Original articles

A Prospective Audit of Blood Loss and Blood Transfusion in Patients Undergoing Coronary Artery Bypass Grafting After Clopidogrel and Aspirin Therapy

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ABSTRACT

Objective: *Platelet dysfunction is a common cause of bleeding after coronary artery bypass graft (CAG) surgery. This prospective observational audit explored the effects of clopidogrel and aspirin on chest drain output for the first 24 hours after CAG surgery.*

Methods: *During a 7 week period from July to Aug 2003, all patients who underwent CAG at the London Chest Hospital were audited. Patients undergoing concomitant valvular surgery were excluded. The study population included patients who had previous cardiac surgery and patients undergoing emergency procedures. Patients were sub-divided into those who were exposed within 7 days of surgery to clopidogrel alone, aspirin alone, both aspirin and clopidogrel and those not exposed to either agent.*

Results: *During the study period, 91 patients were audited. Two patients were excluded due to concomitant valvular surgery. The remaining 89 patients, included those who were exposed within 7 days of surgery to clopidogrel alone (n = 2), both aspirin and clopidogrel (n = 12), aspirin alone (n = 65) and those not exposed to either agent (n = 10). The groups were comparable in age, gender, body weight and baseline haematocrit.*

The clopidogrel and aspirin group had a lower mean chest drain output at 24 hours post CAG compared with both the aspirin alone and non-clopidogrel non-aspirin groups (694.4 mL vs. 831.9 mL vs. 726 mL), although these differences were not statistically significant. Both the clopidogrel-with-aspirin and the aspirin-only groups received blood products more frequently when compared with the non-clopidogrel non-aspirin group and also the mean number of units transfused per patient was greater. Consistent with the highest mean blood loss, the aspirin group was transfused more units of blood than the clopidogrel and aspirin group and non-clopidogrel non aspirin groups (1.67 vs. 1.0 vs. 0.6 units of blood) Again, these differences were not statistically significant. Nevertheless, overall, the frequency and amount of blood transfusion in those patients who were not receiving aspirin or clopidogrel preoperatively was lower than for those receiving clopidogrel and/or aspirin.

Conclusions: *Our audit suggested that continuing to administer clopidogrel and/or aspirin in the 7 days prior to CAG surgery is associated with higher postoperative bleeding and morbidity. However, this increased bleeding tendency did not appear to result in a clinically significant increased requirement for allogenic blood product transfusion.* (**Critical Care and Resuscitation 2004; 6: 248-252**)

Key words: Cardiac surgery, postoperative blood loss, clopidogrel, aspirin, audit

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Clopidogrel is a thienopyridine antiplatelet drug which appears to act via non-competitive antagonism of the platelet adenosine diphosphate receptor, $P2Y_{12}$. Its efficacy has been demonstrated in the setting of the acute coronary syndromes.[1] An addendum to the management of unstable angina guidelines published jointly by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand recommends that whilst "early treatment with aspirin, clopidogrel and tirofiban/heparin should be considered in patients with non-ST elevation acute coronary syndrome and high-risk features (ST depression or elevated serum markers)" that "the use of clopidogrel should be avoided in patients likely to require emergency coronary bypass surgery".[2]

However, many patients receive a combination of aspirin and clopidogrel prior to undergoing coronary angiography when there is a possibility of coronary stent implantation. A proportion of these patients are subsequently found to have disease warranting surgical intervention. An increase in postoperative bleeding has been reported in patients treated with a thienopyridine having cardiac[3] or vascular[4] surgery and so it is recommended that clopidogrel be discontinued 5 - 7 days prior to elective surgery. However, as the indications for the use of clopidogrel expand, an ever increasing number of patients will present for coronary artery graft (CAG) surgery after receiving aggressive antiplatelet therapy.

METHODS

We prospectively audited 91 consecutive patients who underwent CAG during a 7 week period (July - August 2003) at the London Chest Hospital. Patients undergoing concomitant valvular surgery were excluded (n = 2). The study population included patients who had previous cardiac surgery as well as patients undergoing emergency procedures. The 89 remaining patients were further sub-divided (table 1) into those who were exposed to clopidogrel therapy within 7 days of surgery (n = 2), both aspirin and clopidogrel within 7 days of surgery (n = 12), aspirin alone (n = 65) and those exposed to neither agent (n = 10).

Table 1. Proportion of patients receiving aspirin and/or clopidogrel

	n	(%)
Aspirin	65	(74)
Clopidogrel	2	(2)
Aspirin and Clopidogrel	12	(13)
No Aspirin, no Clopidogrel	10	(11)

The groups were assessed for incidence of known predictors of peri-operative transfusion including baseline haematocrit, advanced age, low body weight and female gender. The primary measure of postoperative bleeding assessed was 24 hour chest drain output. Transfusion quantity was also recorded. Both the proportion with blood product exposure and the amount transfused in each group was assessed for each of the four principal blood products (packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate).

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Mean differences between the groups were analysed using the student t test. Dichotomous variables are expressed as percentages. Proportional differences were analysed using the Fisher exact chi-squared analysis. A p value of < 0.05 was considered as statistically significant.

RESULTS

Table 1 shows the proportion of patients receiving aspirin and/or clopidogrel or neither. The largest group received aspirin only. All but 2 of the patients who received clopidogrel were also taking aspirin. As the clopidogrel-only group was small, it was excluded from further analysis. All groups were comparable in age, gender, body weight and preoperative baseline haematocrit levels (Table 2). All CAG surgery was performed on cardiopulmonary bypass.

Table 2. Baseline patient demographic details

	Clopidogrel and aspirin (n=12)	Aspirin (n=65)	No aspirin no clopidogrel (n=10)
Age (yrs)	66.8 ± 6.4	65.0 ± 0.91	67.1 ± 9.9
Female (%)	16.7	27.7	0
Haematocrit	0.39 ± 0.03	0.39 ± 0.04	0.38 ± 0.03
Body wt (kg)	80.0 ± 10.8	77.2 ± 18.0	71.4 ± 20.4

The clopidogrel and aspirin group had a lower mean chest drain output at 24 hours post CAG compared with both the aspirin alone and non-clopidogrel non-aspirin groups, although these differences were not statistically significant (table 3 and figure 1). Both the aspirin and clopidogrel and the aspirin-only groups received blood products more frequently when compared to the non-clopidogrel non-aspirin group (figure 2). Also the mean number of units transfused per patient was greater (figure 3). No group received cryoprecipitate at any stage.

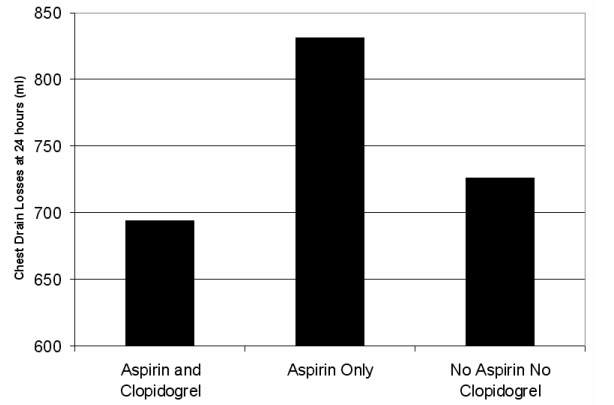

Figure 1. Chest drain losses in the first 24 hours post coronary bypass surgery in the aspirin plus clopidogrel, aspirin and no-aspirin no-clopidogrel groups

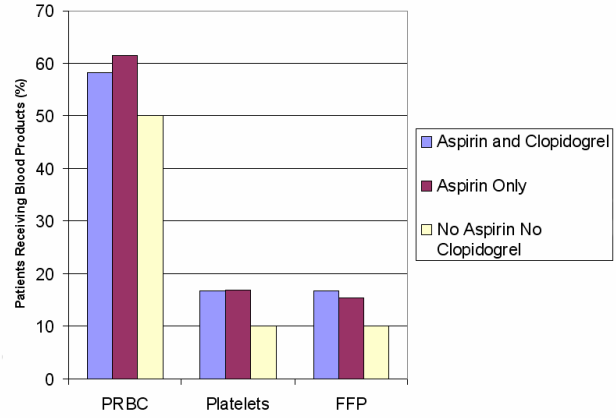

Figure 2. Percentage of patients receiving in the first 24 hours post coronary bypass surgery packed red blood cells (PRBC), platelets and fresh frozen plasma (FFP) in the aspirin plus clopidogrel, aspirin and no-aspirin no-clopidogrel groups.

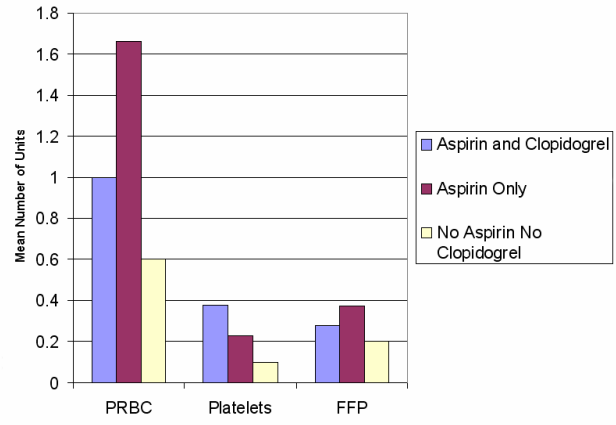

Figure 3. Mean number of units in the first 24 hours post coronary bypass surgery of packed red blood cells (PRBC), platelets and fresh frozen plasma (FFP) in the aspirin plus clopidogrel, aspirin and no-aspirin no-clopidogrel groups.

Consistent with the highest mean blood loss, the aspirin group was transfused with more packed red blood cell units compared with the other groups (Figures 2 and 3). Again, these differences were not significant. Overall, the frequency and amount of blood product transfusion in those patients who were not receiving aspirin or clopidogrel preoperatively was lower than for those receiving clopidogrel and/or aspirin. However, in all groups the frequency and mean amounts of blood products transfused were low.

DISCUSSION

The benefits of clopidogrel and aspirin in those patients with recurrent ischaemic cardiac events are well established. This has to be balanced with the risks of increased bleeding post-CAG. Additionally, aortocoronary grafts have a significant rate of acute thrombotic occlusion. The graft patency rate has been quoted as 77 - 90% within the first few months.[5] Aspirin therapy started after CAG, improves early graft patency along with an improved survival advantage. Initially there were the same concerns regarding preoperative aspirin exposure and bleeding postoperatively as there is now with clopidogrel. More recent studies have disproved these initial concerns with aspirin and preoperative aspirin is now believed to decrease mortality in CAG patients.[6]

In this audit, patients exposed to preoperative clopidogrel and/or aspirin received more platelets per patient when compared with the other groups. We believe that this reflects a policy of caution, where it is presumed that a patient who has had clopidogrel preoperatively will require allogenic platelet transfusion. However, the group receiving clopidogrel in addition to aspirin did not receive more blood products than the group with aspirin alone. Perhaps, of greater clinical significance is the finding that the clopidogrel and aspirin group did not demonstrate a significant increase in postoperative bleeding, although this group did appear to receive blood product transfusions more frequently.

Our study appears to be at odds with the findings of previous investigations. Hungo's study of 224 patients undergoing elective CAGs showed no difference between those who received aspirin alone and those receiving neither.[7] However, in those continuing clopidogrel as well as aspirin for 7 days (or less) prior to CAG, there were higher chest drain losses, and a greater number of transfusions of PRBC and other blood products. Yende's study of 245 CAG patients found the effect of aspirin to be intermediate between that of the aspirin/clopidogrel combination and having neither.[8]

It is possible that the differences between these studies and our findings could have been caused by variations in anaesthetic and surgical techniques or local

Table 3. Post-coronary artery bypass blood loss and blood product transfusion requirements

	Clopidogrel and Aspirin (n=12)	*Aspirin (n=65)*	*p value*	*No Aspirin or Clopidogrel (n=10)*	*p value*
Chest drain output in 24 hours (mL)	694.4 ± 373.6	831.9 ± 490.0	0.34	726.0 ± 437.7	0.85
Patients transfused PRBC (%)	58.3	61.5		50.0	
Mean number of units PRBC transfused	1.0 ± 1.28	1.67 ± 2.07	0.29	0.6 ± 0.70	0.39
Patients transfused platelets (%)	16.7	16.9		10.0	
Mean number of units platelets transfused	0.38 ± 0.83	0.23 ± 0.56	0.41	0.10 ± 0.32	0.33
Patients transfused FFP (%)	16.7	15.4		10.0	
Mean number of units FFP transfused	0.28 ± 0.60	0.38 ± 1.0	0.74	0.20 ± 0.63	0.63
Patients transfused cryoprecipitate (%)	0	0		0	

p value is derived for aspirin group and no-aspirin, no clopidogrel group compared with Clopidogrel and aspirin group

availability and indications for transfusion. Certainly, from the inverse relationship between the amount of blood lost and platelet exposure we speculate that the enthusiastic prophylactic transfusion of platelets in those with pre-operative clopidogrel exposure may have contributed to the lower blood losses in this group.

A significant limitation in our work was the introduction of bias. As with any audit, the patients included in our study were not randomised. These patients were selected by cardiologists prior to angiography, and so unrecognised confounding factors exist which individually may effect surgical outcome. Also, the staff involved in caring for patients throughout the perioperative period are not blinded to clopidogrel or aspirin exposure, again allowing for the introduction of bias. A further source of bias may be due to our intermittent use of aprotinin to reduce postoperative blood loss.[9,10] Unfortunately, this could not be considered in our audit as its use was dependent on surgical choice.

The optimal management of patients presenting for CAG surgery who have previously received clopidogrel is still unknown. In the CURE study, patients who stopped taking clopidogrel within 5 days of CAG had a trend towards increased bleeding when compared with those receiving placebo. Current practice describes the cessation of clopidogrel 7 days prior to elective CAG surgery, except if the benefit of the antiplatelet effect outweighs the risk of perioperative bleeding. For an elective case, it would be prudent to delay surgery and wait for the 7 day period to elapse. However, if a patient required urgent bypass grafting or had unstable anginal symptoms, then clopidogrel should be continued regardless of timing of surgery.

CONCLUSIONS

Our audit suggests that the continuation of aspirin in the 7 days prior to CAG surgery is associated with higher postoperative bleeding and morbidity. However, this increased bleeding tendency did not appear to result in a clinically significant increased requirement for allogenic blood product transfusion. It is difficult to comment on the effect of clopidogrel, even when in combination with aspirin, due to the low numbers of patients receiving clopidogrel in our audit As a result, we have continued to allow patients with unstable angina to continue aspirin and clopidogrel until their surgical revascularisation, with a view to better preservation of the myocardium.

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