Safety and efficacy of antiplatelets in the treatment of acute ischemic stroke: a randomized double-blind controlled trial

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Context
The crude prevalence of stroke is high in Assiut. Most patients arrived beyond the approved time for reperfusion therapy due to a lack of health facilitation and instead received antiplatelet therapy. There is controversy about the safety and efficacy of single or dual antiplatelet therapy in the treatment of acute ischemic stroke (AIS).

Aims
Evaluation of the safety and efficacy of aspirin and clopidogrel either as a monotherapy or combined therapy in patients presenting with AIS within 24 h of symptom onset.

Settings and design
A randomized double-blind controlled trial involving patients with AIS within 24 h of symptom onset and are not eligible for any revascularization therapy.

Patients and methods
Random allocation of 315 patients into three groups with a ratio of 1:1:1 to be administered either combined aspirin and clopidogrel or aspirin plus placebo or placebo plus clopidogrel.

Statistical analysis used
SPSS, version 20, was used for the management and analysis of data, χ^2 test, and analysis of variance test.

Results
Stroke recurrence was insignificantly ($P = 0.40$) higher in the aspirin group (11.5%) in comparison to the clopidogrel group (6.7%) and combined group (3.8%) but a significant ($P = 0.01$) higher intracranial hemorrhage risk was noticed in patients who received combined therapy (2.9%).

Conclusion
Patients with AIS who administered combined therapy had an insignificant low risk of recurrent ischemic stroke but had a highly significant risk of severe hemorrhage than patients who administered clopidogrel or aspirin alone.

Keywords:
aspirin, clopidogrel, hemorrhage, ischemic stroke

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Introduction

Stroke was considered as a second leading cause of disability-adjusted life-years in 2019 [1].

Eighty percent of strokes occur in developing countries [2]. In Upper Egypt, the stroke incidence is 2·5/1000 with a prevalence of 5·6/1000 [3]. In Assiut crude prevalence of stroke is high [4]. Studies have reported a 1.1–15% recurrence rate within 30 days after stroke [5] and have been increased up to 17% after a TIA [6]. Patients having rapidly resolving deficits are not considered for thrombolytic treatment, although one-third of them are at high risk for recurrent vascular events [7]. Initiation of antiplatelet agents early in acute ischemic stroke (AIS) patients is significant to prevent stroke recurrence [8]. Intravenous thrombolytic therapy is considered the main medical treatment for AIS [9]; however, the rate of administration of it is still low [10].

There is controversy about the safety and efficacy of single or dual antiplatelet therapy in the treatment of AIS. The CHANCE trial resulted in that both aspirin and clopidogrel are better than aspirin alone for decreasing stroke risk within the first 90 days and does not increase the hemorrhagic risk [11]. The POINT study concluded that both aspirin and clopidogrel were associated with a lower risk of major ischemic events risk and a higher major hemorrhage risk within 90 days than those who were given only aspirin [12].

A meta-analysis of more than 15 clinical trials, which were randomly conducted concluded that combined therapy of any antiplatelet combination with aspirin was

statistically significant in decreasing stroke recurrence although not statistically significant (P = 0.25) in increasing bleeding risk, and combined clopidogrel and aspirin was the best couple therapy for the prevention of stroke recurrence but had the highest bleeding risk [13]. The present study aims to estimate the safety and efficacy of clopidogrel and aspirin either as a monotherapy or combined therapy in the treatment of patients with AIS within 24 h of symptom onset.

Patients and methods

The present study was a prospective, randomized, double-blind, placebo-controlled registered trial on ClinicalTrial.gov with the identified number (NCT03266731) conducted from January 2019 to December 2020 in the Neurology Unit in the hospital of Assiut University. All patients or relatives provided informed consent and The Assiut University Medical Ethics Review Board approved the study. The Assiut University Medical Ethics Review Board approved the study. The sample size was calculated using the G power program, to detect the difference between groups under study based on recurrent stroke in 90-day follow-up duration, 12% in the aspirin group, and supposed 3% in the dual use of aspirin and clopidogrel. A total of 105 patients will be needed to be recruited in each group. Another group will be added to the 105 study participants to evaluate the effect of isolated use of clopidogrel. Patients will be allocated randomly into one of the three groups randomly based on a serial number of patients into one of the three groups using the SPSS program. We recruited patients who presented with mild to severe acute stroke where mild stroke was defined to have a score between 1 and 4, moderate stroke was between 5 and 15, moderate to severe stroke was between 16 and 21, and severe stroke was more than 21 according to the National Institutes of Health Stroke Scale (NIHSS) within 24 h of the onset of symptoms. We included patients aged 40 years or older not eligible for thrombolytic therapy presented with clinical symptoms of acute stroke within 24 h before starting any treatment. We exclude patients with any history of systemic blood diseases, patients presented with failed medical or surgical thrombectomy, patients with a history of allergy to clopidogrel or aspirin or both of them, patients with platelet counts of less than 100 000/mm3, and patients with blood glucose lower than 50 mg/dl or greater to exclude hypoglycemia-induced focal neurological deficit. This study allocated randomly 315 patients into three groups with a ratio of 1:1:1 to be administered either combined aspirin and clopidogrel or aspirin plus placebo or placebo plus clopidogrel based on a serial number of patients using the SPSS program. Placebo tablet plus aspirin or clopidogrel and both aspirin and clopidogrel were packed and labeled as 1, 2, and 3 by a pharmacist. Neither the patient nor the clinician knew the preparation type. The clinician was giving drugs according to the order of enrollment of patients and used 1, 2, or 3 according to the card. Patients allocated randomly to the clopidogrel–aspirin group were prescribed 75 mg of clopidogrel and 75 mg of aspirin and two placebo tabs per day on day 1 and then clopidogrel and aspirin at a dose of 75 mg on day 2 through 90 days. Patients randomly assigned to the aspirin group received a loading dose of aspirin of 300 mg on day 1 and then a placebo tab and aspirin at a dose of 75 mg per day on day 2 through 90 days. Patients randomly assigned to the clopidogrel group received a loading dose of clopidogrel of 300 mg on day 1, then a placebo tablet and clopidogrel at a dose of 75 mg on day 2 through 90 days.

Outcome measures

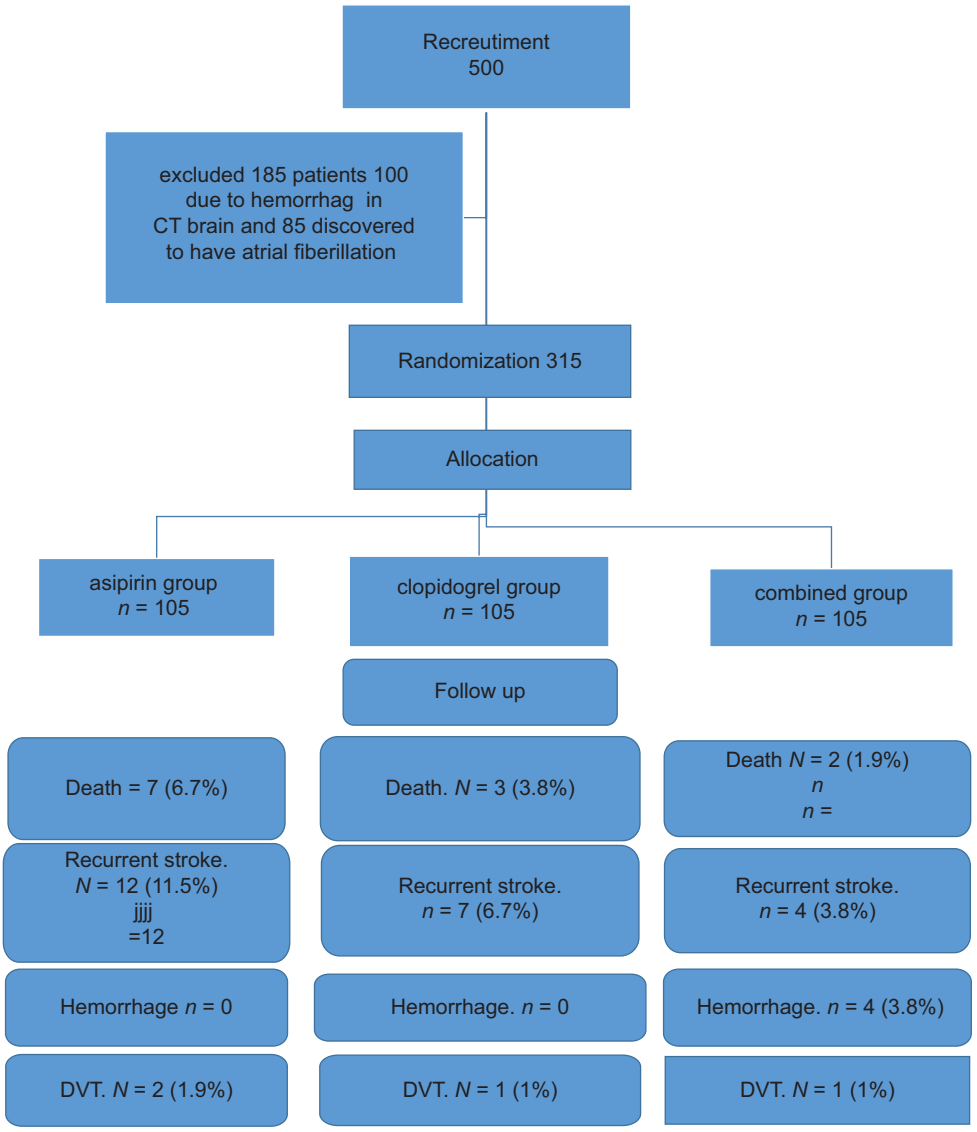
Reduction of the risk of ischemic vascular death and recurrent ischemic stroke within 90 days of follow-up, which was defined as a two-point increase on the NIHSS, and evidence of new brain infarction in computed tomography brain was the primary efficacy outcome. Reducing the hemorrhage risk according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries definition was the primary outcome of safety [14]. Intracranial hemorrhage evidenced by computed tomography brain or other hemorrhage making patients hemodynamically unstable in need of blood or fluid replacement, inotropic support, or surgical intervention was defined as severe hemorrhage; hemorrhage that needs a blood transfusion but did not make the patient hemodynamically unstable. The secondary outcome was to decrease the risk of other new events such as pulmonary embolism, myocardial infarction, and deep vein thrombosis, which were identified clinically by chest pain, dyspnea, desaturation, tachycardia, tachypnea redness, hotness, swelling, and investigated by ECG, ECHO, computed tomography chest, and venous duplex, respectively (Fig. 1).

Results

Baseline data of enrolled patients (n = 315)

The three studied groups showed no significant differences as regards baseline laboratory data (P > 0.05). It was noticed that most of the cases were males and came from rural areas. Hypertension was present in 64 (61%), 62 (59%), and 66 (62.9%) patients of aspirin, clopidogrel, and combined group, respectively, while diabetes mellitus was present in

Figure 1



Flowchart of the study participant's randomization and follow-up. This figure demonstrates that there was recruitment of 500 patients with the exclusion of 185 patients, 100 patients due to hemorrhage in CT brain and 85 patients discovered to have atrial fibrillation and allocated into three groups and their follow-up. CT, computed tomography.

32 (30.5%), 40 (38.1%), and 33 (31.4%) patients of these groups, respectively. Data are shown in Fig. 2.

Data was expressed as frequency (percentage) and mean (SD). *P* value was significant if less than 0.05. Nominal data was compared with χ^2 test, while analysis of variance test compared continuous data.

Presentation among enrolled patients (*n* = 315)

Nearly all patients presented with hemiplegia/hemiparesis in the different groups. Other presentations were disturbed conscious level, dysarthria, and aphasia as shown in Fig. 3. The different groups showed no significant differences as regards presentation ($P > 0.05$).

Data was expressed as frequency (percentage). *P* value was significant if less than 0.05. DCL, disturbed conscious level.

Data compared with χ^2 test.

Grades of stroke of enrolled patients

It was noticed that most of the enrolled patients were of moderate stroke with no significant differences between different groups as shown in Table 1.

Comparison between the three groups regarding efficacy and safety among enrolled patients

The stroke recurrence frequency was insignificantly higher among patients, who received aspirin (10.5%) in comparison to the clopidogrel group (6.7%) and combined therapy (6.7%). Hemorrhage was noticed only in four patients and all of them received combined therapy. Two patients in the aspirin group and one patient in each other group developed deep vein thrombosis (Table 2).

Table 1 Stroke grades according to National Institutes of Health Stroke Scale among enrolled patients

	Aspirin (*n*=105)	Clopidogrel (*n*=105)	Combined (*n*=105)	*P*
Grade of stroke				
Minor stroke	7 (6.7)	6 (5.7)	14 (13.3)	0.38
Moderate stroke	82 (78.1)	84 (80)	75 (71.4)	
Moderate to severe stroke	11 (10.5)	13 (12.4)	13 (12.4)	
Severe stroke	5 (4.8)	2 (1.9)	3 (2.9)	

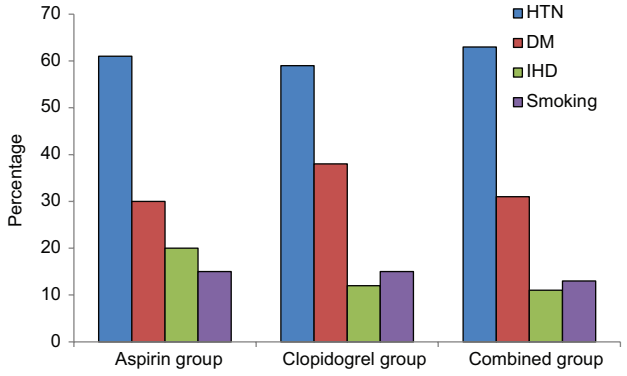
Data expressed as *n* (%). National Institute of Health Stroke Scale data compared with χ^2 test. *P*<0.05.

Table 2 Comparison between the three groups regarding efficacy and safety among enrolled patients

	Aspirin (*n*=105)	Clopidogrel (*n*=105)	Combined (*n*=105)	*P*
Vascular death	7 (6.7)	3 (2.9)	2 (1.9)	0.22
Recurrent stroke	12 (11.5)	7 (6.7)	4 (3.8)	0.10
Hemorrhage	0	0	4 (3.8)	0.01
Deep venous thrombus	2 (1.9)	1 (1)	1 (1)	0.67
NIHSS*				
Baseline	11±5.58	10.26±4.58	9.97±5.39	0.33
After 3 months	7.70±4.37	9.08±5.73	6.91±4.72	0.30

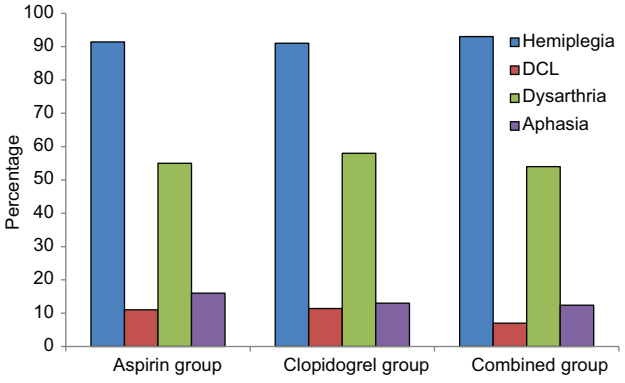
Data expressed as *n* (%). NIHSS, National Institutes of Health Stroke Scale. Data compared with χ^2 test. *Data compared with analysis of variance test. *P*<0.05.

Figure 2



Frequency of risk factors among the enrolled groups. This figure demonstrates that hypertension was present in 64 (61%), 62 (59%), and 66 (62.9%) patients of aspirin, clopidogrel, and combined group, respectively, while diabetes mellitus was present in 32 (30.5%), 40 (38.1%), and 33 (31.4%) patients of these groups, respectively.

Figure 3



Presentations among enrolled groups. This figure demonstrates that nearly all patients presented with hemiplegia/hemiparesis in the different groups. Other presentations as disturbed conscious level, dysarthria, and aphasia.

Statistical analysis

SPSS (Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA) was used in collecting and analyzing the data. Nominal data were expressed in the form of frequency (percentage), while continuous data were expressed in the form of mean ± SD.

χ^2 test was used to compare the nominal data of different groups in the study, while analysis of variance test was used for the comparison of different means of the studied groups followed by *post-hoc* analysis. The level of confidence was kept at 95% and hence, the *P* value was considered significant if less than 0.05.

Discussion

In this study, 65.4% of the total number of enrolled patients are male and 34.4% are females. This may be due to factors such as smoking and stress, which are higher among males and the lack of the vascular protective role of endogenous estrogens in males. In agreement with our study was the study by Appears *et al.* [15], which concluded that male stroke incidence rate was 33% higher and stroke prevalence was 41% higher. The mean age of stroke in our study was 62 years old in the same line with our study was [3]. In this study, 61.9% of enrolled patients belonged to rural residences and 38.1% belonged to urban residences. This may be attributed to factors related to the environment as a stressor (more hypertension) and less well-established health systems and a high rate of illiteracy. Contrary to our study is the study by Khedr *et al.* [4], which concluded that the rural and urban difference in the prevalence rate areas was insignificant and this may be attributed to different sample sizes and methods. In line with this study is the CAN HEART stroke study in the province of Ontario, Canada [16], which concluded

that there was an increased rate of stroke among rural inhabitants and all-cause mortality in both primary and secondary prevention cohorts. In our study, the more common risk factors of stroke were hypertension and diabetes mellitus in agreement with the study of [4]. In our study, the most common presentations are hemiparesis/hemiplegia and dysarthria, which agree with the study of Nor *et al*. [17], which concluded that side weakness and speech disturbance are the most common presentation of stroke. Contrary to that was the study by Fekadu *et al*. [18], where headache, aphasia, and hemiparesis were the most common registered presentation, which may be attributed to the study being prospective with face to face interviews in which most patients complained of headache despite the variable degrees of severity due to the nature of the disease and may be due to recordation of hemiplegia separately not as one category. Most of the enrolled patients were of moderate ischemic stroke with a mean NIHSS of 10. It was noticed that the NIHSS showed no significant differences between different groups but in each separate, it showed a significant improvement after 3 months with a mean NIHSS of 7. This study found that patients with mild-to-severe ischemic stroke who received a dual therapy of aspirin and clopidogrel had a nonsignificant and lower risk of major ischemic events (P = 0.40) but significant higher risk of intracranial hemorrhage (P = 0.01) than those receiving clopidogrel or aspirin alone, where the frequency of recurrent stroke was insignificantly higher among patients who received aspirin (11.5%) in comparison to the clopidogrel group (6.7%) and combined therapy (3.8%) (P = 0.10). Severe hemorrhage was noticed only in four patients and all of them received combined therapy (2.9%) (P = 0.01). Two patients in the aspirin group and one patient in each other group developed deep vein thrombosis as confirmed by venous duplex, in line with the study of POINT trial [12], where there was a significant increase in the risk of hemorrhage in patients receiving combined clopidogrel and aspirin compared with aspirin alone. Major hemorrhage occurred in 0.9% receiving combined clopidogrel and aspirin and in 0.4% receiving aspirin plus placebo (P = 0.02). CHANCE trial [11] disagrees with the current study regarding the increased risk of intracranial hemorrhage with combination therapy, which may be due to the difference in patients and methods that were used in our study (dual therapy for the first 21 days), followed by only clopidogrel with a starting loading dose of 300 mg, as compared with 75 mg of clopidogrel plus 75 mg of aspirin per day through the 90-day duration . in addition to olymorphisms of the encoding gene that encode for, CYP2C19 that is responsible for the metabolism of clopidogrel into its active form are incomplete are common in Asia. Also as most of the patients in this study were of moderate stroke which may be a cause of the increased risk of intracranial hemorrhage. In agreement with our study, the study by Diener *et al*. [19] found insignificant reduction in major ischemic events, which occur in 15.7% of patients receiving aspirin and clopidogrel compared with 16.7% in the clopidogrel-alone group (P = 0.244). Life-threatening hemorrhage was higher in the group combined aspirin and clopidogrel in comparison to clopidogrel alone (P = 0.0001). Our study concluded that patients with acute, mild, or severe ischemic stroke, who were given both clopidogrel and aspirin had a higher significant risk of severe hemorrhage and insignificant lower risk of recurrent ischemic stroke or vascular deaths than patients, who were given aspirin or clopidogrel alone during the 90-day study period. So aspirin or clopidogrel alone is preferred than both of them in a patient with moderate ischemic stroke.

The strength of our study involves that it was a double-blind, randomized, clinical trial with neither allocated patient nor the clinician being aware of the group assignment. Also, this study enrolled patients with AIS of different grades.

The limitations of our study include the small sample size, exclusion of patients with cardioembolic strokes, and majority of the allocated patients had moderate and moderate to severe stroke, which generalized the results to all grades of stroke difficult. So, we hope that future studies include a large number of patients to confirm the results and to be generalized.

Conclusion

Patients with AIS who administered combined therapy had an insignificant lower risk of recurrent ischemic stroke, myocardial infarction, or death from vascular ischemic causes, but had a significantly higher risk of severe hemorrhage than patients who administered aspirin or clopidogrel only.

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Conflicts of interest

None declared.

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