Evaluation of Efficacy of Clopidogrel Plus Aspirin vs. Aspirin Alone of Early Clinical Outcomes Following Off Pump Coronary Artery Bypass Graft Surgery

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Abstract

Introduction: Clopidogrel improves intravascular stent patency reduces ischemic events but there are little data on its effect following OPCAB. This study was designed to evaluate the effect of aspirin and Clopidogrel on early clinical outcomes of patients undergoing OPCAB.

Material and Method: In this randomized clinical trial, 413 patients undergoing OPCAB were randomized to receive aspirin 80 mg plus Clopidogrel 75 mg (n=214, intervention group) or aspirin 80 mg (n=199, control group) for three days after surgery and then were treated in accordance with the common guidelines. Patients with coagulation disorders and those who rejected taking drugs were excluded. The data were then analyzed by using Student t-test and Chi-square test through SPSS ver. 20.

Result: Mean age of patients was 61.081 ± 10.84 years. There was no significant difference between in two groups in pre and perioperation data. Mean of bleeding in the first day in aspirin plus Clopidogrel group was 713.55 ± 368.85 ml whereas in the aspirin group was 792.89 ± 548.73 ml (p=0.044) but, There was significant difference in mean of bleeding during three days between two groups (p: 0.013).

Conclusion: According to our findings patients treated with Clopidogrel plus aspirin had significantly less bleeding compared with the group treated with aspirin alone during three days. It seems that the effect of Clopidogrel on outcomes of operation is considerable and Clopidogrel can be introduced as a qualified supplement therapy for aspirin although the side effect of recombinant antiplatelet therapy is also controversial.

Keywords: Aspirin • Clopidogrel • Off pump coronary artery bypass • Early clinical outcomes

Introduction

Off-Pump Coronary Artery Bypass Grafting (OPCAB) is an effective therapeutic intervention in coronary artery disease [1]. In this operation, because of non-use of Cardiopulmonary Bypass (CPB), we rarely see complications such as bleeding [2]. Instead, we see many patients who suffer from complications such as thrombogenicity [3]. Surgeons can usually solve this problem by using antithrombin drugs. Antiplatelet drugs after surgery reduce the tendency to form clot and to deteriorate cardiac events [4]. Aspirin is an antithrombin agent that is used to reduce serious cardiovascular events [5]. Although aspirin is an antithrombin base in patients undergoing Coronary Artery Bypass Graft (CABG), its resistance is relatively common after surgery [6]. Clopidogrel is a new derivative of thienopyridine that inhibits platelet aggregation related to Adenosine Diphosphate (ADP) [7]. Despite the use of Clopidogrel in cardiology, its use in cardiac surgery varies from one center to another that is probably known to have detrimental effect of preoperative Clopidogrel on postoperative hemostasis [8]. For the CURE (the CURE in Unstable angina to prevent Recurrent ischemic Events) trial and randomized controlled trials, sufficient information was offered for the benefit and safety of Clopidogrel in patients undergoing surgery. Clopidogrel administered with aspirin improved outcomes in patients undergoing CABG for acute coronary syndrome of non-ST-elevation [9]. Clopidogrel when compared with aspirin has different effects on platelet activity and patency in reducing thrombosis. This study was designed to evaluate the effect of Clopidogrel used in combination with aspirin and aspirin alone on short term clinical outcomes after OPCAB.

Material and Methods

Study population

This randomized clinical trial was designed on 413 patients who underwent OPCAB from May 2009 to October 2014. Approval for study protocol was obtained from the ethics committee of Yazd Cardiovascular...
Research Center and written consent was taken from all patients. In summary, patients were qualified for study enrollment if they were programmed to tolerate the surgery and drug regimen. Patients that had coagulation disorders including history of aspirin, Clopidogrel before surgery, gastrointestinal bleeding after taking warfarin before surgery, an ultrasound evidence of hepatic and renal lesions, valve surgery, gastrointestinal bleeding after surgery and patients referral after one month were excluded from the study. All surgeries were completed by a certain surgical team.

**Study design**

After surgery, patients were monitored in Intensive Care Unit (ICU). Patients divided into two groups randomly who had received oral medication in two parallel groups, when chest tube drainage after surgery had reduced to less than 50 ml/h for two continuous hours after extubation. Clopidogrel 75 mg/d per day combined with aspirin 80 mg/day (intervention group) was given to 214 patients and aspirin alone (control group) was given to 199 patients. Both anticoagulant regimens were continued postoperatively in both groups during the three days and then patients were treated in accordance with the common guidelines [10]. After discharge of hospital, the patients were examined clinically after one month for recorded clinical events. Demographic variables and early postoperative complications include preoperative renal failure, hypertension, chronic obstructive pulmonary disease, preoperative ejection fraction, history of preoperative myocardial infarction, addiction, smoking, the number of involved vessels, the number of proximal and distal anastomosis, arrhythmia, bleeding, the need for re-operation due to bleeding, cerebrovascular accident, deep venous thrombosis, Pulmonary embolism, length of stay in ICU, and mortality. All patients were controlled by Holter monitoring during hospitalization. The data were analyzed by using Student t-test and Chi-square test through SPSS ver. 20.

**Results**

From all patients, the mean age of patients in the intervention group (aspirin plus Clopidogrel) was 61.85 ± 10.57 years, whereas the average age of the control group (aspirin group) was 59.94 ± 11.17 (p: 0.075). The intervention group included 67 males (31.3%) and 147 females (68.7%) whereas in the control group there were 61 males (30.7%) and 138 females (69.3%). (p: 0.886). Due to the importance of cardiac ejection fraction in coronary artery bypass surgery plan, mean cardiac ejection fraction was assessed in both groups. The reported rates for the intervention group were 46.85% ± 11.09% and for the control group 45.81% ± 12.38% (p:0.389). Before starting the study, cardiovascular risk factors were assessed in both of experimental and control groups (Table 1).

Perioperative conditions and the number of vessels involved and emergency surgery were not significantly different between the two groups (p>0.05) (Table 2). Mean of bleeding in the first day in the group treated with Clopidogrel and aspirin was 713.55 ml ± 368.85 ml whereas mean of bleeding in the first day in the group treated with aspirin alone was 792.89 ml ± 548.73 ml (p: 0.044). Average of the second and third day of bleeding are described in the two study groups in Table 3. There was significant difference in mean of bleeding during three days between two groups (p<0.05) (Figure 1). On the other hand, patients treated with Clopidogrel plus aspirin had significantly less bleeding compared with the group treated with aspirin alone. Outcomes were assessed after surgery in both groups for one month (Table 4). Reoperation due to bleeding and intra-hospital mortality had no significantly difference in the two groups. While the number of transfusion in patients treated with Clopidogrel plus aspirin was significantly lower than the group treated with aspirin alone (p: 0.011). Side effects of platelet dysfunction after surgery were evaluated in two groups for one month (Table 4). According to the results, there was no significant difference in the frequency of renal failure, stroke, pulmonary embolism and arrhythmias in both groups (p>0.05).

**Table 1. Distribution of risk factors for cardiovascular diseases in the study population.**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Experimental group</th>
<th>Control group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Failure</td>
<td>Yes 17 (7.9%)</td>
<td>No 197 (92.1%)</td>
<td>0.557</td>
</tr>
<tr>
<td></td>
<td>Yes 16 (8%)</td>
<td>No 183 (92%)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>Yes 18 (8.5%)</td>
<td>No 195 (91.5%)</td>
<td>0.107</td>
</tr>
<tr>
<td></td>
<td>Yes 9 (4.5%)</td>
<td>No 190 (95.5%)</td>
<td></td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td>Yes 74 (34.7%)</td>
<td>No 139 (65.3%)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Yes 60 (30.2%)</td>
<td>No 139 (69.8%)</td>
<td></td>
</tr>
<tr>
<td>Addiction</td>
<td>Yes 34 (15.9%)</td>
<td>No 180 (84.1%)</td>
<td>0.467</td>
</tr>
<tr>
<td></td>
<td>Yes 37 (18.6%)</td>
<td>No 162 (81.4%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative Myocardial Infarction</td>
<td>Yes 61 (28.8%)</td>
<td>No 151 (71.2%)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Yes 43 (21.6%)</td>
<td>No 156 (78.4%)</td>
<td></td>
</tr>
</tbody>
</table>

*Chi-square*
Table 3. Mean of bleeding in the first, second and third days in the two groups after the intervention.

<table>
<thead>
<tr>
<th>Postoperative bleeding (ml)</th>
<th>Experimental group</th>
<th>Control group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First day</td>
<td>713.55 ± 368.85</td>
<td>792.89 ± 548.73</td>
<td>0.044</td>
</tr>
<tr>
<td>Second day</td>
<td>283.72 ± 195.66</td>
<td>320.74 ± 218.61</td>
<td>0.037</td>
</tr>
<tr>
<td>Third day</td>
<td>91.03 ± 53.94</td>
<td>142.03 ± 108.19</td>
<td>0.043</td>
</tr>
<tr>
<td>Mean of three days</td>
<td>352.25 ± 163.88</td>
<td>396.55 ± 229.54</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*Independent sample T-test

Table 4. Distribution of postoperative complications in the two groups.

<table>
<thead>
<tr>
<th>Postoperative Complications</th>
<th>Experimental group</th>
<th>Control group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Re-operation due to bleeding</td>
<td>3 (1.4%)</td>
<td>212 (98.6%)</td>
<td>8 (1.4%)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>3 (1.4%)</td>
<td>212 (98.6%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>Number of transfusion</td>
<td>0 - 79 (36.9%)</td>
<td>- 65 (32.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 - 90 (42.1%)</td>
<td>- 64 (32.2%)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>2 - 24 (11.2%)</td>
<td>- 33 (18.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 3 - 21 (9.8%)</td>
<td>- 37 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>Renal Failure</td>
<td>14 (6.5%)</td>
<td>200 (93.5%)</td>
<td>20 (10.1%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.9%)</td>
<td>212 (99.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>1 (0.5%)</td>
<td>213 (99.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>None - 208 (97.2%)</td>
<td>- 196 (98.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AF - 5 (2.3%)</td>
<td>- 1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VT - 0</td>
<td>- 2 (1%)</td>
<td>0.482</td>
</tr>
<tr>
<td></td>
<td>VF - 1 (0.5%)</td>
<td>- 0</td>
<td></td>
</tr>
</tbody>
</table>

*Chi-square

Discussion
To date, many studies have been performed to determine the efficacy of Clopidogrel in patients with acute coronary syndrome and patients after CABG surgery [11]. This study has also been performed in line with previous studies to determine the efficacy of combining Clopidogrel with aspirin in patients undergoing CABG surgery. However, like previous studies, this study showed consistent and inconsistent results. In the present study, both treatment groups had no significant difference in outcomes after CABG surgery such as DVT, renal failure, in-hospital mortality, and need for reoperation, pulmonary embolism, postoperative arrhythmia and stroke. However, in previous studies, some were consistent with these findings [5]. On the contrary, some studies demonstrated that outcomes after operation in the group receiving Clopidogrel and aspirin are less than in Group receiving aspirin alone [12]. But the most important outcome in both regimens was bleeding rate and postoperative transfusion requirement in patients and...
Discussion

To date, many studies have been performed to determine the efficacy of Clopidogrel in patients with acute coronary syndrome and patients after CABG surgery [11]. This study has also been performed in line with previous studies to determine the efficacy of combining Clopidogrel with aspirin in patients undergoing CABG surgery. However, like previous studies, this study showed consistent and inconsistent results. In the present study, both treatment groups had no significant difference in outcomes after CABG surgery such as DVT, renal failure, in-hospital mortality, and need for reoperation, pulmonary embolism, postoperative arrhythmia and stroke. However, in previous studies, some were consistent with these findings [5].

On the contrary, some studies demonstrated that outcomes after operation in the group receiving Clopidogrel and aspirin are less than in Group receiving aspirin alone [12]. But the most important outcome in both regimens was bleeding rate and postoperative transfusion requirement in patients and results of this study showed that the combination regimen has a significant effect on the rate of postoperative bleeding. But a question that has been posed repeatedly over the last few years and especially in similar clinical trials is that preoperative or postoperative administration of this combination regimen has different results of clinical trials in this field as were published in 2008. American College of Cardiology (ACC) and American Heart Association (AHA) in new guidelines proposed that Clopidogrel drug is discontinued 5 days before surgery if stability of the patient's clinical condition has been not missing [13]. Discontinuation of the Clopidogrel drug five days before surgery reduces the risk of perioperative bleeding in patients undergoing long-term treatment with Clopidogrel drug and before surgery. In line with the new guidelines, similar results were found by Enoch and Anthony, they noted in two separate studies that there is no significant difference in term of bleeding during surgery among patients with no history of Clopidogrel use and those taking it for 5 days before surgery [14,15]. But the most important point was about emergency surgery in which taking Clopidogrel reduced the risk of death and ischemia but increased significantly the risk of bleeding during and after surgery. However, our intervention was after surgery and perioperative bleeding was not considered in this study. Other notable findings from previous studies are those of Mclean and Cannon [16]. They found a measuring tool of platelet disorders that could measure the level of platelet inhibition after CABG surgery in patients and it made doctors aware of a condition called Clopidogrel resistance that changed drug instructions in patient with risk of drug resistance and subsequently reduced length of stay in the ICU and required mechanical ventilation and prolonged hospital staying. Although within 72 hours of using drug was a significant lowering rate of bleeding and need for transfusion in both groups with a combined regimen, there is evidence from previous studies that the aprotinin drug can also be useful to reduce bleeding and the need for blood transfusions greatly due to use of Clopidogrel [17-19]. Although CABG surgery without CPB versus CPB has a lower risk of bleeding during surgery and after surgery [20,21], another report has indicated that the effects of the platelet ADP receptor antagonists with heparin infusion to protect of coagulation factors such as plasma fibrinogen will reduce bleeding after CABG surgery [22]. There is a question that despite multiple clinical trials around the world, there is no information about prescription or non-prescription of combination regimen, but there exists information about prescribing indices of this combination regimen that includes Prescription at the effective time with different doses, discontinuation of the drug at critical moments and most importantly, how to balance its effects. Partly favorable, the combination regimen of this study has answered to this question according to the necessities of clinical or at least, it has made clear the answer to the treatment of this study in the city of Yazd.

Conclusion

Clopidogrel in combination with aspirin appears to be safe for postoperative bleeding in patients. Also it can reduce the need for blood transfusion after surgery, although it has no significant impact in reducing postoperative complications. In term of administration time of this combination regimen, the results of this study compared with previous studies showed that a significant effect after CABG surgery. However, according to the new guidelines of America Heart College, stop Clopidogrel five days before surgery seems to be necessary in patients taking Clopidogrel a long time before CABG surgery.

Recommendations

Evaluation of probable complications in a longer post operation follow up and consideration of the time and the doses of these two regimens should be noticed. Also evaluation of patency of grafts after CABGs using coronary angiography and spiral CT-Scan for future studies is recommended.

Clinical Registry

Processing.

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References

Trials' (ATT) Collaboration. Aspirin in the Primary and Secondary
Prevention of Vascular Disease: Collaborative Meta-Analysis of Individual

in Addition to Aspirin in Patients with Acute Coronary Syndromes without St-

Aspirin and Clopidogrel Therapy on Cardiovascular Outcomes: A Systematic

13. Mitka, Mike. "Results of CURE Trial for Acute Coronary Syndrome." *JAMA*

14. Akowuah, Enoch, Vivek Shrivastava, Binal Jammadas, and David Hopkinson,
et al. "Comparison of Two Strategies for the Management of Antiplatelet

15. Bavry, Anthony A, and Michael Lincoff A. "Is Clopidogrel Cardiovascular

Point-of-Care Assay to Assess Interindividual Variability in Platelet
Aggregation Among Patients Taking Clopidogrel." *Crit Pathways Cardiol* 5

17. Ouattara, Alexandre, Hassine Bouguenda, Yannick Le Manach, and
Philippe Léger, et al. "Impact of Aspirin with or without Clopidogrel on
Postoperative Bleeding and Blood Transfusion in Coronary Surgical Patients
Treated Prophylactically with a Low-Dose of Aprotinin." *Eur Heart J* 28

18. van der Linden, Jan, Gabriella Lindvall, and Ulrik Sartipy. "Aprotinin
Decreases Postoperative Bleeding and Number of Transfusions in Patients
on Clopidogrel Undergoing Coronary Artery Bypass Graft Surgery: A Double-
Blind, Placebo-Controlled, Randomized Clinical Trial." *Circulation* 112 (2005):
1-276.

19. Lindvall, Gabriella, Ulrik Sartipy, and Jan Van der Linden. "Aprotinin Reduces
Bleeding and Blood Product use in Patients Treated with Clopidogrel before

20. Kapetanakis, Emmanouil L, Diego A Medlam, Steven W Boyce, and
Elizabeth Haile, et al. "Clopidogrel Administration Prior to Coronary Artery
Bypass Grafting Surgery: The Cardiologist S Panacea or the Surgeons

"Clopidogrel and Bleeding after Coronary Artery Bypass Graft Surgery." *Ann

22. Pothula, Suryanarayana, Vajubhai T Sanchala, Basavaraj Nagappala, and
Mario A Inchiosa Jr. "The Effect of Preoperative Antiplatelet/Anticoagulant
Prophylaxis on Postoperative Blood Loss in Cardiac Surgery." *Anesth
Anaesthes* 98 (2004): 4-10.

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