

Table 3: TOAST subtype according to age group.

| Subtypes	18-50 years (n= 58)	51-85 years (n=110)	P value	Odds ratio (95%CI)
Large artery disease	20 (34.4%)	58 (52.7%)	0.02	0.47 (0.24 to 0.91)
Small vessel disease	28 (48.2%)	26 (23.6%)	0.001	3.01 (1.53 to5.93)
Cardio-embolic	8 (13.7%)	18 (16.3%)	0.66	0.81 (0.33 to 2.01)
Other determined cause	0	2 (1.8%)	0.52	0.37 (0.01to7.85)
Undetermined cause	2 (3.4%)	6 (5.4%)	0.56	0.61 (0.12 to3.16)

Risk factors associated with TOAST subtypes

All patients underwent CT scan and MR angiographies. Additionally neck vessel Doppler scan was conducted in 96.4% patients.
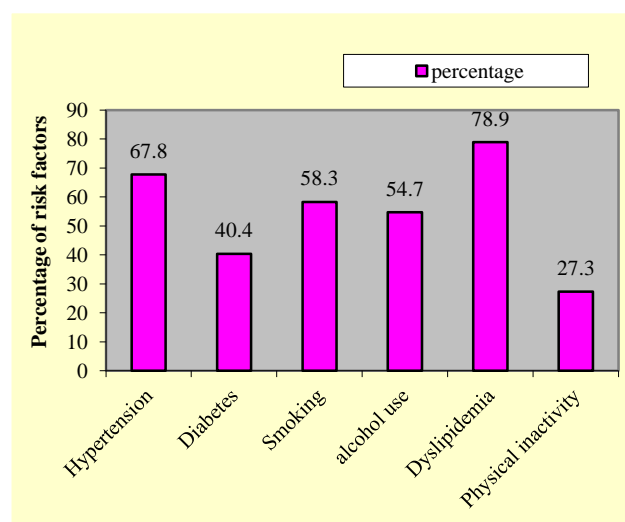
Figure 3: Frequency of risk factors in ischemic stroke.

Lipid test was done in 124 (73.8%). Overall the most frequent risk factor observed was dyslipidemia (78.9%), followed by hypertension in 67.8%, smoking (58.3%), alcohol use (54.7%), diabetes mellitus (40.4%) and physical inactivity in 27.3% (Figure 3).
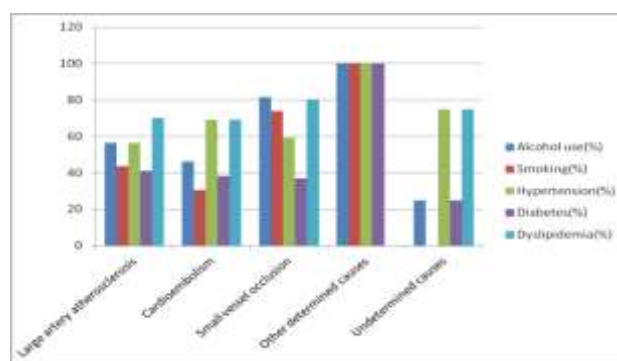
Figure 4: The risk factors in TOAST subtypes.

Dyslipidemia (70%), hypertension (56.4%) and alcohol use (56.4%) was the major risk factor associated with LAA. Alcohol use (81.4%), dyslipidemia (80%), smoking (74.1%) and hypertension (59.2%) were the risk factors associated with SVO.

The most common associations observed were smoking (P value 0.004) and alcohol use (P value 0.003) with LAA and SVO (Table 4), dyslipidemia and hypertension with LAA and SVO.

Table 4: Comparison of risk factors with other stroke subtype.

Risk factors	Cardioembolic stroke (n=26)	Other determined cause (n=2)	Undetermined aetiology (n=8)	P Value
Alcohol use	12 (46.1%)	2 (100%)	2 (25%)	0.15
Smoking	8 (30.7%)	2 (100%)	0	0.01
Hypertension	18 (69.2%)	2 (100%)	6 (75%)	0.63
Diabetes Mellitus	10 (38.4%)	2 (100%)	2 (25%)	0.15
Dyslipidemia	18 (69.2%)	0	6 (75%)	0.11

Of total dyslipidemia cases (78.9%), majority had multiple lipid fraction abnormality (59.6%). Extra cranial atherosclerosis was observed in 41.1% and intracranial atherosclerosis in 36.9% in LAA subtype of ischemic stroke.

Cardio embolism was associated with dilated cardiomyopathy (38.4%) followed by ischemic cardiomyopathy (30%) and rheumatic valvular heart disease (30%). Stroke of undetermined cause was associated with mixed etiology in 7 (87.5%) and negative evaluation in 1 case (Table 4). Dehydration producing border zone infarcts was seen in 2 of the cases of other determined etiology.

Dyslipidemia and hypertension emerged as significant risk factor for ischemic stroke independent of subtype on multivariable analysis using logistic regression.

Small vessel disease

73.8% patients had symmetrical white matter changes (Periventricular or deep white matter) suggestive of small vessel disease irrespective of the TOAST subtype.

Comparison of TOAST classification subtype studies conducted in India

LAA was the major subtype reported from India.[13-16] Pattern of stroke subtype differed in younger and older age in different parts of the country.
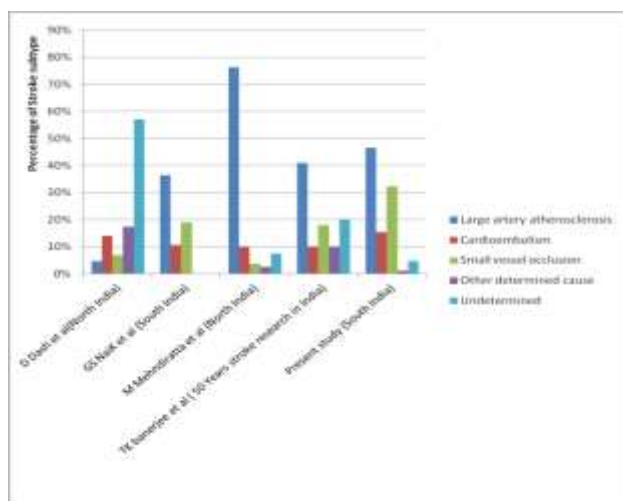
Figure 5: Comparison between TOAST subtypes from different regions of India.

DISCUSSION

Stroke is one of the leading causes of death and disability in India. Accurate classification of ischemic stroke subtype and their risk factor is critical for guiding treatment decisions and prevention. However few studies have focused on the TOAST subtype of ischemic stroke and associated risk factors. The current study is first of its kind, which focuses on low economic status group who are fully benefited by Employees state insurance act.

Recent studies worldwide have reported that average age of patients with stroke in developing countries is usually 15 years younger than developed countries. In the present study mean age was 53.9±12.3 years, indicating prevalence of stroke in older age. Our findings were in concordance with Mumbai, Trivandrum and Bangalore stroke registries.[18-20]

Male sex is considered as an important risk factor for stroke.[21,22] Present study also had male preponderance. This may be attributable to a sociocultural bias in India that men are more likely to seek treatment than women, as they may be the soul-earning member of the family. Secondly men are habituated to smoking and alcohol use in India than women, when compared to western world where both sexes are equally affected.[22,23] LAA was the most common stroke subtype observed and was at higher rate than that reported from India.[13,15] This may be due to availability of MR angiography's and duplex scan in our center. Frequency of LAA (46.4%) was higher than that reported from Asian (China, Japan, Pakistan, and Korea) and Western stroke registries.[24]

SVO was the second frequent subtype observed .We found that majority of SVO subtype belonged to younger age group (odds ratio 3.01) than compared to other TOAST subtypes. This can be attributed to westernization of life style, stress of urbanization and increased prevalence of tobacco use, cigarette smoking and alcohol use in these groups. Our finding differed from that reported in North India where undetermined etiology was the frequent TOAST subtype reported in young.[13] The frequency of SVO (32.4%) was lower than Asian (35-55%) and higher than Western studies (15-22%).

The third subtype of stroke observed was cardio embolism. We found that cardiac risk factors were of higher frequency in women than men. This may be attributed to higher prevalence of rheumatic heart disease and longer life expectancy in females, findings were similar to previous studies.[15,22] Dilated cardiomyopathy was the most common association with cardio embolism observed in present study. Present findings differed from that reported by GS Naik[15] et al where Ischemic heart disease was the major cardiac risk factor. Cardio embolism (15.4% present study) was lower in frequency when compared to Western (25-30%).[24]

This indicates that proportion of stroke subtypes are known to differ from regions of a country to continents. This unique pattern can be attributed to differences in race, ethnicity, socioeconomic status, and risk factor profiles. Literature review showed hypertension as the major risk factor for stroke worldwide.[25,26] We found dyslipidemia as the major risk factor than hypertension for ischemic stroke being present in 79% of the cohort,

higher than reported.[25,26] This is attributed to the life style changes and consumption of fatty foods (Biryani, ice creams, fast foods and meat products) in these region. Plasma lipids and lipoproteins have an influence on the risk of cerebral infarction, but the relationships between dyslipidemia and stroke have not been consistently elucidated.[25]

Dyslipidemia increases atherosclerosis, thrombosis, and stroke. Hence life style changes with consumption of low fat diet should be the most important preventive strategies for stroke. Furthermore presence of atherogenic dyslipidemia as a major risk factor would have attributed to such a large proportion of LAA subtype in present study. Hypertension (67.8%) was the second frequent risk factor for ischemic stroke. Frequency was however similar to west but less than other African countries (82%).[27] Hypertension and dyslipidemia was most commonly associated with LAA and SVO in present study.

Alcohol consumption and smoking were significantly associated with LAA and SVO in present study. Although the increased risk of stroke associated with smoking and alcohol is acknowledged, still prevalence of tobacco and alcohol use has remained largely unchanged.[28] This is attributed to the social background, low educational status and laborious working environment and lack of health education.

The great frequency of dyslipidemia, hypertension, smoking, alcohol consumption and diabetes noted among stroke patients have implications for preventive strategies and organization of health care services to overcome the burden of stroke. Present data highlights that risk factors (modifiable, non-modifiable) are different among TOAST subtypes. Hence thorough evaluation for modifiable risk factors and subtype classification are essential for treatment plan and prevention of recurrence.

CONCLUSION

Pattern of ischemic stroke subtype differed from that reported from Asian and western world. Higher incidence of large artery atherosclerosis (LAA) and small vessel occlusion (SVO) was noted, in our study. Small vessel occlusion was frequent in younger age group, in contrast to the other subtypes. Stroke of other determined cause and undetermined etiology was observed frequently in women than men. Dyslipidemia emerged as major risk factor than hypertension among cases of ischemic stroke. LAA and SVO were significantly associated with alcohol use and smoking. Present study highlights potential role for targeting lipids and hypertension in a subset of Ischemic stroke patients.

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