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**Dr. Nagendra S**  
Associate Professor,  
Department of General  
Medicine, Subbaiah Institute  
of Medical Sciences,  
Shivamogga, Karnataka, India

**Dr. Riyas C**  
Assistant Professor,  
Department of General  
Medicine, Subbaiah Institute  
of Medical Sciences,  
Shivamogga, Karnataka, India

**Corresponding Author:**  
**Dr. Riyas C**  
Assistant Professor,  
Department of General  
Medicine, Subbaiah Institute  
of Medical Sciences,  
Shivamogga, Karnataka, India

## Comparative study of acute ischemic stroke in Indian patients on dual anti-platelet therapy clopidogrel and aspirin versus aspirin using modified ranking scale

**Dr. Nagendra S and Dr. Dayananda AS**

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### Abstract

**Background:** Stroke is a major cause of morbidity and mortality in an aging population. In the elderly, ischemic stroke accounts for more than 80% of all stroke cases. Stroke is the second leading cause of disability after ischaemic heart disease (IHD) and is the sixth leading cause worldwide. The aim of this study was to evaluate the effects of clopidogrel and aspirin (combination therapy) and aspirin alone (monotherapy for Acute Ischemic Stroke patients).

**Material and Methods:** This is a Prospective, non-randomized and observational study conducted in the Department of General Medicine, Subbaiah Institute of Medical Sciences, Shimoga among 70 acute ischemic stroke patients from January 2019 to September 2019. 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 aspirin (75 mg per day for 90 days) group.

**Result:** In our study, majority of patients were more than 60 years and least were less than 40 years in both the groups. Predominant were male than female in both the groups. An mRS of 3–6 at 90-day assessment occurred in 3 patients in the clopidogrel-aspirin group, and in 3 patients in the aspirin group ( $p=0.039$ ). Poor quality of life at 90 days occurred in 1 patients in the clopidogrel aspirin group and in 2 in the aspirin group ( $p=0.081$ ).

**Conclusions:** For patients with acute Acute Ischemic Stroke, treatment with clopidogrel and aspirin provided significantly greater inhibition of platelet activity than aspirin alone. Thus, dual therapy can be safer and more effective in reducing ischemic stroke recurrence.

**Keywords:** acute ischemic stroke, dual anti-platelet therapy, clopidogrel, aspirin

### Introduction

The WHO has defined stroke as “rapidly developed clinical signs of focal and at times global disturbances of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin.” It is one of the leading causes of adult disability and the second most common cause of death <sup>[1]</sup>. Stroke is a major cause of morbidity and mortality in an aging population. In the elderly, ischemic stroke accounts for more than 80% of all stroke cases <sup>[2]</sup>.

Stroke is the second leading cause of disability after ischaemic heart disease (IHD) and is the sixth leading cause worldwide. Women have a higher lifetime risk of stroke than men: about one in five women (20% to 21%) and one in six men (14% to 17%) will suffer a stroke in their lifetime, according to a study <sup>[3]</sup>. The prevalence of stroke events is expected to increase across the globe as the global population aged over 65 increases. The number of stroke events is projected to rise from 1.1 million in 2000 to 1.5 million per year by 2025, largely due to the ageing population <sup>[4]</sup>. Clopidogrel is one of the most widely used antiplatelet agents worldwide. It has an established position as an antagonist of platelet function, leading to a reduced risk of recurrent ischemic events. Due to the updated guidelines on stroke, this drug is also increasingly being used for the secondary prevention of ischemic stroke. <sup>[5]</sup> It might be used as a monotherapy as reasonable and equivalent option to aspirin in nonembolic ischemic stroke patients or in combination with aspirin for 21 days of dual antiplatelet therapy following a minor ischemic stroke or transient ischemic attack (TIA) in patients with a higher risk of recurrent stroke.

Aspirin is also known as Acetylsalicylic acid (ASA), irreversibly inactivates platelet cyclooxygenase, which is responsible for prostaglandin and thromboxane synthesis.

In particular, aspirin irreversibly blocks production of thromboxane A<sub>2</sub>. Thromboxane A<sub>2</sub> is a potent platelet activator and pro-aggregant; hence by blocking thromboxane A<sub>2</sub> synthesis, ASA is able to achieve an antiplatelet effect<sup>[6]</sup>. Aspirin and may then be continued longer term or switched to a different antiplatelet agent. Aspirin has the advantage of being less expensive than the other antiplatelet medications<sup>[7]</sup>.

Some relevant papers have demonstrated clopidogrel efficacy and safety and, in some cases, its advantage over aspirin<sup>[8]</sup>. However, the inhibition of platelets among different subjects might be limited and variable. This phenomenon is caused by multiple factors, leading to a reduced response of platelets, which may limit the therapeutic effect of the drug. Failure to achieve a drug response is referred to as clopidogrel resistance or high on-treatment platelet reactivity, and this has become the most important factor inhibiting the antiplatelet effect of the agent, resulting in ineffectiveness<sup>[9]</sup>. Therefore, various assays are used to assess platelet function for monitoring antiplatelet therapy<sup>[10]</sup>. They not only allow the phenomenon to be detected but can also estimate the level of platelet inhibition, thus allowing the effectiveness of the therapy to be assessed. It is extremely important for stroke subjects for whom responsiveness to antiplatelet agents is crucial.

## Material and Methods

**Study Design:** This is a Prospective, non-randomized and observational study conducted in the Department of General Medicine, Subbaiah Institute of Medical Sciences, Shimoga among 70 acute ischemic stroke patients from January 2019 to September 2019. 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 aspirin (75 mg per day for 90 days) group.

**Inclusion criteria:** Patients who were at least 18 years of age were enrolled if they could undergo randomization within 12 hours after having an acute ischemic stroke with a score of 3 or less on the National Institutes of Health Stroke Scale (NIHSS) (scores range from 0 to 42, with higher scores indicating greater stroke severity). They were also required to undergo computed tomography or magnetic resonance imaging to rule out intracranial bleeding or other conditions that could explain the neurologic symptoms or detect any contraindications to a study treatment.

**Exclusion Criteria:** Patients who have received thrombolysis, endovascular therapy, or endarterectomy; had planned use of antiplatelet therapy or anticoagulation therapy (including those with presumed atrial fibrillation or cardiovascular disease, in whom anticoagulation would be indicated).

- Patients who have symptoms numbness, isolated visual changes, or isolated dizziness or vertigo or if they had received any thrombolytic therapy within 1 week before the event.
- Patients who have serious liver and kidney dysfunction or heart and lung diseases, malignant tumours, gastrointestinal disorders seriously affect drug absorption, coagulopathy or systemic bleeding illness or history and thrombocytopenia or neutropenia or

history, pregnancy or breastfeeding women, recent surgery, trauma, or any plan for major surgery.

- Patients had a contraindication to aspirin or clopidogrel; or had anticipated use of a nonsteroidal anti-inflammatory drug for more than 7 days during the trial period.

**Modified Rankin Scale (mRS):** Severity of functional outcome was measured by mRS (scores range from 0 [no symptoms] to 6 [death]) at 90 days. The primary outcome was dependence or death, defined as mRS of 2–6.

We also compared ordinal stroke severity of 2 treatment groups, that is, 3-level ordinal stroke scale with stroke ordered by its severity using mRS at 90 days: no stroke, nondisabling stroke (mRS 0–1), or disabling stroke including fatal stroke (mRS 2–6).

## Statistical analysis

We performed the nonparametric test to see if there was a difference in the original mRS (0–6) as an ordinal variable between treatment and control groups. Meanwhile, we built the ordinal logistic regression model with the aspirin group as reference to test whether patients on clopidogrel and those on aspirin had the same mRS scores by grouping mRS into 3 levels (0–2, 3–4, and 5–6). With regard to quality of life, we made exploratory analysis for comparing differences in each of 5 EQ-5D domains (mobility, self-care, usual activity, pain or discomfort, and anxiety or depression) by using the  $\chi^2$  test. We also made overall comparison on rate of 3-level ordinal stroke scale (no stroke, nondisabling stroke, and disabling stroke) between 2 treatment groups using the  $\chi^2$  test and further looked at these 2 contrasts with Bonferroni correction (no stroke vs nondisabling stroke, no stroke vs disabling stroke). The reason for stratified analysis by stroke was to determine whether better outcomes in functional status or quality of life were due to reduction in stroke as reported in main chance results. All analyses were conducted with SPSS version 20<sup>th</sup> software. *p* values less than 0.05 were considered to be statistically significant.

## Result

In table 1, majority of patients were more than 60 years and least were less than 40 years in both the groups. Predominant were male than female in both the groups.

**Table 1:** Distribution of Age group between two groups

Age (Years)	Aspirin (n=35)	Clopidogrel and aspirin (n=35)
<40	7	6
41-60	13	15
>61	15	14
Total	35	35

**Table 2:** Distribution of gender between two groups

Gender	Aspirin (n=35)	Clopidogrel and aspirin (n=35)
Male	26	22
Female	9	13
Total	35	35

In table 2, in our study, predominant were male than female in both the groups.

**Table 3:** Distribution of Modified Rankin Scale between two groups

mRS score before the onset of index events	Aspirin (n=35)	Clopidogrel and aspirin (n=35)
0	25	26
1	9	7
2	1	2

**Table 4:** Functional outcome and quality of life at 90 days in patients after the index ischemic stroke

Outcomes at 90 days	Aspirin (n=35)	Clopidogrel and aspirin (n=35)	p value
mRS score: 2 to 6 vs 0 to 1			0.041
0 to 1	28	29	
2 to 6	7	6	
mRS score: 3 to 6 vs 0 to 2			0.039
0 to 2	31	32	
3 to 6	4	3	
Poor quality of life measured by EQ-5D	2	1	0.081

Poor functional outcome (mRS of 2–6) at 90 days occurred in 6 patients in the clopidogrel aspirin group, as compared with 7 patients in the aspirin group (absolute difference of poor outcome, 1.70%; 95% CI 0.03%–3.42%;  $p=0.041$ ); the number needed to treat to avoid a functional disability over 90 days is 59. An mRS of 3–6 at 90-day assessment occurred in 3 patients in the clopidogrel-aspirin group, and in 3 patients in the aspirin group ( $p=0.039$ ). Poor quality of life at 90 days occurred in 1 patients in the clopidogrel aspirin group and in 2 in the aspirin group ( $p=0.081$ ) (table 4).

**Table 5:** Distribution of 3-level ordinal stroke scale by treatment regimen in acute ischemic stroke

3-level ordinal stroke	Aspirin (n=35)	Clopidogrel and aspirin (n=35)
No stroke	25	26
Non disabling stroke	9	7
Disabling Stroke	1	2

**Table 6:** Adjusted odds ratios for poor functional outcome and quality of life among patients with subsequent stroke or not

Outcomes No stroke	Overall	Number of poor outcomes (%)		Adjusted odds ratio (95% CI)
		Aspirin	Clopidogrel and aspirin	
mRS score: 2 to 6	7	3	4	1.01 (0.63-1.21)
mRS score: 3 to 6	5	2	3	1.11 (0.53-2.11)
Poor QoL	3	1	2	1.03 (0.43-2.12)
<b>Stroke</b>				
mRS score: 2 to 6	16	7	9	1.13 (0.73-1.83)
mRS score: 3 to 6	12	5	7	1.12 (0.63-1.32)
Poor quality of life	11	6	5	1.02 (0.63-1.62)

Adjusted ORs in 2 subgroups stratified by stroke are reported in table 6. Among patients with no stroke at 90 days, there were no differences between 2 study groups in 90-day mRS of 2–6 (adjusted OR 1.01; 95% CI 0.63–1.21;  $p=0.63$ ), in 90-day mRS of 3–6 (adjusted OR 1.11; 95% CI 0.53–2.11;  $p=0.51$ ), or in poor quality of life (adjusted OR 1.03; 95% CI 0.43–2.12;  $p=0.73$ ), after the adjustment of baseline age remaining unbalanced in 2 study groups. Among patients with a stroke during follow-up, there were also no differences between 2 study groups in 90-day mRS

of 2–6 (adjusted OR 1.13; 95% CI 0.73–1.83;  $p=0.36$ ), in 90-day mRS of 3–6 (adjusted OR 1.12; 95% CI 0.63–1.32;  $p=0.48$ ), or in poor quality of life (adjusted OR 1.02; 95% CI 0.63–1.62;  $p=0.46$ ).

## Discussion

The events resulting from any subtype of ischemic stroke result in the loss of blood supply, oxygen, nutrients and elimination of metabolic wastes. These resulting changes obstruct normal neuronal functioning [11]. This ultimately results in neuronal death/necrosis from occlusion of the vessel. The brain tissue is exquisitely sensitive to these changes, and the therapeutic window that is needed to prevent reversible ischemia from becoming irreversible infarction is narrow and stresses the phrase “time is brain” [12]. This concept is especially important to minimizing evolving insult and controlling the propagation of ischemic penumbra [13]. Furthermore, from a therapeutic point of view, this crucial time provides a “window of opportunity” in reversing the neurological symptoms either partly or completely through acute interventional approaches, either invasively or non-invasive [14].

In our study, we found that the combination of clopidogrel and aspirin appeared to improve poor functional outcome at 90 days compared to aspirin, and this was consistent with a reduction in rate of disabling stroke in the dual antiplatelet arm. The rate of disability or death at 90 days was high, and clopidogrel was associated with 1.3% absolute reduction of poor functional outcome, which is equivalent to a number needed to treat of 21 patients to prevent a functional disability. Stratified analysis by stroke showed that there was no difference between 2 treatment groups in functional outcome and quality of life between 2 subgroups of no stroke or stroke.

Our data showed that clopidogrel plus aspirin reduced the absolute proportion of poor functional outcome (mRS of 2–6) by 1.3% when compared with those on aspirin alone. The proportion of patients in the dimensions of mobility and activities associated with quality of life was also lower in the clopidogrel-aspirin group. This might be achieved through an absolute risk reduction of 7 patients for subsequent stroke, especially for disabling stroke. Furthermore, of patients experiencing subsequent stroke, approximately three-quarters were disabled or died (mRS of 2–6), while 7 patients without strokes had this poor outcome. Thus, the majority of strokes in the short term after ischemic stroke are disabling and the combination of clopidogrel and aspirin might lower this risk. With regard to more aggressive inhibition of platelet aggression for improving stroke disability, the ongoing Triple Antiplatelets for Reducing Dependency After Ischaemic Stroke (TARDIS) trial will determine whether triple antiplatelet strategy will be superior to dual antiplatelet therapy for reducing functional disability and dependence in patients with high risk of stroke [15].

According to Nonparametric analysis in the original mRS did not show statistical difference in the functional outcome between 2 study groups but  $X^2$  analysis in the categorical mRS did; the reason for the difference in results between the ordinal mRS and the categorical mRS might be the unbalanced distribution of patients in each value of mRS. With regard to mRS as an ordinal or a categorical variable, which one has more power or whether they have equivalent power would be dependent on the pattern of treatment effect

of intervention <sup>[16]</sup>. However, it might not be easy to determine patterns of clinical improvement, because real trials will generally show less pure patterns of response. Thus, given the unbalanced distribution of patients in each value of mRS and characteristics of the target population in this trial, the dichotomized mRS for this study might be a more appropriate approach than the ordinal mRS.

## Conclusion

Our study shows that among patients with ischemic stroke who can be treated within 24 hours after onset of symptoms, the combination of clopidogrel and aspirin appears to be superior to aspirin alone in improving poor functional outcome measured by mRS 90 days after the initial event, and this is consistent with a reduction in the rate of disabling stroke in the dual antiplatelet arm. Together with its overall impact on stroke risk, this reinforces the evidence supporting its use.

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