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Dual Antiplatelet Therapy after Coronary Artery Bypass Graft Surgery: A Review

Hala Soomro[1], Salik Aleem[1], Ali Alam[1], Mohammad Ali Qadeer[1], Nabeeha Essam[2], Anas Ahmed Siddiqui[3], Muhammad Fasih Mansuri[2], Huda Fatima[3], Ali Raza[3], Ayyaz Alam Sultan[3], Rohail Jameel[1], Maha Begg[3], Maaz Hasan Khan[4], Muhammad Bazil Musharraf[5], Arbab Burhan[3] & Muhammad Nawaz Lashari[6]

[1] Ziauddin Medical University, Karachi, Pakistan

[2] Jinnah Sindh Medical University, Pakistan

[3] Dow University of Health Sciences, Karachi, Pakistan

[4] United Medical and Dental College, Karachi, Pakistan

[5] Karachi Grammar School, Karachi, Pakistan

[6] Civil Hospital, Karachi, Pakistan

Correspondence: Hala Soomro, Ziauddin Medical University, Karachi, PK. 4/B, Shahrah-e-Ghalib, Block 6, Clifton, Karchi, PK. Tel: 92-300-232-6587. E-mail: hala.soomro@gmail.com

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Abstract

Coronary artery bypass graft surgery (CABG) is the gold standard treatment for relieving angina symptoms and reducing mortality among ischemic heart disease patients. As post-operative thrombosis of the grafts has been a frequent complication of CABG, antiplatelet therapy remains essential to maintain graft patency. Since a long time, aspirin has been used as a single anti-platelet agent post CABG. However, in some high risk patients aspirin alone is insufficient in preventing graft occlusion. Therefore, dual antiplatelet therapy involving aspirin plus clopidogrel is becoming increasingly popular. Aspirin plus clopidogrel therapy has proved to be highly efficacious in patients with acute coronary syndrome; however, its role in patients after CABG has remained unclear. In this review, we outline the effects of dual antiplatelet therapy involving aspirin plus clopidogrel with respect to graft patency, post-operative angina/myocardial infarction, major bleeding event and mortality.

Keywords: coronary artery bypass graft surgery, antiplatelet therapy, clopidogrel, aspirin

Abbreviations:

CABG: Coronary Artery Bypass Grafting

LIMA: Left Internal Mammary Artery

SVG: Superior Venous Graft

1. Introduction

Coronary artery bypass graft surgery (CABG), one of the most frequent cardiac procedures performed worldwide, is a highly effective treatment for ischemic heart disease. However, as the success of the surgery is largely based on the vascular bypass remaining open, thrombosis is considered to be a dreaded post-operative complication (Rafiq et al., 2012). With platelets regarded as the main cause of thrombosis, antiplatelet therapy is the main stay treatment to reduce mortality and morbidity in post CABG patients (Fuster, Moreno, Fayad, Corti, & Badimon, 2005).

The administration of aspirin in post CABG patients has been well established since a long time. However, due to the concerns that aspirin is not sufficient to prevent adverse outcomes in high risk patients, a dual antiplatelet therapy with clopidogrel was considered (Bhatt et al., 2006). While recent studies have clearly shown that clopidogrel plus aspirin is significantly superior in reducing cardiovascular events compared with aspirin alone in patients with acute coronary syndrome, the role of dual antiplatelet therapy after CABG has remained controversial (Kulik, Chan, & Ruel, 2009). It has been proposed by few studies that adding clopidogrel after CABG has no beneficial effect with some studies even reporting dual antiplatelet therapy as a significant risk

factor for bleeding (Kulik et al., 2009).

With multitude of recent studies reporting various outcomes for post CABG patients after dual antiplatelet therapy, we conducted an updated literature review to compare and contrast the major outcome variables between aspirin alone group and aspirin plus clopidogrel group. This review will particularly focus on graft patency, post-operative angina/myocardial infarction, major bleeding event and mortality as the major outcome variables.

2. Graft Patency

Graft patency is a deciding element for long term competency of CABG. Studies have shown that approximately 10.9%-26.4% of grafts undergo occlusion 1 year after CABG (Desai, Cohen, Naylor, & Fremes, 2004; Alexander et al., 2005). The prevalence of graft obstruction within 3 months post CABG has also been shown to be significant (Lingaas et al., 2004). Thus thrombosis can be considered as a very common complication after CABG, making combined antiplatelet therapy extremely important.

Mujanovic et al studied the efficacy of combination antiplatelet therapy on graft patency versus aspirin alone (Mujanovic, Nurkic, Caluk, Terzic, Kabil, & Bergsland, 2009). A total of 20 patients had undergone off-pump CABG surgery and were divided into two groups: group A received aspirin only, and group B received aspirin plus clopidogrel. Angiography was performed 3 months after the procedure and it was found that although all left internal mammary artery (LIMA) grafts were patent through the interval, 8 venous grafts from group A and 2 from group B were found obstructed. The authors believed that clopidogrel may have synergist action with aspirin. The study concluded that the aspirin-clopidogrel therapy helped improve graft patency post Off-pump CABG, particularly in saphenous vein grafts.

Gao et al conducted a randomized control trial to test the curative effects of antiplatelet combination therapy on Saphenous Vein Graft (SVG) disease (Gao et al., 2010). Angiography was performed 3 months post CABG to test for SVG patency. The patients were divided into two groups: Group AC (aspirin plus clopidogrel) and group A (aspirin plus placebo). Angiography results showed that 8.4% of grafts had lost patency [AC group = 6.5%, A group = 10.3%]. Although graft patency is a multifactorial outcome depending on patients as well as the procedures performed, the trial suggested that combination regimen plays a significant role in prevention of graft occlusion and notably improves patency, particularly of venous grafts.

To study this further, Sun et al. conducted a placebo-controlled study in the PAPA trial to compare the effects of combined antiplatelet therapy with aspirin alone in on-pump CABG surgery patients (Sun et al., 2010). The patients were again divided into two groups based on the interventions they were administered: with aspirin + clopidogrel group and aspirin + placebo group. Graft patency was studied for both groups at an average interval of 50 days post CABG. Final outcomes revealed that the overall graft patency was marginal, occlusion rate for placebo group was 7.1% and clopidogrel group was 5.0%. However, the results for radial artery grafts showed compelling difference, graft occlusion rate for placebo and clopidogrel being 43.8% and 10.0% respectively.

Moreover, the CASCADE trial conducted by Kulik et al. also discussed the effects of aspirin-clopidogrel regimen on SVG disease (Kulik et al., 2010). Intravascular ultrasonography and angiography were performed at one year post operatively. The all-inclusive graft patency rate was 95.6% for aspirin-placebo and 95.2% for aspirin-clopidogrel, whereas SVG patency rate was 94.3% in the former and 93.2% in the latter. These results showed that the graft patency for the clopidogrel group was not significantly different when compared with the placebo group.

Also, Ebrahimi et al. compared the outcomes of combined antiplatelet therapy with aspirin alone in the ROOBY trial (Ebrahimi et al., 2014). One year graft patency was not statistically different between patients who received aspirin plus clopidogrel (clop+) as compared to patients who received aspirin alone (clop-). The overall graft patency rates for on-pump CABG subjects in clop+ group and clop- group were 84.5% and 82.6% respectively. For off-pump CABG subjects, 81.3% graft patency for clop+ and 77.4% graft patency for clop- groups was found. This is the most recent and the largest study available that compares the efficacy of aspirin plus clopidogrel in CABG patients postoperatively and the results imply that the supplementation of clopidogrel with aspirin does not play any additive role in improving graft patency in on-pump CABG patients after a year's interval but the patency rates for off-pump CABG subjects are notable.

The CRYSSA trial conducted by Manacio et al studied the synergistic effects of aspirin-clopidogrel compared with aspirin alone after off pump coronary revascularization and found a higher patency of grafts for the combination antiplatelet group (Mannacio, Di Tommaso, Antignan, De Amicis, & Vosa, 2012). The patients were administered with these regimens for 12 months after which they were evaluated for graft occlusion by

angiography. Graft occlusion rates for aspirin-clopidogrel and aspirin alone were 15.2% and 27% respectively. The results showed a significant difference between the outcomes of two antiplatelet regimens. The authors concluded that clopidogrel has an evident synergistic effect when given with aspirin to keep SVG patent. Conclusively, the study concluded that patients started early on combination antiplatelet therapy showed a reduced SVG occlusion and improved graft survival.

3. Post CABG Angina/Myocardial Infarction

The trials by Gao et al. and Sun et al. reported no significant difference in rates of myocardial infarction (MI) or angina between aspirin-placebo group and aspirin-clopidogrel group (Gao et al., 2010; Sun et al., 2010). Also, the study by Kulik et al. did not show much of a difference between the two groups either (Kulik et al., 2010). However, the MI rates in the CRYSSA trial by Mannacio et al suggested otherwise; the rates for clopidogrel plus aspirin group and aspirin alone group were found to be 2% and 4% respectively (Mannacio et al., 2012). Furthermore, several trials have reported that the use of clopidogrel post CABG independently reduces MI, angina and other major cardiovascular events (Sørensen et al., 2011). These findings favor the use of clopidogrel as a synergist with aspirin after CABG.

4. Major Bleeding

It has been estimated that around 30% of patients experience bleeding after CABG and 2% may require surgery to control it (Mehta et al., 2009). Clopidogrel is a strong antiplatelet agent and surgeons tend to put a halt to its intake a few days before CABG as it increases perioperative episodes of bleeding (Mehta et al., 2009). Major bleeding is defined as fatal or symptomatic bleeding occurring in a critical area or region of the body, such as intraocular bleeding resulting in vision loss, causing hemoglobin level to drop and needing blood transfusion of 2 units of packed red blood cells right away.

Sun et al. reported the same rate of major bleeding events for both groups of patients; the one receiving combination therapy and the other receiving aspirin only, as 6% of patients in both the groups were found to suffer from major bleeding postoperatively (Sun et al., 2010). Likewise, Mannacio et al also reported the same frequency of major bleeding in both the groups (aspirin-placebo = 1.3%, aspirin clopidogrel = 1.3%) (Mannacio et al., 2012). However, the study by Kulik et al showed that during early postoperative phase the rate of bleeding in patients from aspirin- clopidogrel group was greater than aspirin-placebo group. Median chest tube drainage during early postoperative hours was 400 mL for aspirin-clopidogrel group and for aspirin-placebo group, it was 260 mL. The late postoperative bleeding rates were not significantly different between the two groups with major bleeding occurring in only one patient from the aspirin-clopidogrel group (Kulik et al., 2010).

Therefore it can be concluded that combined antiplatelet regimen may results in major bleeding outcomes during the early postoperative hours. This is an important point of consideration for surgeons as major bleeding may lead to mortality.

5. Mortality

The overall rates of post CABG mortality range from 1.4% to 3.5% (Desai et al., 2004; Alexander et al., 2005; Serruys et al., 2009). The overall mortality rates for patients administered with aspirin-clopidogrel and aspirin-placebo have not been found to be significantly different (Gao et al., 2010; Sun et al., 2010; Kulik et al., 2010; Mannacio et al., 2010). Therefore it can be concluded that adding clopidogrel neither increases nor decreases this risk.

6. Conclusion

In sum, it can be concluded that clopidogrel given in combination with aspirin to post CABG patients is beneficial in terms of graft patency especially in off-pump CABG patients. Moreover, according to literature the dual antiplatelet therapy also helps to significantly reduce the incidence of MI in post CABG patients as suggested by recent trials such as CRYSSA. However, clopidogrel increases the risk of bleeding during the early postoperative phase making close monitoring an absolute necessity to prevent any major bleeding events. Nevertheless, as adding clopidogrel can have a tremendous advantage of reducing graft occlusion, the dual antiplatelet therapy is essential in further improving the morbidity in post CABG patients.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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