Pre-operative strategies on clopidogrel use in coronary artery bypass grafting

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Abstract

There is a lack of standards pertaining to stopping antiplatelet agents in patients with acute coronary syndromes prior to coronary surgery. We conducted a national survey of all centres performing cardiac surgery in the UK and Ireland into practices and standards in relation to clopidogrel and aspirin before coronary artery surgery (n=36).

The response rate was 89%. The majority of centres used combination antiplatelet therapy in either some or all pre-operative acute coronary syndrome patients (79%). Aspirin alone is given in 19% of this surgical subpopulation. Aspirin is stopped 4.9 ± 0.5 days (mean ± SEM) and clopidogrel 6.5 ± 0.5 days prior to surgery. There are no clear departmental policies in most cases (21 of 32 units) regarding cessation of clopidogrel. A subjective increase in bleeding was reported in 69% of centres; in 15 centres (47%) patients had returned to theatre for bleeding.

Many units in the UK still do not have a policy regarding antiplatelet therapy in those patients with acute coronary syndromes who are awaiting coronary bypass surgery. A randomised controlled trial is probably the correct way of evaluating the best strategy on use and omission of aspirin and clopidogrel in this setting.

Key words: clopidogrel, acute coronary syndrome, coronary surgery, morbidity.

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Introduction

Antiplatelet treatment for patients with stable and unstable angina is now established. The last few years have seen a change in practice in the management of patients with acute coronary syndromes. Since the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial was published, a change towards double antiplatelet treatment as a preventative measure for myocardial infarcts has found increasing popularity in patients with acute coronary syndrome.[1] In this study, patients were randomised to aspirin plus clopidogrel or aspirin plus placebo within 24 hours after onset of chest pain. Patients who received clopidogrel had an increased incidence of major (9.6% *vs.* 6.3%) and minor bleeding (5.1% *vs.* 2.4%) if the clopidogrel was stopped less than five days prior to surgery. In this subset of patients who had undergone surgery, the majority of the bleeding sites were found to be mediastinal.

Clopidogrel inhibits platelet aggregation in two ways. After activation by cytochrome P450-mediated hepatic metabolism, it selectively and irreversibly inhibits platelet aggregation by preventing ADP-mediated activation of the glycoprotein (GP) IIb/IIIa complex, the final common pathway for platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover. After five days 96% of the compounds, which are plasma-protein bound, are excreted in the urine and faeces.[2]

The effect of clopidogrel on bleeding was also assessed in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.[3] With a single antiplatelet agent strategy, clopidogrel showed a tendency to reduction in bleeding complications (1.8% *vs.* 2.2%) but this did not reach significance (p=0.059).

A prospective observational study published recently which looked at the effects of bleeding after coronary artery bypass surgery showed that 10.4% of patients receiving both aspirin and clopidogrel had re-explorations for bleeding, as compared to 2.3% of those receiving aspirin alone.[4] There was also an increased transfusion requirement in those patients on combination therapy.

Another study published recently looked at patients who had been given clopidogrel and aspirin before elective non-urgent percutaneous coronary intervention, to prevent stent thrombosis, and who had been found to have surgical disease on angiography.[5] Patients who had been exposed to clopidogrel within seven days of surgery had a 10-fold increase in re-operations for bleeding after coronary artery bypass compared to controls. Moreover, they also had a higher mean 24-hour chest drain out-

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put, more transfusions and a lower rate of extubation within eight hours after surgery.

A recent case report in a patient on aspirin and clopidogrel who underwent an elective repair of an abdominal aortic aneurysm described diffuse bleeding, need for numerous blood transfusions and eventual death due to multiple organ failure.[6]

Nevertheless, many cardiac surgeons are forced to operate on these patients as many unstable angina patients present themselves to the surgeon while taking this combination of antiplatelet drugs. Because of lack of clear standards pertaining to stopping antiplatelet agents, we conducted a national survey of all the centres performing cardiac surgery in the UK and Ireland into current practices and standards in relation to clopidogrel and aspirin use prior to coronary artery bypass grafting (CABG).

Methods

A questionnaire was sent by post to one representative from each of the centres performing cardiac surgery in the UK and Ireland (n=36).

The following seven questions were asked:

a). Do the cardiologists in your centre follow CURE trial evidence and prescribe clopidogrel and aspirin for patients with recent acute coronary syndrome, even if requiring CABG?
b). Do your cardiologists prescribe aspirin and clopidogrel simultaneously pre-operatively?
c). How many days prior to surgery do you stop aspirin? Is this a personal or a Unit policy?
d). How many days prior to surgery do you stop clopidogrel? Is this a personal or a Unit policy?
e). Have you had a subjective increase in bleeding peri-operatively in those patients who had been on both?
f). Are you aware of patients on this combination of medication needing to undergo re-sternotomy for bleeding?
g). Do you currently use clopidogrel post-operatively following CABG?

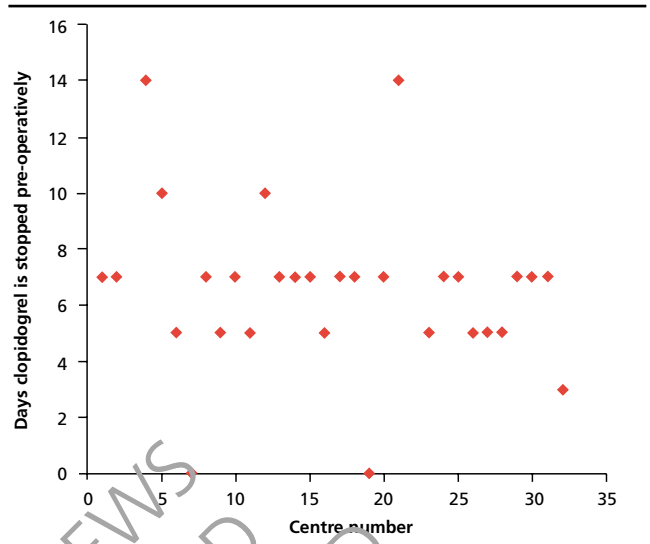
Results

The overall response rate was 89% (32 centres). In two centres, CURE trial evidence was not employed. Clopidogrel alone was used in one centre and in another centre it was felt that there was not enough evidence for combination therapy in unstable angina.

Patients who are on the in-patient waiting list for urgent surgery receive combination therapy in 12 out of 32 institutions (38%). In 13 out of 32 centres (41%) only a proportion of this type of patients, varying between 10% and 75%, receives combination therapy and six institutions (19%) use aspirin as monotherapy in these situations. The predominant reported reason for not giving clopidogrel in addition to aspirin pre-operatively is that it had been agreed between surgeons and referring cardiologists that patients who are awaiting surgery would not be given clopidogrel.

Aspirin is stopped 4.9 ± 0.5 days (mean ± SEM) (range 0–10 days) and clopidogrel is stopped 6.5 ± 0.5 days (range 0–14 days) prior to surgery (see figure 1). It is a Unit rather than personal policy that there should be a period before surgery during which aspirin is stopped in 18 of the 32 respondents, and for clopidogrel in 11 of the 32 respondents.

Figure 1. Scattergram of the minimum number of days that clopidogrel is stopped prior to surgery in centres across the UK



Twenty-five of the 32 centres (79%) use combination therapy in all or some of their unstable angina patients. A subjective impression of an increase in bleeding was reported in 22 of these centres (69%). In 15 centres (47%) patients had gone back to theatre for bleeding if they had been on both antiplatelet agents. It was reported that chests had been packed on numerous occasions in several centres, and in one centre a patient had died on the third post-operative day of multiple organ failure related to massive blood transfusions. It was observed that this patient was still bleeding four hours after he died. Some centres responded that where patients are on combination therapy prior to surgery, use of aprotinin during surgery is standard; other centres use prophylactic peri-operative platelet transfusions.

When asked if clopidogrel is used post-operatively, the majority (91%) of centres answered that they still use aspirin as their standard post-operative antiplatelet agent. Two centres use clopidogrel as their standard antiplatelet agent and one centre uses a combination of aspirin and clopidogrel. In 13% of centres clopidogrel would be used as an alternative to aspirin if patients are aspirin-intolerant. Some of the centres (16%) would also consider using clopidogrel if the coronary vessels are small and badly diseased.

Discussion

Diversity in the management of patients with unstable angina still exists in the UK and Ireland. Not all patients are prescribed CURE evidence-based combination therapy. When unstable angina patients awaiting surgery receive antiplatelet therapy,

Key messages

- Since publication of the CURE trial, double antiplatelet therapy for acute coronary syndromes has become more popular
- There is a lack of consensus about stopping antiplatelet agents before cardiac surgery
- A randomised controlled trial is probably the correct way of working out the best strategy for these patients

there is controversy about whether and when to stop clopidogrel or even aspirin. As we have described, many of the units in the UK still do not have a policy regarding patients on antiplatelet therapy, which might cause significant delay in treatment and inefficient use of resources because of cancellation and is associated with significant post-operative complications. Given the increasing use of different antiplatelet agents for the treatment of acute coronary syndromes, clinicians should be aware of the increased risk of bleeding in patients taking these agents who undergo emergency and urgent CABG.

Even though the response rate of the questionnaire was relatively good, the influence of the 11% non-responders on the overall conclusion could have been quite large. Nevertheless, the general body of opinion amongst surgeons still seems to be that there is uncertainty regarding pre- and peri-operative management of patients on clopidogrel, and this is mirrored by the diversity of opinions. This study was not designed to assess qualitative or quantitative outcome, but rather to assess general opinions and approaches to this clinical problem.

The product literature from the manufacturer still seems to be unclear about how long clopidogrel should be stopped prior to surgery. It advises at least seven days, but also states that after eight days of treatment the effects on clotting time have returned to baseline.[2] CURE showed that in the subset of patients in whom clopidogrel was stopped at least five days prior to surgery, there was no apparent excess in major bleeding.

A randomised controlled trial is probably the correct way of looking at the best strategy regarding aspirin and clopidogrel use and discontinuation prior to coronary surgery, although from our survey it would appear that there is a large body of opinion amongst surgeons that these antiplatelet agents in combination should be discontinued if possible prior to surgery. The limited evidence available would seem to suggest that a period of at least five days should be enough before surgery in unstable patients. With patients who are too unstable to wait for five days, there is no evidence to guide the best management of their clotting.

References

1. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494-502.
2. Jarvis B, Simpson K. Clopidogrel. A review of its use in the prevention of atherothrombosis. *Drugs* 2000;**60**:347-77.
3. Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Reduction in the need for hospitalisation for recurrent ischaemic events and bleeding with clopidogrel instead of aspirin. *Am Heart J* 2000;**140**:67-73.
4. Yende S, Wunderink RG. Effects of clopidogrel on bleeding after coronary artery bypass surgery. *Crit Care Med* 2001;**29**:2271-5.
5. Hongo RH, Ley J, Dick SE, Yee RR. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol* 2002;**40**:231-7.
6. Chapman TWL, Bowley DMG, Lambert AW, Walker AJ, Ashley SA, Wilkins DC. Haemorrhage associated with combined clopidogrel and aspirin therapy. *Eur J Vasc Endovasc Surg* 2001;**22**:478-9.