RESEARCH ARTICLE

EFFECTS OF COMBINATION THERAPY ON PLATELET COUNT IN PATIENTS OF MYOCARDIAL INFARCTION

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ABSTRACT

Aspirin and clopidogrel are usually used individually to prevent adverse cardiovascular events and stroke. They are used in stabilizing the blood pressure in patients of myocardial infarction while combination therapy of aspirin and Clopidogrel (dual anti-platelet therapy) is used for preventing adverse cardiovascular events in myocardial infarction patients. A cross-sectional observational study is conducted through a structured questionnaire from 110 patients of K.I.H.D (Karachi Institute of Heart Disease) hospital, Karachi, Pakistan. Indoor/admitted patients with diagnosis of acute coronary syndrome (ACS), non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), supra ventricular tachycardia (SVT) were included along with those with previous or current onset of angina pectoris or heart attack. Information from the test reports of these patients was included in the data. Patients without proper test reports were excluded from the study. Combination therapy duration is considered as key tool for evaluation. Out of 100 patients (after exclusion criteria applied) almost 18% patients were using combination therapy for 10 to 25 years while 52% of patients were using the combination therapy for 1 to 10 years. Platelet count of 88% patients was found to be in between 1,50,000–3,50,000/µl. Remaining patients had less than 1,50,000 µl to more than 3,50,000 to 4,50,000 µl. Most frequently reported side effects were chest pain, respiratory issues, headache and depression. On the basis of our data analysis it is concluded that long duration dual anti-platelet therapy will not harm platelet count in human blood but it can create drug dependency in patients. Hypertension is not completely cured with this therapy but can help in stabilizing blood pressure.

Keywords: Acute coronary syndrome, non-ST elevation myocardial infarction, ST elevation myocardial infarction, supra ventricular tachycardia.

1. INTRODUCTION

The platelet has emerged as an essential factor in cardiovascular diseases during the last decade. Due to this importance of platelets, a wide range of drugs affecting this particular blood component have appeared in large-scale randomized trials to improve patient outcomes in acute coronary syndromes. Previously, platelets were seen only as a bystander in hemostasis but it is now clear that the platelets are in fact a key mediator of thrombosis as well as of inflammation. New discoveries at the cellular and genomic levels will one day develop new drugs to better inhibit platelet function in a safer manner than previously possible1. Platelet activation and aggregation plays a key role in initiating and propagating coronary artery thrombosis. Two of the most useful drugs used today for antiplatelet therapy are aspirin and clopidogrel, each having its own importance and significance that is hard to deny. Aspirin (acetylsalicylic acid) is a common drug and according to an international study of Infarct Survival, conducted in patients with acute myocardial infarction, aspirin reduced the odds of death from vascular causes by 23% and the odds of reinfarction by 46%2. Aspirin has also been shown to reduce the rate of angiographic re-occlusion by 22% as compared with placebo3. Clopidogrel is an adenosine diphosphate receptor antagonist that belongs to the
class of oral antiplatelet agents that block the P2Y12 component of the adenosine diphosphate receptor and thus inhibit the activation and aggregation of platelets. Clopidogrel has been shown to prevent death and ischemic complications in patients with symptomatic atherosclerotic disease and patients with unstable angina or myocardial infarction.

The important role of antiplatelet therapy for the prevention and treatment of thrombotic complications of atherosclerotic disease is well established. Recently, an Antithrombotic Trialists' Collaboration group reported a 22% overall reduction of serious vascular events in patients receiving antiplatelet therapy. Currently, the antiplatelet agents in common clinical use are clopidogrel and acetylsalicylic acid (ASA). The first antiplatelet agent to be evaluated was ASA, which is inexpensive, relatively safe, and widely used. It produces antiplatelet effect by irreversibly inactivating cyclooxygenase enzyme in platelets thus inhibiting thromboxane A2 mediated platelet activation. Clopidogrel and its precursor ticlopidine are thienopyridines. They produce their antiplatelet effect through active metabolites that irreversibly modify the adenosine diphosphate (ADP) receptor (the P2Y12 receptor) on platelets, thereby inhibiting ADP-mediated platelet activation. Clopidogrel, the safer and more convenient of the 2 thienopyridines, was approved for the prevention of thrombotic complications of atherosclerotic diseases. It is as safe as ASA but comparatively more expensive. The major question regarding their use is whether the combined effect of these two drugs is any different from their individual effects in patients of myocardial infarction. This study aims to provide an answer to this question and to find out whether it has any notable adverse effects.

2. METHODS
A cross-sectional observational study was conducted through a structured questionnaire from 110 patients of K.I.H.D (Karachi institute of Heart Disease) hospital, Karachi, Pakistan. Information from test reports of the patients was included in the data. Indoor/admitted patients (both male and female of all ages) with diagnosis of acute coronary syndrome (ACS), non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), supra ventricular tachycardia (SVT) were included along with those with previous or current onset of angina pectoris or heart attack were also eligible for the study. Patients without proper test reports and those that were being treated with drugs other than ASA and clopidogrel were excluded from the study. The protocol was approved by the institutional review board of K.I.H.D and informed consent was obtained from all patients. Combination therapy duration, platelet count, prothrombin time, troponin-I readings, maximum blood pressure and pulse rate were monitored during the study.
The effectiveness of the treatment was evident from the results that were obtained. Platelet count of 88% patients was in between 1,50,000–3,50,000/μl. Remaining patients had less than 1,50,000 µl to more than 3,50,000 to 4,50,000 µl. Normal value is 150,000–400,000 platelets / µl (Fig. 2). A rise was observed in the people aged 50 to 60 years while a decline was noted on either side of this age group. This is in contrast to older studies which suggest that age and platelet counts have no correlation (Fig. 3).

![Fig. 2. Normal platelet range ×10⁴ µl (y-axis).](image)

![Fig. 3. Distribution of platelets ×10⁴ µl (y-axis) in different age groups (x-axis).](image)

### 4. DISCUSSION

Combination antiplatelet therapy, typically with clopidogrel and ASA, is commonly used for the prevention of cardiovascular diseases. When used for appropriate indications and duration, their benefits clearly outweigh the associated risks. However, it is not uncommon for the combination to be used outside the recommended indications or for longer than recommended durations. In these circumstances data are at best unclear and, at worst, indicative of harm. This study reviews the evidence surrounding combination antiplatelet therapy with clopidogrel and ASA with an emphasis on identifying whether there are any substantial adverse effects.

This combination offers certain theoretical benefits. Platelet activation is a critical step in the formation of thrombotic clots. ASA inhibits the production of thromboxanes, which play a prominent role in platelet activation. Clopidogrel, a thienopyridine, acts by inhibiting adenosine receptors, which play a major role at a different step in platelet activation. Thus, their mechanisms are complementary and may decrease clot formation as compared to their individual activity. Furthermore, resistance to the effects of each agent has been well reported, but resistance to both agents is less frequent. This combination of antiplatelet agents has showed clinical benefits under certain situations but at the same time has caused few problems. Most significantly, the reiterative platelet inhibition resulted in increased risk of bleeding. It is therefore incumbent on the primary care physician to understand the evidence because of the use of combination therapy and the point at which possible benefits may outweigh its risks.

The primary determinant of using combination therapy is, of course, the indication. Some clinical trials investigating the efficacy of the combination of clopidogrel and ASA have identified conditions where combination therapy offers no benefits over monotherapy. Combination therapy has been shown to be no more effective than ASA alone in primary prevention of coronary or cerebral events in patients at high risk. ASA at a dose of 75 to 162 mg daily is the preferred therapy for primary prevention of such diseases. Clopidogrel is the sole drug used in patients with ASA allergy. Similarly, combination therapy is not appropriate in patients with a recent stroke or transient ischemic attack because it increases the occurrence of major and minor bleeds without offering any therapeutic advantage over clopidogrel alone. The best indications for the use of combined clopidogrel and ASA therapy are the treatment of acute coronary syndromes.

The efficacy and safety of clopidogrel and ASA have been compared with multiple clinical trials. The results of these trials are important...
from two points of view. First, these trials provide information on the relative importance of blocking platelet activation mediated by thromboxane A₂, by ADP, or by the combination of the two antagonists. Second, the clinical trials provide information that assists clinicians in choosing the most appropriate antiplatelet therapy in different clinical settings. In a study of Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)¹⁴, clopidogrel was compared with ASA in a broad spectrum of patients with atherothrombosis. Similarly, in other studies, i.e. Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)¹⁵, the drug was used in patients with unstable angina to prevent recurrent events¹⁵ and Clopidogrel for the Reduction of Events During Observation (CREDO), it was used for the reduction of symptoms during observation trial and was compared either in combination with ASA or ASA alone¹⁶. In the analysis of CAPRIE and CURE, subgroups of patients have been identified who experienced higher than average event rates while receiving ASA therapy alone. These higher risk patients also appeared to derive greater benefit from clopidogrel compared with the general patient populations¹⁴,¹⁵.

Four terms are generally used to compare the efficacy of clopidogrel with ASA i.e. event rate (ER), absolute risk reduction (ARR), relative risk reduction (RRR), and number needed to treat (NNT). The ARR is the absolute arithmetic difference in event rates between experimental and control groups, calculated as ER experimental minus ER control. The RRR is the proportional reduction in event rates between experimental and control group, calculated as ER experimental minus ER control divided by ER control, expressed as a percentage. The NNT is the number of patients that must receive a particular intervention, for a specified length of time, to prevent 1 bad outcome, which is calculated by dividing the ARR to 100.

High-risk subgroups of patients participating in the CAPRIE and CURE studies have been identified¹⁴,¹⁵. All subgroups were at least as responsive to the beneficial effects of clopidogrel, either used alone or in combination with ASA. Some of the identified high risk groups assigned to clopidogrel showed a greater RRR compared with the population as a whole, suggesting the possibility that these subgroups might be more responsive to the antiplatelet effects of clopidogrel than to ASA. The risk of bleeding was similar with both antiplatelet agents¹⁴,¹⁵.

The subgroup analyses of the CAPRIE study and of two of the groups in the CURE study have shown limitations because the identified high risk groups were not pre-specified. Accordingly, the results should be considered as hypothesis and the observed event rates in the identified subgroups could overestimate the real situation¹⁴,¹⁵. This shortcoming does not apply to the PCI-CURE study, which was a pre-specified companion study to CURE. On the other hand, the CAPRA study suggests that in the real world, patients with atherothrombosis are at much higher risk compared with those enrolled in clinical trials such as CAPRIE and therefore more likely to derive benefit from effective therapies¹⁴.

In addressing the question of the relative importance of thromboxane A₂- and ADP-mediated platelet activation in thrombogenesis, the clinical trial data indicate that a greater antithrombotic effect is achieved by blocking ADP-mediated activation and that this advantage extends into patient groups with a high baseline risk of thrombotic complications. More importantly, the results of the CURE study indicate that the impressive additive effect that is achieved by blocking both mechanisms of platelet activation also extends to patients with a high baseline risk of thrombotic complications. From a clinical perspective, the results of subgroup analyses provide data that help clinicians to balance the increased benefit of clopidogrel with the lower cost of ASA and the greater benefit and small increase in major bleeding of the combination of clopidogrel and ASA.
with the lower cost of ASA. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial also helped further to define the effectiveness and cost-efficacy of dual antiplatelet therapy versus ASA monotherapy in secondary prevention of coronary, cerebral, and peripheral arterial diseases as well as in high-risk primary prevention.11,16

5. CONCLUSION
On the basis of our data analysis it is concluded that dual administration of antiplatelet therapy for long durations will not harm platelet count in human blood but it can create drug dependency in patients. Hypertension is not completely cured with this therapy but it can help in stabilizing blood pressure to normal ranges.

REFERENCES


