



## Original Article

# ANTIPLATELET IN CEREBROVASCULAR ACCIDENT(CVA)

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### ABSTRACT

**Objective:** To determine the efficacy and safety of Aspirin alone and of combined Aspirin and Clopidogrel in treatment of acute Ischemic CVA. **Method:** A hospital based randomized controlled trial conducted at Abbasi Shaheed Hospital, Karachi from March 2013 to August 2013. Patients with Ischemic stroke > 12 hours not known to have past ischemic symptoms with confirmation of ischemia on Head CT or MRI Brain were included. Patients with hemorrhage or other pathology such as vascular malformation, tumor, abscess, and patients with known hypersensitivity to aspirin or clopidogrel, patients with recurrent stroke were excluded. **Result:** Among 56 patients with ischemic stroke the mean age of the patients was  $57.50 \pm 13.68$  years. There were more females  $n=35(62.5\%)$  compared to males 21 (37.5%) with sex ratio of 1.6:1. The risk factors like Diabetes was found in  $n= 32 (57.1\%)$ , hypertension in 44 (78.6%), ischemic heart disease  $n=10 (17.9\%)$ , hypercholesterolemia  $n=33 (58.9\%)$ , obesity in  $n=38 (67.9\%)$ . The treatment groups receiving aspirin+ placebo in group 1 and group 2 receiving aspirin + Clopidogrel, the rate of restroke was found in only  $n=3 (5.3\%)$  patients taking aspirin alone. However in group 2 receiving aspirin + Clopidogrel, patients reported gastrointestinal bleeding  $n=2 (3.5\%)$  and intracerebral hemorrhage. The mortality rate was  $n=6 (0,7\%)$ . **Conclusion:** CRP levels are important predictors of myocardial damage and can be used as prognostic marker for acute coronary syndrome.

**Key words:** Ischemic Stroke, Dual antiplatelet

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### INTRODUCTION

Cerebrovascular accident (CVA) is the second most common cause of death worldwide and third leading cause of death in U.S<sup>2</sup>. It is a medical emergency resulting in permanent neurological damage to brain. Overall mortality rate is 30% after 30 days of stroke while one year mortality rate of ischemic

stroke is 77 % according to Framingham and Rochester study. Due to large burden of disease, prevention of the modifiable risk factors may reduce its occurrence; however primary prevention is less effective than secondary prevention<sup>3</sup>. Antiplatelet i-e; Aspirin has role in both primary as well as the secondary prevention of stroke causing reduction in recurrence when aspirin alone was given after 48 hours of stroke<sup>4</sup>.

Clopidogrel another approved antiplatelet drug also has shown efficacy in patients with stroke, myocardial infarction (MI), or peripheral artery disease (PAD). The Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial found Clopidogrel 75 mg/d to be superior to Aspirin 325mg/d with relative risk reduction of 8.7%<sup>5</sup>, however beneficial effect of Clopidogrel was mainly seen in peripheral artery disease (PAD).

The largest clinical trial on secondary prevention of stroke i-e; PROFESS trial found no statistical significant difference between two drugs. Another MATCH & CHARISMA trial compared Clopidogrel, 75 mg/d, with the combination of Aspirin, 325 mg/d and Clopidogrel, 75 mg/d, in patients with stroke, TIA, or other vascular risk factors found no significant difference among two groups; however the risk of bleeding was very much higher among the patients with combined regime (2.6% vs 1.3%)<sup>6j</sup>.

The CHANCE trial<sup>8</sup> conducted a randomized control study on patients with high risk TIA or a minor stroke with one group given monotherapy with Aspirin and other group Aspirin and Clopidogrel. After 3 months of therapy, there was a significant benefit in ischemic stroke with relative risk reduction of 23% and 30% relative risk reduction in stroke, myocardial infarction, and vascular death. But the trial was done on Chinese population, now recently another POINT trial is underway, study being conducted in the United States and Canada.

Due to insufficient data available on its treatment in Pakistani population, our study was aimed to review the effectiveness and safety of antiplatelet therapy in treatment of acute ischemic stroke in our setup.

## SUBJECTS AND METHOD

Present study was a hospital based randomized controlled trial conducted at Department Of ICU in Abbasi Shaheed Hospital Karachi March 2013 to August 2013. The study was approved after ethical committee. All patients were prospectively enrolled. The sample size of 56 patients

of both gender was taken by taking prevalence of ischemic stroke 83% from previous studies. Patients with Ischemic stroke > 12 hours not known to have past ischemic symptoms with confirmation of ischemia on Head CT or MRI Brain were included. Patients with hemorrhage or other pathology, such as vascular malformation, tumor, or abscess, patients with known hypersensitivity to aspirin or clopidogrel, patients with recurrent ischemic stroke were excluded. Informed consent was taken from the patient or the patient's attendant and by researcher. Neither the patient nor the doctor giving treatment knew about assigned groups. Two groups were made n=28 in each group with random selection and equal number of slips were made and at the time of inclusion of patients in the study, patient was able to pick up one slip. Patients of Group A received Aspirin and placebo while patients of Group B / received Aspirin and Clopidogrel. Patients undergone detailed physical and neurological assessment, with particular note being made on consciousness level which was assessed by Glasgow coma score or for any deterioration or any gastrointestinal hemorrhage or for any bleeding from any site. A venous blood was taken for hematological, biochemical test and Computed tomography or MRI Brain was performed. Patients assigned previously as group A and B and were given treatment: Group (A): first loading dose of 300 mg/d then 75mg OD and group (B): Clopidogrel 75 mg/d and Aspirin loading dose of 300mg/d then followed by 75mg/d. Treatment was monitored for the response at one week, four weeks, 12 weeks and 6 months. In cases of any systemic bacterial infection patients or any adverse event like deterioration in consciousness level, seizures, bleeding from any site was recorded specifying the time of onset, the duration, the severity and the relationship to the test medication.

Data was analyzed by statistical software package SPSS version 20.0. Statistical analysis was expressed as frequencies and percentages. Descriptive statistics including patient's age, gender, admission number, history of comorbidities like Diabetes mellitus, Hypertension, Hypercholesterolemia, Ischemic heart disease and Obesity was entered. Differences in drugs between groups were tested with chi-squared test and P < 0.05 was considered significant. Mean +/- SD was calculated for quantitative variables like age of patient, any adverse effects of aspirin or clopidogrel were also entered. Outcome of treatment was also computed and analyzed.

Stratification was done with regards to age, gender, duration of co-morbid conditions, to see effect on the outcome.

## RESULTS

Out of 56 patients with ischemic stroke the mean age of the patients was  $57.50 \pm 13.68$  years (Table 1). There were more females  $n=35(62.5\%)$  compared to males  $21(37.5\%)$  with sex ratio of 1.6:1 (Table 1). The mean age among both males and females was 53.76 years and 59.74 years. The age most commonly affected by stroke was 61-70yrs  $n=21$ , 35-50yrs  $n=16$ , 51-60yrs  $n=14$  cases, and  $n=5$  in 20-35yrs of age has also been reported (Figure 1).

The risk factors like Diabetes as found in  $n=32(57.1\%)$ , hypertension in  $44(78.6\%)$ , ischemic heart disease  $n=10(17.9\%)$ , hypercholesterolemia  $n=33(58.9\%)$ , obesity in  $n=38(67.9\%)$ . The smoking history was found in with current smokers  $n=20(35.7\%)$ , exsmokers in  $n=20(37.5\%)$  and non smokers in  $n=16(28.6\%)$  (Table 1).

The treatment groups receiving aspirin+ placebo in group 1 and group 2 receiving aspirin and clopidogrel has equal number of hypertensive's i-e;  $n=22$  in each group, but statistical nonsignificant value was found (p value-1.000) (Table 2). While diabetes was slightly more common in group 2  $n=17$ ,  $n=13$  in group 1 with statistically non significant value (p value-0.589) (Table-2). The ischemic heart disease was more commonly found in group 1 compared to group 2 i-e;  $n=8$ ,  $n=2$  with hypercholesterolemia was also seen commonly in group 1 i-e;  $n=18$ , compared to group 2 with  $n=15$  but statistically non significant value was found for both ischemic heart disease and hypercholesterolemia (p value 0.036 and 0.415) The obesity was found in  $n=38(67.9\%)$  (Table 2).

The two groups after giving/treatment were followed over the period of six months. The rate of restroke was found in only  $n=3(5.3\%)$  patients (figure 2). The restroke i-e; ischemic infarction was found in patients taking aspirin alone. The patients have also reported gastrointestinal bleeding  $n=2(3.5\%)$  especially hematemesis which was managed after giving antiulcer treatment. Upper gastrointestinal endoscopy was not performed because of functional debilitating condition of elderly patients with stroke. There were two patients presented after three months of treatment with intracerebral hemorrhage. The hemorrhage was seen in patients taking dual antiplatelet therapy i-e; Aspirin and clopidogrel. The mortality rate was  $n=6(10.7\%)$  with mortality seen more in group 1 i-e;  $n=4$  and group 2 i-e;  $n=2$  (figure 2).

## DISCUSSION

Our study is Randomized trial with analysis done on patients with stroke getting treatment for single versus dual antiplatelet therapy. Numerous pooled data and randomized controlled trials have found efficacy of dual antiplatelet therapy in patients with ischemic stroke<sup>9,13</sup>. The data from previous randomized trials has also shown decreased stroke recurrence in patients with dual antiplatelet therapy. A Metanalysis of pooled data has shown short-term aspirin in combination with clopidogrel to be more successful in secondary prevention of stroke with little or no risk intracranial bleed and major hemorrhage<sup>10,12</sup>. There is risk of recurrence of stroke is debatable both for short and in case of long-term<sub>x</sub> treatment but long-term treatment appears to be associated with increased major bleeding events as evident from different studies<sup>12,14</sup>.

In our study the patients recruited mostly belong to elderly age 61-70yrs with increasing incidence seen in females. Studies have also shown an increased incidence of stroke in patients with age greater than 55-60years<sup>14-17</sup>. Durrani et al has found increased incidence of stroke in patients with elderly age group<sup>15</sup>. Increasing incidence with elderly age is due to unhealthy lifestyle, increasing comorbid and immobilization.

Increased morbidity and mortality has been seen in patients with multiple comorbid like Diabetes Mellitus, Hypertension, Hypercholesterolemia and Smoking. In our study too most of the patients have diabetes, hypertension, smoker with hypercholesterolemia and ischemic heart disease in patients presented with ischemic stroke. Different studies have shown increased incidence of stroke in patients with increasing risk factors<sup>18,21</sup>. Abid et al has found 37.1% patients with hypercholesterolemia, 9.6% with Diabetes Mellitus, 10.1% hypertensive's<sup>18</sup>. Zahra et al has found recently diagnosed diabetes with hypertension in 26 (52%), smoking 18 (36%) and hyperlipidemia 14 (28%)<sup>19</sup>.

The increased recurrence rate has been seen in patients with ischemic stroke. Different treatment strategies have shown reduction in stroke recurrence with antiplatelet treatment. Different Trials like CLAIR trial has shown reduction in rate of recurrence of stroke with dual antiplatelet therapy<sup>14</sup>. Zhang et al in his meta-analysis has shown improved short term outcomes in patients with dual antiplatelet treatment<sup>14</sup>.

In our study too, the rate of recurrence was 5.3% seen in patients with single antiplatelet therapy with no cases of recurrence has been reported in patients with

dual antiplatelets. However the, risk of gastrointestinal and intracranial risk of bleeding was increased in patients with dual antiplatelet treatment. In our study there were 3.5 % cases presented with intracranial bleed and 3.5% cases with upper gastrointestinal bleeding in patients with dual antiplatelet treatment. Both the cases of hemorrhage were managed conservatively with mild gastritis seen after upper gastrointestinal endoscopy and minor intracranial bleed with no neurological deficit. However the mortality in our series of patients was 10.7% with more mortality seen in patients with single antiplatelet 7.14% compared to dual antiplatelet treatment 3.5%. The AHA/ ASA guidelines recommends use of dual antiplatelet treatment for patients with minor strokes or TIA presenting within 24 hrs while the long term use has not been associated with decreased recurrence rate rather increased bleeding risk is present<sup>20</sup>.

Therefore we conclude from our study that the recurrence rate is nearly not present in patients with dual antiplatelet therapy. And thus the dual antiplatelet therapy seems to be beneficial for patients with acute stroke but the risk of hemorrhage outweighs benefit but should also be considered for the patients at risk of hemorrhage.

### CONCLUSION

Dual antiplatelet treatment was helpful in prevention of recurrence of stroke over single antiplatelet treatment. Large scale studies are required to decrease debilitating condition and its, associated morbidities.

### AUTHORS INPUT

**LS**, Main Researcher **SN**, Input of Data Collection, **AS**, Research methodology **MS**, Main reviewer and bibliography

**Conflict of Interest:** Author declare non conflict of interest

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