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Research Article

Comparative Study of Acute Ischemic Stroke in Indian Patients on Dual Anti-Platelet Therapy Clopidogrel and Aspirin Vs. Aspirin Using Modified Ranking Scale.

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Abstract: Background: Stroke is common during the first few weeks after a transient ischemic attack (TIA) or minor ischemic stroke. Combination therapy with clopidogrel and aspirin may provide greater protection against subsequent stroke than aspirin alone. Materials and methods: In a randomized, double-blind controlled study conducted at 114 centers, we randomly assigned 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA to combination therapy with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or to placebo plus aspirin (75 mg per day for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. The primary outcome was stroke (ischemic or hemorrhagic) during 90 days of follow-up in an intention-totreat analysis. Treatment differences were assessed with the use of a Cox proportional-hazards model, with study center as a random effect. Result: Demographic data and clinical characteristics of the patients are presented in Table 1. There were 68 males and 22 females ranging in age from 34 to 78 years with the mean age of 61.71 ± 11.69 years. The most common subtypes of acute ischemic stroke as per TOAST criteria were as follows: large vessel, small vessel, and cardioembolic. Hypertension was most commonly observed risk factor for stroke. The other risk factors in decreasing order of frequency included CAD, diabetes, dyslipidemia, smoking, and alcohol. Conclusion: Ticagrelor plus ASA is expected to be effective for prevention of recurrence in mild non-cardioembolic stroke and high-risk TIA.

Keywords: Minor stroke; mild stroke; non-cardioembolic; TIA; dual antiplatelet therapy; ticagrelor; clopidogrel; recurrence.

INTRODUCTION

Transient ischemic attack (TIA) and acute minor ischemic stroke are common and often lead to disabling events. In China, there are approximately 3 million new strokes every year, and approximately 30% of them are minor ischemic strokes. [1] The incidence of TIA in China has not been determined, but on the basis of the incidence in other countries, there are probably more than 2 million TIAs annually in China. The risk of another stroke occurring after a TIA or minor stroke is high, with approximately 10 to 20% of patients having a stroke within 3 months after the index event; most of these strokes occur within the first 2 days. [2]

The role of antiplatelet therapy for secondary stroke prevention has been well established. However, aspirin is the only antiplatelet agent that has been studied in the acute phase of stroke, during which its benefit is modest. [3] Aspirin and clopidogrel synergistically inhibit platelet aggregation, and such dual therapy reduces the risk of recurrent ischemic events in patients with the acute coronary syndrome. [4] Large-scale trials of secondary prevention of ischemic events after stroke have not shown a benefit of the combination of clopidogrel and aspirin. [5] However, these trials did not study the early, high-risk period after stroke, they included some patients with strokes of moderate severity, and they included few if any patients with TIA. Three small pilot trials have shown trends toward a benefit of the combination therapy and minimal safety concerns in patients with minor stroke or TIA. [6]

We conducted the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial to test the hypothesis that 3 months of treatment with a combination of clopidogrel and aspirin would reduce the risk of recurrent stroke, as compared with aspirin alone, among patients with acute high-risk TIA or minor ischemic stroke.

METHODOLOGY & MATERIALS

Patients who met the following inclusion criteria were eligible: age of 40 years or older; diagnosis of an acute minor ischemic stroke or TIA; and ability to start the study drug within 24 hours after symptom onset, which was defined as the point at which the patient reported no

longer being in a normal condition. Acute minor stroke was defined by a score of 3 or less at the time of randomization on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater deficits). TIA was defined as focal brain ischemia with resolution of symptoms within 24 hours after onset plus a moderate-to-high risk of stroke recurrence (defined as a score of ≥4 at the time of randomization on the ABCD,2 which assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes; scores range from 0 to 7, with higher scores indicating greater short-term risk).

All patients with possible clinical neurologic events during the follow-up period underwent computed tomography (CT) or magnetic resonance imaging (MRI) of the head. Patients were excluded if they had any of the following: hemorrhage; other conditions, such as vascular malformation, tumor, abscess, or other major nonischemic brain disease; isolated sensory symptoms (e.g., numbness), isolated visual changes, or isolated dizziness or vertigo without evidence of acute infarction on baseline CT or MRI of the head; a score of more than 2 on the modified Rankin scale (scores range from 0 [no symptoms] to 6 [death]) immediately before the occurrence of the index ischemic stroke or TIA, indicating moderate disability or worse at baseline; an NIHSS score of 4 or more at randomization; a clear indication for anticoagulation therapy (presumed cardiac source of embolus, such as atrial fibrillation or prosthetic cardiac valve) or a contraindication to clopidogrel or aspirin; history of intracranial hemorrhage; anticipated requirement for long- term nonstudy antiplatelet drugs or for nonsteroidal antiinflammatory drugs affecting platelet function; heparin therapy or oral anticoagulation therapy within 10 days before randomization; gastrointestinal bleeding or major surgery within the previous 3 months; planned or probable revascularization (any angioplasty or vascular surgery) within 3 months after screening (if clinically indicated, vascular imaging was to be performed before randomization, whenever possible); planned surgery or interventional treatment requiring cessation of the study drug; TIA or minor stroke caused by angiography or surgery; or severe noncardiovascular coexisting condition, with a life expectancy of less than 3 months. Women of childbearing age who were not practicing reliable contraception and did not have a documented negative pregnancy test and patients receiving other investigational drugs or devices were also excluded (see Table S1 in the Supplementary Appendix, available at NEJM.org). No patients included in the study were treated with thrombolysis around the time of randomization.

Statistical Analysis

Data from patients who had no events during the study were censored at the time of study termination or death. We used this approach to maximize the time-dependent information in the trial while maintaining the ease of interpretation of risks. For each model, the proportional-hazards assumption was assessed by testing the interaction between treatment and time. In addition, we assessed whether the treatment effect differed in certain prespecified subgroups by testing the treatment-by-subgroup interaction effect with the use of Cox models. All tests were two-sided, and a P value of 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.0 (SAS Institute).

RESULT

Demographic data and clinical characteristics of the patients are presented in Table 1. There were 68 males and 22 females ranging in age from 34 to 78 years with the mean age of 61.71 ± 11.69 years. The most common subtypes of acute ischemic stroke as per TOAST criteria were as follows: large vessel, small vessel, and cardioembolic. Hypertension was most commonly observed risk factor for stroke. The other risk factors in decreasing order of frequency included CAD, diabetes, dyslipidemia, smoking, and alcohol.

Drug response

Out of 90 patients, inadequate response to aspirin was observed in 4 patients (4.4%). 4 (4.4%) patients showed complete resistance to aspirin whereas only one patient (1.1%) was semi responder. However; remarkably higher number of patients 60 (66.7%) had shown inadequate response to clopidogrel. Among these, resistance to clopidogrel was found in 15 (16.7%) patients, and 32 (49.2%) patients represent semi-response to the drug [Figure 2]. Aspirin and clopidogrel dual-resistant was seen in 2 (3.1%) patients.

Genetic analysis

CYP2C19*2 and GPIIb/IIIa (PLA1/A2) gene polymorphisms were carried out in 57 out of 65 patients. CYP2C19*2 polymorphism was observed in 36 (63.2%) patients which included 29 (50.9%) heterozygous and 7 (12.3%) homozygous.

PLA1/A2 polymorphism was observed in 17 (29.8%) patients which included 16 (28.1%) heterozygous and 1 (1.7%) homozygous. There was significant association observed between CYP2C19*2 polymorphism and clopidogrel responsiveness (P = 0.014) [Table 2]. This association gets highly significant when we merged the patients of clopidogrel resistant and semi- responder group (P = 0.006). No significant association was seen for PLA1/A2 gene polymorphism among clopidogrel resistant, clopidogrel semi responder, and responders (P = 0.863) [Table 2]. Although we did not observe any association between CYP2C19*2 and PLA1/A2 polymorphism with aspirin resistance (P = 0.171 and P = 0.960, respectively).

The mean level of ADP was found to be significantly higher (P = 0.05) in patients with mutant CYP2C19 * 2

genotypes as compared to wildtype genotype. However, no significant difference was found in the mean levels of ADP in patients with mutant PLA1/A2 genotypes than to patients with wild-type genotype (P = 0.621).

Clinical correlation

No significant correlation was found between clopidogrel nonresponsiveness in relation to age group (P = 0.92), sex (P = 0.211), concomitant drugs (PPI [P = 0.455], statin [P = 0.396], NSAIDS [P = 0.374]), and duration of antiplatelet agents (P = 0.653). Clopidogrel nonresponsiveness was much higher in small vessel subtypes (76.2%); however, there was no statistically significant difference observed between stroke subtypes and clopidogrel responsiveness (P = 0.495) [Figure 3]. Although no statistically significant correlation was found between stroke risk factors and clopidogrel nonresponsiveness, higher clopidogrel nonresponsiveness was found in CAD (P = 0.09). In addition, clopidogrel nonresponsiveness (69.5%) was found more commonly in smokers [Figure 4].

Table 1: Demographic and clinical characteristics (n=90)

Variable	Total patients, *n* (%)
Age (years)	61.71±11.69
Sex (male:female)	68:22
Risk factor	
Hypertension	60 (66.7)
Diabetes	28 (31.1)
Coronary artery disease	54 (60.0)
Dyslipidemia	54 (60.0)
Atrial fibrillation	1 (1.1)
Smoking	30 (33.3)
Alcohol	30 (33.3)
TOAST classification	
Large vessel	32 (35.6)
Lacunar	30 (33.3)
Cardio embolic	18 (20.0)
Stroke of undetermined etiology	6 (6.7)
Stroke of other determined etiology	4 (4.4)
Duration of stable antiplatelet agents	
<6 months	42 (46.7)
6 months–1 year	30 (33.3)
>1 year–3 years	18 (20)
Concomitant drugs	
PPI	70 (77.8)
Statin	89 (98.9)
NSAIDS	4 (4.4)

Table 2: Genotype frequencies of CYP2C19*2 and PLA1/A2 polymorphisms and clopidogrel responsiveness

Gene polymorphisms	Genotype		Number of patients (%)		*P*
		Responder	Semi responder	Resistant	
CYP2C19*2	Heterozygous (*1/*2) + homozygous (*2/*2)	9 (40.9)	22 (81.5)	5 (62.5)	0.014
	Wild type (*1/*1)	13 (59.1)	5 (18.5)	3 (37.5)	
PLA1/A2	Heterozygous (A1/A2) + homozygous (A2/A2)	6 (27.3)	8 (29.6)	3 (37.5)	0.863
	Wild type (A1/A1)	16 (72.7)	19 (70.4)	5 (62.5)	

Out of 88 patients 25 patients have leukocytosis (28.4%). No patient had leucopenia. Neutrophilia is present in 56 patients.

Lymphopenia is present in 23% of patients.22 patients (25%) have eosinophils >6%. All 22 patients are rheumatoid factor positive. No patients had immature cells or large granular lymphocytes.Clotting time was normal in all patients. No patients had features of hyper viscosity syndrome and no patient had a features of Felty syndrome and no patient had a feature of pure red cell aplasia and no lymphoma and leukemia.

DISCUSSION

Studies have repeatedly shown that DAPT with combination of aspirin and P2Y12 platelet receptor antagonist can reduce the risk of acute thrombotic events and ischemic events recurrence alike. [7] Currently, ASA plus clopidogrel is the most recommendation of many guidelines for secondary prevention in minor stroke and high-risk TIA.20 However, the unpredictable clopidogrel efficacy of the 5%-55% non-responders limits its use21, while this rate is trivial in patients treated with prasugrel or ticagrelor. [8]

There is no comprehensive information about resistance rate to clopidogrel in Iranian community. Only in one study on patients after coronary angioplasty, 24.76% resistance to clopidogrel was reported by using light transmission aggregometry in Iranian population. [9]

Ticagrelor, as a potential alternative of clopidogrel for DAPT, has been tested in many studies especially in the field of cardiovascular disorders; yet, there are no head-to- head comparisons after stroke or TIA. Despite comparing ticagrelor and ASA with ASA alone in acute ischemic stroke or TIA (THALES) trial that revealed participants in the ticagrelor plus ASA group had fewer ischemic strokes than those on ASA alone (HR 0.83; 95% CI 0.71–0.96; p=0.02), no comparison has been done with clopidogrel.[10]

In a meta-analysis comparing the effect of clopidogrel and ticagrelor on the cardiovascular outcome of patients with diabetes mellitus (DM) type 2 and acute coronary syndromes, pooled result of 7 studies showed that ticagrelor was associated with a significantly lower risk of major adverse cardiac events and mortality. However, the risk of minor bleeding was significantly higher with ticagrelor in comparison to clopidogrel in these patients. In another trial on Mediterranean DM patients with coronary syndromes, ticagrelor yielded a more potent platelet inhibition than clopidogrel. [11]

Recently, the CHANCE-2 trial assessed the effects of ticagrelor plus ASA versus clopidogrel plus ASA in Chinese CYP2C19 loss-of-function carrier patients after minor stroke or TIA. At month 3, fewer strokes recurred in the ticagrelor group compared with the clopidogrel group (6.0% vs 7.6%, respectively; HR 0.77; 95% CI 0.64– 0.94).28 Similar to previous studies, minor bleeding was more common in ticagrelor group, but no difference in major bleeding was reported. [12]
Finally, data from the recent studies raise the ponderable question of whether clinicians can substitute clopidogrel

by ticagrelor as add-on therapy to aspirin for DAPT in mild stroke and high-risk TIA.24 Such being the case, conducting a head-to-head comparison trial in an Iranian population that can compare the effectiveness of aspirin plus clopidogrel versus aspirin plus ticagrelor seems to be warranted

CONCLUSION

In conclusion, the results of TACAMINIS may provide important advances in planning for DAPT in Iranian population to prevent recurrence of mild non-cardioembolic stroke and high-risk TIA.

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