Title: Clinical Efficacy, Safety, and Tolerability of Dual versus Single Antiplatelet Therapy in Acute Ischemic Cerebrovascular Disease with Lacunar Stroke in Indian Patients: One Year Prospective Study with Outcome Assessed at 90 Days

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Abstract

Introduction & Background: Lacunar stroke, comprising 18% of Ischemic stroke, is the second most common subtype of stroke in India. Available data on the effect of dual antiplatelets treatment with aspirin plus clopidogrel vs single antiplatelet therapy with aspirin alone and their doses in Lacunar stroke happens to be very limited.

Aim: The aim of our study was to decipher the efficacy, safety & tolerability of dual versus single antiplatelet therapy in the treatment of patients with recent occurrence of lacunar stroke.

Materials& Methods: It was a prospective, single centre study conducted at the Department of Neurology. Patients with recent occurrence of Lacunar stroke were randomly divided into 4 groups to receive Aspirin 150 mg (Group1), Aspirin 150 mg plus clopidogrel 75 mg (Group 2), aspirin 75mg plus clopidogrel 75 mg (Group 3), and aspirin 75 mg (Group 4) once daily and were closely monitored for 90 days.

Results: 360 patients were recruited and followed for 90 days. Mean age of the patients was 57.8 ±14.1 years. 188 patients (52.2%) were males. Recurrence of Ischemic stroke occurred highest in group 4 (22%) with no recurrence in group 2. Comparisons of recurrence of Ischemic stroke between group 1 and group 4 (95% CI: 2.6829% to 31.73551%) and between group 3 and group 4 (95% CI: 3.9439% to 32.1542%) showed a statistically significant value <0.05. Haemorrhagic events occurred among recipients on dual antiplatelets therapy.

Conclusions: Efficacy wise, Group 2 with 150 mg aspirin plus 75 mg clopidogrel, was found superior to other groups in the prevention of Lacunar stroke. Groups with dual antiplatelet therapy manifested a worrisome thread of bleeding events.

Keywords: Lacunar stroke, Hyderabad, Antiplatelets, Doses.

Introduction:

Ischemic stroke accounts for the major cause of disability and death among adults. Statistics have shown that in every 20 seconds one Indian suffers a brain stroke, and every year it debilitates around 1.54 million Indians. This was reported at the 3-day Fourth Congress of Society of Neuro-Vascular Intervention (SNVICON), held in Mumbai, in June 2019. Small vessel disease or Lacunar stroke is the second common subtype of stroke in India comprising 18% [1] of Ischemic stroke and 20-30% of stroke worldwide [2]. Antiplatelet therapy has been proven to play a crucial role in the secondary prevention of stroke. And significantly, low-dose aspirin is effective in minimizing ischemic events in patients above certain risk threshold [3]. A study on clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) has indicated the efficacy of clopidogrel over aspirin in the ischemic stroke patients [4].

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which administered Dual antiplatelet therapy (DAPT) versus 75 mg aspirin monotherapy within 24 hours of presentation in Chinese patients with minor stroke (NIHSS < 4) or TIA for 3 weeks after the index event, has proved a reduction in stroke recurrence at 90 days (8.2% versus 11.7%, P< .001) without an associated increase in haemorrhagic stroke [5]. However, the adequacy and risks of DAPT have not yet been evaluated specifically for Lacunar stroke though 56% cases in CHANCE trial had Lacunar stroke. The Platelet-Oriented Inhibition in New TIA and the minor ischemic stroke (POINT) trial tested a similar regimen of DAPT against aspirin (50-325mg) monotherapy, but the treatment lasted for an extended period of 3 months rather than 3 weeks [6]. And the POINT study inferred that those who received a combination of clopidogrel and aspirin had a lesser risk of major ischemic events but a higher risk of major haemorrhage at 90 days than those who obtained aspirin alone.

In MATCH trial (Management of Atherothrombosis with Clopidogrel in High-Risk Patients), the combination of clopidogrel and aspirin was compared with clopidogrel alone in patients with recent ischemic stroke or TIA with at least 1 additional vascular risk factor [7]. In their study, more than half of the patients (53%) had been diagnosed with small vessel disease which was the cause of their qualifying event. And the MATCH study concluded that dual antiplatelet therapy in high-risk patients could lead to a non-significant decline in major vascular events coupled with an increased risk of major bleeding. The SPS3 trial (Secondary Prevention of Small Subcortical Strokes) found no benefit in adding clopidogrel to aspirin especially when compared with placebo administered to patients with a recent small vessel lacunar stroke taking aspirin at the time of their index event [8].

Published recent guidelines endorse the use of single antiplatelet without a fixed dose regime for acute ischemic stroke, while dual antiplatelets for 3 weeks is recommended in patients with minor stroke or Transient Ischemic attack (TIA). The available data on the effect of dual antiplatelets treatment with aspirin plus clopidogrel vs single antiplatelet therapy with aspirin alone and their doses in Lacunar stroke among the Indian population is rather inadequate. Accordingly, our study aimed at determining the effectiveness, safety & tolerability of dual versus single antiplatelet therapy in the treatment of patients with recent lacunar stroke, from among the local population.

Materials &Methods:

Study design: This was a prospective, single centre study conducted at the Department of Neurology, at our Institute for a period of 12 months from December 2018 to December 2019. Patients with clinically evident acute cerebral infarction or TIA who had lacunar stroke were enrolled for the study. Lacunar infarctions are defined as small subcortical infarcts with a size less than 15 mm in diameter seen in the deep cerebral white matter, basal ganglia, or pons, presumed to result from the occlusion of a single small perforating artery supplying the subcortical areas of the brain, caused by occlusion of a penetrating artery from a large cerebral artery, most commonly from the Circle of Willis [9].

Participants: During the study period, patients with possible clinical ischemic cerebrovascular events during their period of hospitalization were subjected to computed tomography or magnetic resonance imaging of the head and neck. Diagnosis was made using TOAST criteria for Lacunar stroke [10]. TOAST criteria (1993) consisted of 1) A traditional lacunar syndrome without cortical signs, 2) supporting features such as hypertension and diabetes mellitus, (3) the lack of an infarct explaining deficits on computed tomography (CT) /magnetic resonance imaging (MRI) examination or a subcortical lesion less than 15 mm in diameter, and (4) the absence of features that suggest a high likelihood of cardioembolism or embolism from upstream arterial stenosis being greater than 50%.

Eligibility of a patient was determined by the following inclusive criteria: patients from 18 - 80 years age, diagnosis of an acute cerebral infarction (CI) or TIA and Lacunar infarction confirmed by CT/MRI brain. Exclusion criteria included large-area Cerebral infarction or haemorrhagic infarct, cardiogenic brain embolism, Cortical infarction, current peptic ulceration or history of systemic bleeding, systemic diseases like terminal malignancy or serious renal or liver disease, known contraindication to clopidogrel or aspirin, major surgery or trauma in the past 3 months or planning operation in the near future, gastrointestinal disorders or inability to obtain oral drugs and discontinuation of the study drug before testing. Baseline characteristics like age, sex, smoking history, alcohol use and also vascular risk factors including diabetes mellitus, hyperlipidaemia, hypertension, TIA and coronary heart disease, were assessed at baseline.

Procedure: The patients were randomly categorized into 4 groups; Group 1 was to receive Aspirin 150 mg (A150); Group 2: Aspirin 150 mg plus clopidogrel 75 mg (A150+C75); Group 3: aspirin 75mg plus clopidogrel 75 mg (A75+C75), and Group 4: aspirin 75 mg (A75) once daily and were diligently followed for 90 days. Loading dose of antiplatelets was not given to patients in the study groups. Neurological deficit was measured using NIHSS stroke scale and functional status was assessed using Modified Rankie scale (MRS) at baseline and subsequent follow ups. All the four groups received atorvastatin 80 mg, along with antihypertensive and diabetic medication respectively. All the patients were required to return at 90 days for a consultation with the neurophysician. If not feasible, the follow-up evaluations were done by telephonic contacts with the patient or his/her family doctor or occasionally a caregiver. Patients were instructed to report immediately on detecting an external bleeding tendency or a worsening headache or a deficit or new deficit. Tolerability was decided based on minor

adverse reactions. Data was collected using a proforma consisting of demographic profile, risk factors, details about drugs, clinical profile, and radiological profile, their respective group, endpoints and follow ups (2 weeks, 1month, 2nd & 3rd month). During contacts with the patients, details regarding the occurrence of possible outcome events, changes in trial medication, and adverse events were earnestly recorded.

Endpoints: Our focus was largely on the main end points**.** Endpoints were the recurrence of stroke, cardiovascular death and bleeding events. Efficacy of drug was determined by clinical improvement or any recurrence at follow up. Safety of drug was determined by intracranial and extracranial bleeding tendencies, and tolerability of drug**.**

Statistical analysis: Data obtained in the study were subjected to statistical analysis with SPSS (version 18.0, IBM) and were tabulated in Microsoft software excel sheet. A two-tailed probability value <0.05 was considered significant. All confidence intervals (CI) were set at 95%. All data were shown as the mean ±standard deviation (SD). Differences in baseline factors (sex, age, clinical characteristics, and risk factors) among the groups were compared using 2x2 Fisher's exact test for significance. Multivariate analysis included adjustments for age and sex. Analysis of efficacy and safety data were calculated using 95% CI of difference in proportions**.**

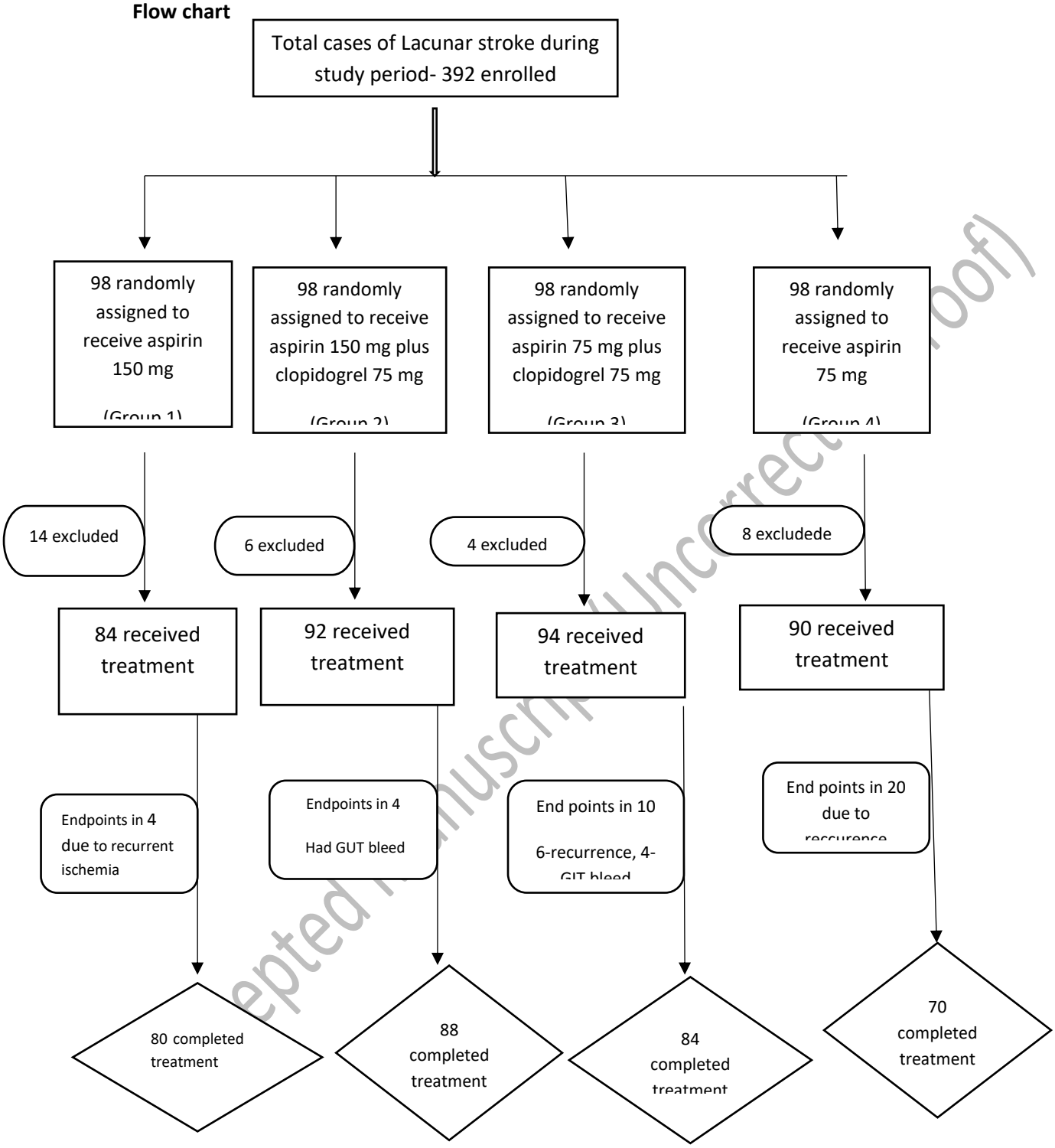
Ethics statement: All the information necessary for the conduct of the study was collected prospectively, with the approval of the Institutional Ethics Committee. Informed consent of either the patients or their relatives was secured prior to their inclusion in the study**.**

Results:

Out of the 392 patients diagnosed with Lacunar stroke, 360 patients were included in the study [figure 1-flow chart] and followed for 90 days. Participants were randomly assigned into 4 groups. 84 patients received aspirin 150 mg (group1: A150) alone, 92 patients received aspirin 150mg plus clopidogrel 75 mg (group2: A150+ C75), 94 patients received aspirin 75mg plus clopidogrel 75mg (group 3: A75+C75), and the remaining 90 patients were treated with aspirin 75mg alone (group4:A75).

Figure 1

Flow chart



Baseline characteristics

Patients' age ranged between 24-80 years and mean age was 57.8 ±14.1 years. 188 patients (52.2%) were males. The most prevalent risk factors among these 4 groups were hypertension

(62.2%), Diabetes mellitus (33.3%), smoking (4.4%), alcohol consumption (11.1%) and tobacco use (7.7%). There were no significant differences among these risk factors nor among individual groups [Table1].

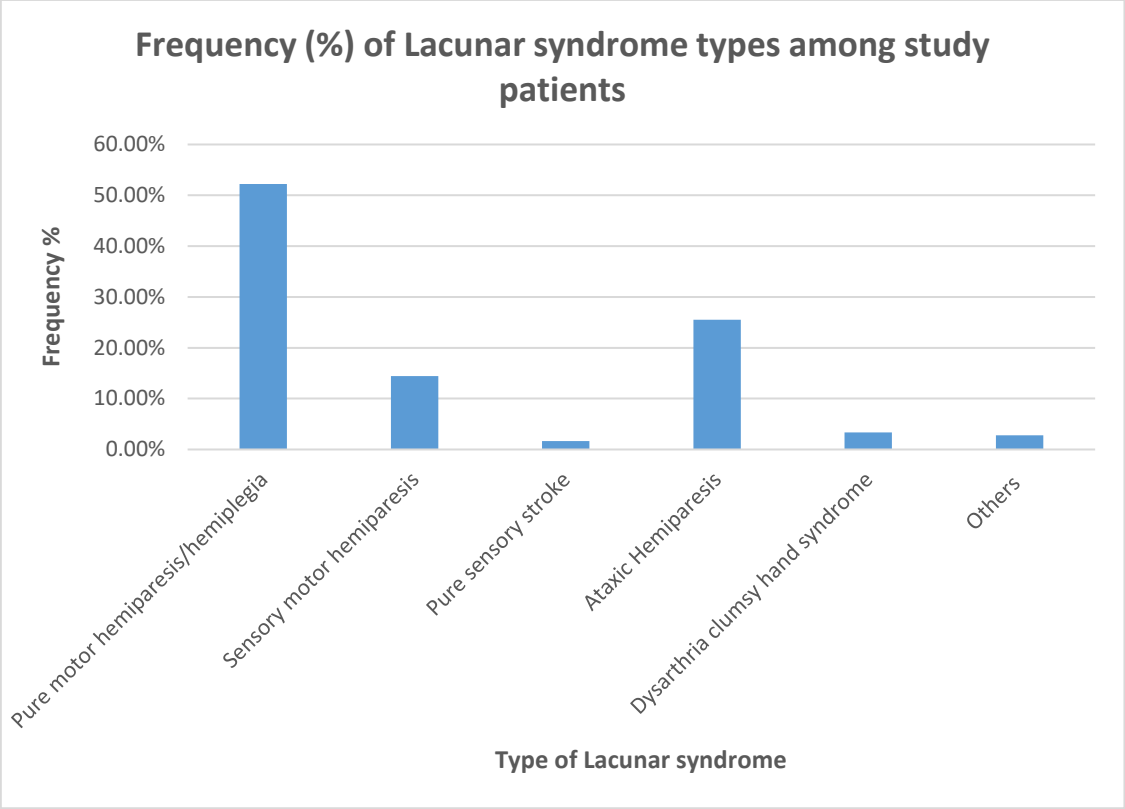
Table 1: Baseline characteristics

	Group 1 (A150) N=84	Group 2 (A150+C75) N=92	Group 3 (A75+C75) N=94	Group 4 (A75) N=90
Median age (Years)	**60**	**60.12**	**60.22**	**60**
Males n (n %)	**44(52.38%)**	**40 (43.47%)**	**50(53.19%)**	**42(46.66)**
Diabetes	**24(28.57%)**	**30(32.60%)**	**32(34.04%)**	**28(31.11%)**
Hypertension	**52(61.90%)**	**50(54.34%)**	**56(59.75%)**	**56(62.22%)**
Smoking	**8(11.90%)**	**12(13.04%)**	**16(17.02%)**	**12(13.33%)**
Alcohol use	**10(11.90%)**	**14(15.21%)**	**10(10.63%)**	**10(11.11%)**
Dyslipidemia	**40(47.62%)**	**46(50%)**	**46(48.93%)**	**42(46.6%)**

Clinical Characteristics

A majority of patients belonged to mild (NIHSS ≤8) to moderate (NIHSS9-15) stroke scale range. There were no significant differences among individual groups. Baseline NIHSS ranged from 2-17, with modified Rankie Scale (mRS) of 1-4 in the groups and mRS at 90 days was 0-1 in all groups. Mean baseline NIHSS was 7.92±4.05 and mRS of 3.18±0.77 among the groups. A majority of the patients had baseline NIHSS of 8 and m RS of 3. And pure motor hemiparesis was the most common type of lacunar syndrome observed, comprising 52.22% followed by ataxic hemiparesis in 25.55% patients [Figure 2].

Figure 2: Lacunar syndrome types among study patients



Efficacy and Safety Endpoints

Among the 360 participants, recurrence of Ischemic stroke occurred in 4 patients(4.7%) who were treated with150 mg aspirin alone, 4 patients (4.2% %) receiving 75 mg aspirin and 75 mg clopidogrel, and a much higher number of 20 patients (22%) in the group administered 75 mg aspirin alone. The 95% confidence interval was 2.6829% to 31.73551% with P value of 0.01 when patients belonging to group 1 (A150) were compared with group 4 (A75). Similarly P value was statistically significant when group 3 (A75mg+ C75) patients were compared with patients in group 4 (A75); 95% confidence interval was 3.9439% to 32.1542%, and P value 0.0114 (Statistically significant). None of the patients on aspirin150 mg plus clopidogrel 75 mg (group 2) developed recurrence of ischemic stroke.

There were haemorrhagic events among 4 recipients on dual antiplatelets therapy (4.3%) in the ecosprin 150 mg plus clopidogrel 75 mg group and 4 patients (4.2%) in the aspirin75mg plus clopidogrel 75 mg group than among the aspirin-alone group [aspirin 150 mg (0%), aspirin 75 mg (0%)]. The major haemorrhages observed were genitourinary tract bleeding among group 2 (aspirin150mg plus clopidogrel 75mg) and gastrointestinal bleeding among group 3 (aspirin 75mg plus clopidogrel 7mg) [Table 2]. No intracranial haemorrhage occurred in any of the 4 groups.

Table 3: Showing efficacy and safety end points of dual versus single antiplatelets drugs

End points	Group 1 (A150) N=84	Group 2 (A150+C75) N= 92	Group 3 (A75+C75) N=94	Group 4 (A75) N=90
EFFICACY				
Death (any cause)	**0**	**0**	**0**	**0**
Death due to cardiac cause	**0**	**0**	**0**	**0**
Recurrence of stroke	**4 (4.7%)**	**0**	**4 (4.2%)**	**20 (22%)**
SAFETY				
ICH	**0**	**0**	**0**	**0**
GIT bleeding	**0**	**0**	**4(4.2%)**	**0**
GUT bleeding	**0**	**4 (4.3%)**	**0**	**0**
Subcutaneous bleed	**0**	**0**	**0**	**0**
Gum/Ear/Nasal bleed	**0**	**0**	**0**	**0**
		GUT bleed onset<2 weeks	**GIT bleed onset>2 months**	

ICH- Intracranial haemorrhage, GIT- Gastrointestinal tract, GUT-Genitourinary tract.

On comparing patients on DAPT (group 2-A150+C75 and group 3-A75+C75) with that of patients with Single antiplatelet therapy (SAPT) that is group 1 (A150) and group 4 (A75), significant difference were noted in terms of efficacy and safety of the antiplatelet regime planned .DAPT was superior in preventing recurrence of Ischemic stroke when compared to SAPT (P value < 0.0001).However bleeding trends were noted in DAPT when compared to SAPT and these differences were significant (P value=0.005) [Table 3]. Average time to recurrence of stroke was shorter in patients who were on aspirin 75 mg (8 days), while those on aspirin 150 mg developed recurrence of stroke in 52 days. Patients in group 3 (A 75+ C75) who were on dual antiplatelets developed recurrence of stroke in average of 59 days. Thus patients on SAPT developed recurrence earlier than those on dual antiplatelets. We could not

establish any relationship between recurrences of stroke attributed to the progression time of lacunar stroke.

Table 4: Calculation of P value and confidence interval on Comparing groups with dual antiplatelet therapy (DAPT) versus groups with single antiplatelet therapy (SAPT)

	DAPT group Group 2 + Group 3	SAPT group Group 1+ group 4	95% CI	P value
Total cases	92 (group2) + 94 (group3) N=186 (51.6%)	84 (group1)+ 90 (group4) N= 174 (48.3%)	-6.9703% to 13.4725%	0.532
Recurrence of Ischemic stroke	0 (group2)+ 4 (group 3) N= 4 (2.15%)	4 (group 1)+ 20 (group 4) N=24 (13.7%)	6.1376% to 17.5920%	< 0.0001
GIT bleeding	0 (group2)+ 4(group3) N= 4 (2.15%)	0 (group1)+ 0 (Group 4) N=0	-0.3767% to 5.3974%	0.052
GUT bleeding	4 (group2)+ 0 (group3) N= 4 (2.15%)	0 (group 1)+ 0 (group4) N=0	-0.3767% to 5.3974%	0.052
Combined GIT and GUT Bleeding	N =8 (4.30%)	N=0	1.2836% to 8.2549%	0.005

Group 2: Aspirin 150mg+ Clopidogrel 75 mg, Group 3: Aspirin 75mg+ Clopidogrel 75 mg, Group1: Aspirin 150 mg alone, Group 4: Aspirin 75mg alone, GIT: Gastrointestinal tract, GUT: Genitourinary tract

Discussion:

It is noteworthy that in Japan, an Asian country, a lower maintenance dose of clopidogrel (50 mg) is widely used for the prevention of vascular events [11], while in the United States and Europe [12] 75mg clopidogrel is utilized. A Chinese study [5, 13] has shown dual antiplatelet as safer in the prevention of Ischemic vascular events. Unfortunately, studies that compare the

efficacy and safety of a combination of aspirin and clopidogrel over aspirin alone, in patients with Lacunar stroke, continue to be meager. Most of the studies conducted in the past were focused on patients with all the subtypes of Ischemic stroke, rather than a single subtype. To the best of our knowledge, there has never been a study from India to ascertain the efficacy and dosage of dual versus single antiplatelets among Indians. Our data proved beyond doubt that a dual therapy with aspirin and clopidogrel over the aspirin alone, is more effective in preventing recurrent vascular events among Indian patients with Lacunar stroke. And between the dual antiplatelet therapies, our study showed that aspirin150 mg plus clopidogrel 75 mg was more efficacious than aspirin 75mg plus clopidogrel 75mg, in preventing recurrent Ischemic stroke. However, the dual therapy led to increased bleeding events when compared with the aspirin alone therapy and the difference was statistically significant. Patients with aspirin 75mg plus clopidogrel 75 mg had lesser bleeding events than those in the aspirin150 mg plus clopidogrel 75mg group, but the disparity was found to be not significant.

It was also seen that a higher dose of aspirin (150 mg) combined with clopidogrel 75 mg had resulted in major genitourinary tract bleeding in many cases while aspirin 75mg plus clopidogrel 75mg led to gastrointestinal tract bleeding events in some. Genitourinary tract bleeding occurred by 2 weeks after initiation of aspirin 150 mg plus clopidogrel 75 mg regime while gastrointestinal bleeding occurred after 2 months of initiation of aspirin 75 mg plus clopidogrel 75 mg regime. These results show that aspirin 75 mg plus clopidogrel 75 mg is safer and can be administered for longer durations when compared to aspirin 150 mg plus clopidogrel 75 mg, among the subset of Indian population. The aggregate of our data also shows that the dual therapy especially aspirin 75mg plus clopidogrel 75 mg, is more effective and safer in the early treatment of patients with Lacunar stroke.

CHANCE trial [5] conducted among Chinese patients, they combined clopidogrel (initial dose 300 mg, followed by 75 mg/d for 90 days) and low-dose aspirin (75 mg/d for the first 3 weeks) was compared with placebo plus aspirin (75 mg/d for 90 days) in 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA.CHANCE trial demonstrated a significant reduction in stroke recurrence at 90 days without a corresponding increase in haemorrhagic stroke [5]. However, the efficacy and risks of DAPT were not evaluated specifically for Lacunar stroke. Similar findings were noted in our study; that aspirin 75mg plus clopidogrel 75 mg was superior to and more appropriate than single antiplatelets (aspirin 150mg or aspirin 75 mg). In the present study, patients were not given the loading dose of clopidogrel or aspirin and haemorrhagic complications developed at 2 months after initiation of DAPT (aspirin 75mg plus clopidogrel 75 mg), indicating better tolerability and safety of the drug when compared to Chinese patients.

SPS3 RCT [8] found no benefit from adding clopidogrel to aspirin compared with placebo in patients (3020 patients) with a recent small vessel lacunar stroke taking aspirin at the time of their index event. In SPS3, aspirin dose was 325 mg and clopidogrel dose was 75 mg. However, the median time from the qualifying event to enrolment in the SPS3 trial was >40 days, and hence, the results might have possibly led to an underestimation of the benefit of the therapy, especially in the early post stroke period [8]. In the present study, we used aspirin 150 mg plus clopidogrel 75 mg as well as aspirin 75 mg plus clopidogrel and found dual antiplatelet therapy

potentially more beneficial when compared to the SPS3 trial. This might probably be due to the aspirin dosage change in SPS3 where aspirin 325 mg itself was sufficient to prevent recurrence in lacunar stroke and the addition of clopidogrel did not benefit. Juxtaposing SPS3 with the present study, it could be inferred that addition of clopidogrel was beneficial in patients with aspirin dose of 150 mg or 75 mg in preventing recurrence of Lacunar stroke. We also found that aspirin alone in either 150 mg or 75mg, was not superior to dual antiplatelets in preventing recurrence of Ischemic event in patients with Lacunar stroke.

Though ours is the first ever prospective study with its primary focus on the dual versus single antiplatelet therapy in lacunar stroke from India and second in the world (SPS3 trial solely focussed on Lacunar stroke), it is not without its own limitations. Firstly, it was a single-center hospital based study design with a small number of patients in each group while large scale sample studies are needed for further confirmation of our findings. Secondly, the findings regarding the efficacy and safety of Aspirin plus Clopidogrel were obtained within a short follow-up period of 90 days, when the patients are still under follow up. Also, the present our study did not use the front-loading method to measure the effect of clopidogrel and aspirin. Nevertheless, our meticulous study brought forth certain valuable evidence-based findings. Our results have proved that the combination regimen of clopidogrel plus aspirin over aspirin alone is most efficacious for secondary stroke prevention in Lacunar stroke. The use of 150mg aspirin plus 75mg clopidogrel was found to be superior to aspirin alone and aspirin 75mg plus clopidogrel 75 mg regime in reducing the incidence of Ischemic stroke for patients with Lacunar stroke, while there was an earlier and a higher rate of occurrence of haemorrhage in the Aspirin 150 mg plus clopidogrel 75 mg group. And the study could decisively conclude that the 75 mg plus clopidogrel 75 mg regimen was the most promising approach in preventing the recurrence of Ischemic stroke among patients with Lacunar stroke in the subset of South Indian Population. Our study would certainly provide the much-needed direction to future studies that may contribute further to an area which urgently requires some evidence-based research data, despite the fact that large scale randomized multicentric controlled trials are required to further confirm our findings among Indians.

Conclusion: As per the study results, it could be concluded unequivocally that 150 mg aspirin plus 75 mg clopidogrel was superior to 75mg aspirin plus 75 mg clopidogrel and aspirin alone 150 mg and aspirin 75 mg alone, in the prevention of stroke in patients with cerebral infarction or transient ischemic attack due to lacunar stroke. The dual therapy of 150 mg aspirin plus 75 mg clopidogrel and 75 mg aspirin plus clopidogrel 75mg resulted in a rather perturbing sequence of bleeding events. Accordingly, balancing between benefits and risks it was inferred that aspirin 75mg plus clopidogrel 75mg is far more superior and safer in preventing recurrent Ischemic stroke among Indian patients with Lacunar stroke.

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