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Research Article

COMPARISON OF SHORT TERM EFFICACY AND SIDE EFFECT PROFILE OF TICAGRELOR, CLOPIDOGREL AND PRASUGREL IN PATIENTS WITH ACUTE CORONARY SYNDROME

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ABSTRACT

Introduction-Use of standard antiplatelet agents like clopidogrel in patients with acute coronary syndrome, has led to a debate due to variation in action and irreversibility of platelet inhibition .This research compared ticagrelor and prasugrel, more potent (hypothesis) newer anti platelets with clopidogrel in such patients in terms of their side effect profile, short term efficacy and cost effectiveness.

Aim- To find the best effective newer antiplatelet drug out of ticagrelor, clopidogrel, and prasugrel in acute coronary syndrome patients.

Materials And Methods-A planned multicentric observational study on 60 patients hospitalized for acute coronary syndrome (with or without ST elevation) assigned to ticagrelor (loading dose 180mg then 90mg BD), prasugrel (loading dose 60mg then 10mg OD) and clopidogrel (loading dose 300mg then 75mg OD) was done and then followed upto 2 months. Composite end points were cardiovascular death, myocardial infraction, need for PCI or stroke.

Results-20 patients were assigned to clopidogrel, 20 to prasugrel and 20 to ticagrelor group. The primary composite end points occurred in fewer patients in prasugrel (15%) and ticagrelor (0%) group than in the clopidogrel group (40%). Statistical analysis using Anova with post hoc turkey test showed that there was significant difference between ticagrelor, clopidogrel and prasugrel in rates of ischemic attacks/week at 2nd, 6th and 8th week. The major side effects found significant statistically were constipation, sleep disturbance and ecchymosis.

The cost of clopidogrel was lowest amongst the three drugs but it differs with different brands.

Conclusion-The newer anti platelets seem to be a better option than clopidogrel for patients with ACS for whom non invasive strategy is planned. But it needs to be studied on larger sample of patients.

INTRODUCTION

Platelets play a key role in the body's response to injury in an artery and also during initial process of blood clot formation. Interrupting this process by antiplatelet therapy including P2Y12 inhibitors, and glycoprotein IIb/IIIa inhibitors has become an important part of the armamentaria in the battle against heart diseases. Acute coronary syndrome (ACS) is a term used for a group of clinical symptoms associated with acute myocardial ischemia encompassing troponin +ve, troponin –ve and ST segment elevation myocardial infarction (STEMI).

Worldwide, of the 17.5 million deaths from cardiovascular diseases, 35% deaths occurred in low income countries including India. India has the highest burden of ACS in the world [1]. Studies show that there were 29.8 million coronary heart disease patients in the year 2004 that are projected to 46.9 million in 2010 and 61.5 million in 2015 according to the Indian national commission on microeconomics and health. As these epidemiological studies exclude many patients with silent and asymptomatic disease the actual numbers may be much greater [2]. According to studies conducted by CREATE (treatment and outcomes of acute coronary syndromes in India) registry, the three major risk factors of ACS were: smoking (40%), high blood pressure (38%) and diabetes (30%) [3]. Other risk factors include hypercholesterolemia and family history of coronary artery disease.

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These factors disrupt endothelium of blood vessel and causes dysfunction of endothelium leading to atherosclerotic process giving rise to ACS. The complication associated with ACS can be understood by study work that about 1/4th patients die before they can be instituted.

Platelets play a crucial role in ACS. Platelets first stick to damaged blood vessel wall and aggregation occurs which lead to release of ADP, TXA2 serotonin and other substances that promote further aggregation by activating Gp IIb/IIIa receptors on the platelet surface. Newer anti platelet drugs continue to be developed with the goal of maximizing the reduction in atherothrombotic events.

Clopidogrel and prasugrel acts as irreversible antagonist of P2Y12 receptors of ADP whereas Newer P2Y12 antiplatelet agents' ticagrelor is directly acting reversible P2Y12 receptor antagonist. There arises a need to weigh the benefits obtained by reduction in risk of cardiovascular events with the risk of side effects borne by the patient with these newer anti platelets. The rationale behind this study is that there is less comparative data about these anti platelets drugs in Indian scenario. This topic was considered for study to review clinical trials prospectively evaluated P2Y12 inhibitors in patients intended for an initial non-invasive management strategy [4]. Various researches show variation and irreversibility of platelet inhibition with clopidogrel which has led to controversy about its optimum dose and timing of administration in patients with ACS [5] . We compared ticagrelor and prasugrel with clopidogrel in such patients. Importance of this study is that it shall act as a preliminary pilot work on comparison of side effects and short term efficacy of clopidogrel, ticagrelor and prasugrel. The study also explored whether ticagrelor is non-inferior to prasugrel in terms of short term efficacy and side effects. The study also compared the cost effectiveness of these newer anti platelet agents with the standard drug- clopidogrel. Gap in existing knowledge about these newer anti platelets is that side effect profile of these newer medicines has never been compared and which of them is better tolerated by the patient is an area of investigation. The planned pilot observational study aims to explore these gaps in existing knowledge by conducting a study on acute coronary syndrome patients who have been prescribed clopidogrel, ticagrelor or prasugrel by their treating physician.

MATERIALS AND METHODS

Study design- This was a multicentric pilot observational study comparing prasugrel, ticagrelor and clopidogrel in 60 Acute coronary syndrome patients (with 20 patients in each group).Duration of study was 2 months and participants were recruited by taking consent and providing information sheet. Participants were followed on mobile phone interview and revisit to hospital planned if needed.

Patients who had been prescribed clopidogrel, prasugrel and ticagrelor and fulfilled the inclusion criteria were included in the study.

ACS patients were selected by following Exclusion/ Inclusion criteria:

Inclusion Criteria

ACS non-smoker patients, >18 years and < 60 years with body weight >60 kg, with no other chronic disease taking statins,, beta blockers, ACE inhibitors, low dose aspirin were included in the study.

Exclusion criteria

- Pregnant women
- Patients with liver or kidney disease
- Age <18 or >60 years
- Having any other chronic disease like diabetes, refractory anemia, etc.
- Smokers
- Having transient ischemic attack (TIA), stroke, bleeding disorders.
- Patient likely to undergo urgent CABG i.e. coronary artery bypass grafting surgery
- Having body weight <60 kg
- Hypotensives
- Those patients who had recently undergone coronary angiography, PCI, CABG, or other surgical procedures
- Have TTP-thrombotic thrombocytopenic purpura and those taking following drugs: Drugs that increase risk of bleeding (e.g. warfarin, heparin, fibrinolytic therapy, chronic use of NSAIDs), Antifungals, Rifampicin. quinidine, Bupropion, Cyclosporine..etc

Patients had been assigned to three groups with 20 patients in each group.

Group 1: Clopidogrel (300mg loading dose then75 mg once daily)

Group 2: Prasugrel (loading dose 60 mg then continue at 10 mg) orally once daily.

Group 3: Ticagrelor (loading dose 180 mg then 90 mg) orally twice daily.

Duration of study- Data had been collected at 0, 2, 4 and 8 weeks after start of treatment.
Data collection::

1. Comparison of the side effect profile after taking the drugs was done.
2. Comparison of the reduction in number of ischemic episodes at 2^{nd}, 4^{th}, 6th and 8th week was done.

Statistical analysis was done by spss software and graphpad.

- Chi-square test was used to examine whether the difference in the frequency of different side effect associated with the drugs is statistically significant or not.
- Annova test followed by post hoc tukeys test was used for comparing significance amongst the three treatment groups in reduction of number of ischemic episodes at 2nd, 4th, 6th and 8th week.

With regard to ethical consideration, each patient had been given a patient information sheet which remained with him/her during trial and patient had to sign a consent form which was in the vernacular language as well as in English. Patients were explained that he/she can leave any time during the study.

Ethical permission was obtained from institutional ethics committee.

Confidentiality- All the information that was collected was anonymous and kept strictly confidential.

End points: End point was the time to first event (a composite of myocardial infarction, stroke or death from vascular causes). Instruments- [Table/fig 2] show the performa that was used for data collection. Routine blood tests that were advised by the treating physician were done and no special instrument was used.

Quality control-Medicines were procured from standard companies that have established quality control standards.

Implications-As the newer anti platelets prasugrel and ticagrelor have never been compared, this pilot study explored the status of these newer agents with regards to the side effect profile and efficacy and also compare them with standard drug clopidogrel.

RESULTS

As depicted in [table/fig 3], 60 patients with acute coronary syndrome were enrolled in the study with median follow up for 2 months.The primary end point, which was considered to be the first event (composite of MI, need for PCI, stroke or CVD) was lower with ticagrelor (0%), prasugrel (15%) than with clopidogrel (40%) taken as a control.

A Log rank test was run to determine if there were differences in the survival distribution (survival assumed to be primary end point) for the different types of drugs: clopidogrel/ prasugrel/ ticagrelor. The survival distribution of clopidogrel and ticagrelor was statistically significantly different $X2(1) = 9.803$, $P < .05$ [table/fig 4and 5] but survival distribution of clopidogrel/prasugrel ($X2 = 2.73$) and prasugrel/ticagrelor ($X2 = 3.16$) was not statistically different at $P < .05$ .The analysis of frequency of ischemic events among the three treatment group at 2nd, 4th, 6th and 8th week was done by one way annova. At 2nd week, significant variation observed among treatment groups, $F(2,27) = 3.39$, $p<.05$ but post hoc turkey test show no significant difference among groups (may be due to their different aims).

At 4th week, annova showed no significant difference among treatment groups 1.4±1.08, $F =2.48$, $P< .05$.

At 6th week, annova showed significant difference $F(2,27)= 8.26$, $p< .05$. A turkey post hoc test reveled that the ischemic attack/week in ticagrelor group was statistically significantly lower than clopidogrel and prasugrel at $p<.05$ but clopidogrel and prasugrel group were not significantly different.

At 8th week, annova showed significant difference $F(2,27) = 5.35$, $p<.05$. A turkey post hoc test reveled that the ischemic attack/week in ticagrelor group was statistically significantly lower than clopidogrel and prasugrel at $p<.05$ but clopidogrel and prasugrel group were not significantly different.

In regard to side effect observed during study [table/fig 7], fisher exact test was used as conditions to satisfy chi-square test was not met (80% data in 2*2 contigency table should be ≥5).
With respect to table/fig 8-9-10:

- Constipation was found to be statistically more in prasugrel as compared to ticagrelor $p< .05$ but not among Prasugrel and clopidogrel.
- Ecchymosis was found to be statistically more in prasugrel as compared to ticagrelor and clopidogrel at $p<.05$
- Decrease sleep was found to be statistically more with clopidogrel as compared to ticagrelor at $p<.05$ but not with prasugrel.
- Other side effect also observed during study but none of them found to be statistically different among treatment groups [table/fig 6].The patient compliance was 80% which was assesed by frequent telephonic reminders.

8% patients (prasugrel group), 6% patients (ticagrelor group) and 0% patient (clopidogrel group), who took additional ayurvedic or homeopathic medicine, showed no significant difference inreduction of ischemic attacks than those who had not taken such additional medications.

With respect to cost effectiveness, the per month cost of ticagrelor (BD), prasugrel (OD) and clopidogrel (OD) were 3000RS, 492RS and 141RS respectively.

DISCUSSION

Ticagrelor appeared to be more effective as compared to prasugrel or clopidogrel as primary end point (myocardial infarction, stroke, need for PCA, death due to cardiovascular causes) with Ticagrelor was not achieved. In Clopidogrel group three deaths were observed but no deaths were observed in prasugrel and ticagrelor groups.

Ticagrelor appeared to be superior in decreasing ischemic attacks/week as compared to prasugrel and clopidogrel by the 8th week [table/fig. 6]. There was significant difference in reduction of ischemic episodes as reported by Anova with post hoc tukey test within the three treatment groups at 2nd, 6th and 8th week. There were 20 different side effects observed during the study but only constipation (with prasugrel), ecchymosis (with prasugrel) and decrease sleep (with clopidogrel) was found to be statistically significant.

As other previous researches observed bleeding events[8,9,10] , in this research two patients out of 20 in prasugrel group showed bleeding from nose but it was not significant. With respect to Researches[11,12] based on effect of genotype on clopidogrel effect, in this research 2 patients in clopidogrel group showed no improvement in their ischemic attacks (by regular dose of 75mg given to all 20 patients) but other 15 patients showed decrease in their ischemic attacks. This could be explained by genetic variation observed earlier by researchers in metabolizing clopidogrel.

As mentioned of researches[12,13,14] comparing end points in patient who underwent PCI(percutaneous coronary intervention), received newer anti platelets and clopidogrel, the mortality was lower with newer anti platelets in comparison to clopidogrel. In this research, it was found that the incidence of ischemic attacks/week was lower for such patients on giving ticagrelor in comparison to prasugrel, however the result was not significant.

Clopidogrel was taken as a CONTROL because it is a part of standard drug regimen[15] to all patients who suspected to have ACS but it appeared to be less effective in terms of primary end point in comparison to newer anti platelets ticagrelor and prasugrel. Clopidogrel was superior for general population in view of its cost effectiveness.

The experimental design of pilot observational study adequately described the hypothesis of superiority of Ticagrelor in comparison to clopidogrel in terms of reduction in number of ischemic episodes observed after 6-8 weeks and Ticagrelor and Prasugrel in comparison to clopidogrel in terms of primary end point. It appeared a rational decision to include Ticagrelor in a private hospital as the cost of ticagrelor could not be borne by general population, who visited government hospital where clopidogrel and prasugrel appeared to be superior.

The hypothesis of superiority of newer anti platelets upon clopidogrel [16] (control as well as standard drug) also proved by ANOVA (in view of ischemic attacks/week), as significant difference in ischemic attacks was observed with newer anti-platelets in many other standard and mega centers researches[13,17,18,19,20,21].

Regarding more accuracy in results, this study needs to be conducted on large no. of patients and also needed a separate comparison of their platelet count. This research also needs to study to explain why side effects were higher with prasugrel? (among 3 treatment groups) which needs further study on large no. of patients and more follow up of more than 2 months to observe their long term efficacy. The limitation of this study was the small sample size and short duration of follow up of the patient.

CONCLUSION

Clopidogrel was less effective in reducing mortality from any cause in ACS patients in comparison to newer anti platelets. Clopidogrel yet chosen as a standard drug in government setup of many countries for patients having ACS but it appeared less effective in decreasing ischemic attack/week after 8 weeks of drug administration in comparison to newer antiplatelet agents. It is preferred in view of its cost effectiveness which is a major factor for patient compliance but prasugrel can replace it in regard of cost (per pill cost prasugrel=16.4RS and clopidogrel=4.7RS)[22].

But side effect profile of prasugrel was highest among 3 drugs which was its major drawback during this research.

Ticagrelor among 3 appeared better than prasugrel and clopidogrel on long term follow up but it was very costly (per pill cost ticagrelor=50RS) which may affect patient compliance and also affordability by low income population group. Further research needed on this topic on large no. of patients to explain the differences observed in results of this research in comparison to other researches and also with respect to comparison of platelet count, to study more side effects and to explain why side effects were higher with prasugrel. The effect of genotype of CYP450 enzymes on regular dose (75mg) of clopidogrel among patients receiving clopidogrel, needs to be studied further as well as their prevalence in patients, which will be possible by involving more no. of patients.

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