

## CLOPIDOGREL AND SURGERY: "BE AWARE"

Liyanage C A H<sup>1</sup>, Jayaweera K K D G<sup>2</sup>, Deen K I<sup>3</sup>

<sup>1</sup>Lecturer, <sup>3</sup>Professor of Surgery, Department of Surgery, University of Kelaniya Medical School, <sup>2</sup>Transfusion Medicine Specialist, Asiri Surgical Hospital.

### Abstract

**Introduction:** Clopidogrel has been used more recently to prevent thrombosis in occlusive arterial disease. It is known that clopidogrel increases bleeding during surgery. We performed a questionnaire survey of surgeons in Sri Lanka regarding their experience with clopidogrel.

**Objectives:** To share the experience of surgeons from diverse fields regarding surgery on patients on clopidogrel.

**Method:** A retrospective descriptive study was performed using a questionnaire.

**Results:** 48 completed questionnaires were received. 21 (44%) Surgeons reported complications relating to clopidogrel. Spontaneous haemorrhage was reported by 8, which manifested as ecchymotic patches in the majority. Most surgeons 36 (75%) preferred aspirin over clopidogrel and 10 (21%) opted for clopidogrel. The majority recommend stopping of clopidogrel at least for 14 days. However, the opinions of the rest varied from 7 to 28 days.

**Conclusions:** Surgeons felt clopidogrel has the potential to cause complications following surgery. Majority were of the opinion that it is safe practice to stop clopidogrel for at least 14 days which is more than the 5 days recommended by the formularies. A significant majority were comfortable to have the patient on aspirin compared with clopidogrel.

### CAH Liyanage

Lecturer, Department of Surgery, University of Kelaniya Medical School, Sri Lanka.

### KKDG Jayaweera

Transfusion Medicine Specialist, Asiri Surgical Hospital, Sri Lanka.

### KI Deen

Professor of Surgery, Department of Surgery, University of Kelaniya Medical School, Sri Lanka.

Corresponding author:

C A H Liyanage

Tel: 0777 749459

E-mail: chandikaliyanage@hotmail.com

### Introduction

Clopidogrel has been used to prevent thrombosis in occlusive arterial disease. It is a thienopyridine

which inhibits platelet function by non-competitive inhibition of the P2Y<sub>12</sub> ADP surface receptor (1). Like aspirin, the antiplatelet effect persists until new platelets are produced and aggregatory responses return to normal after about 7 days (2). It is also postulated that prolonged use of clopidogrel would result in derangements of clotting similar to that of acquired haemophilia (3). With the increase in prescribing clopidogrel in Sri Lanka, it is likely that patients awaiting surgery may be taking clopidogrel. Oversight in a patient taking clopidogrel, having surgical intervention, may result in catastrophic haemorrhage, more than is associated with aspirin (4). Furthermore when aspirin is taken with clopidogrel, this combined effect is often summative (5). The risk of bleeding must be balanced against the risk of an atherothrombotic event when considering stopping of clopidogrel prior to surgery.

We undertook a study to gather experience amongst Sri Lankan surgeons regarding the use and adverse effects of clopidogrel.

## Objectives

The objectives of our study were to gather an audit of morbidity and mortality in patients on clopidogrel, to assess surgeons' preference of antiplatelet therapy in the perioperative period and enquire about when individual surgeons preferred cessation of clopidogrel therapy before surgical intervention.

## Methods

A questionnaire to gather information from surgeons on their personal experience on the use of clopidogrel in surgery was administered. Surgeons were requested to report their experience of clopidogrel related adverse events at surgery. The cohort included the membership of the College of Surgeons, the Surgeons in the government and private sector hospitals.

## Results

Of 76 questionnaires 48 were completed and returned (63%). Between 2006 to 2007, 21 (44%) surgeons reported complications, which were related to clopidogrel without a reasonable degree of doubt. These included spontaneous bleeding, intra- and post-operative haemorrhage and 6 deaths (Table 1). Surgeons also reported adverse haemorrhagic complications in their patients after interventional radiological procedures.

Spontaneous haemorrhage was reported by 8 which manifested as ecchymotic patches in the majority. The incidence of bleeding was experienced in almost all types of specialties in surgery. However, deaths were reported in gastrointestinal, urological, neurosurgical, orthopaedics and in interventional radiology. The mortality of 6/65 (9.23%) was associated with a bleed in which without a reasonable doubt could be attributed to the use of clopidogrel. When questioned on the safety, most surgeons (36, 75%) preferred aspirin over clopidogrel where anti-platelet therapy was

required. Ten, (21%) opted for clopidogrel. The majority recommended stopping clopidogrel at least 14 days before surgery. However, the opinions of the rest varied from 7 to 28 days.

**Table. Cumulative number of incidents reported**

Specialty	Haemorrhage	Deaths
General surgery	23	0
Vascular	4	0
Transplantation	1	0
Cardiothoracic	9	0
Gastrointestinal	3	1
Urology	7	1
Orthopaedics	3	1
Neurosurgery	4	1
Interventional radiology	8	2
TOTAL	65	6

## Discussion

When clopidogrel set its foot in Sri Lanka many physicians embraced it because of its probable gastric protection compared to aspirin. Hence more and more now, and in future, will prescribe clopidogrel in athero-thrombotic occlusive arterial diseases. Through years of experience in its use, the effect on aspirin is more predictable in surgical patients. However, anecdotal experience amongst fellow surgeons from diverse specialties suggested that clopidogrel had unpredictable outcomes especially in the post-operative period.

We had a response rate of 63% which included replies from almost all subspecialties in surgery and from the general surgeons. It is interesting to note that there were 8 reports of spontaneous haemorrhage. This was mainly as ecchymotic patches and also included gastrointestinal bleeding and haematuria. 65 events of clopidogrel related

bleeds amongst 48 surgeons in a span of one year and 6 deaths clearly indicate the gravity of this situation. Deaths were more frequent in surgeries where small volume of bleeding could cause disastrous complications, as in neurosurgery and bleeding from organs where haemostasis is difficult like in the genito-urinary system and the solid organs. In Sri Lanka the incidence of road traffic accidents is rapidly increasing (6) as are the admissions to the Neurosurgical Department of the National Hospital of Sri Lanka (7). Emergency operations on patients already on clopidogrel after road traffic accidents would result in increased morbidity compared to current projections (8).

The major side-effect of antiplatelet therapy is haemorrhage. The risk of bleeding must be balanced against the risk of an atherothrombotic event. There is no doubt that clopidogrel is an effective drug. However, it is interesting to note the following trials on its clinical implications.

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study compared the efficacy of aspirin against clopidogrel over 1-3 years (9). Clopidogrel would be expected to prevent 24 vascular events for every 1000 patients treated over 1 year whereas aspirin would prevent 19. Severe gastrointestinal haemorrhage was slightly more common in the aspirin-treated group (0.49 versus 0.71 per cent;  $P < 0.050$ ).

The combined use of aspirin and clopidogrel has an additive antiplatelet effect but clinical effectiveness depends on the precise indications. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial compared aspirin and clopidogrel with aspirin alone (5). No overall reduction in ischaemic stroke, myocardial infarction or vascular death was noted with dual therapy compared with aspirin alone (6.8 versus 7.3 per cent; RR 0.93 (95 per cent c.i. 0.83 to 1.05)). However, there was a significant increase in moderate bleeding (requiring transfusion) with clopidogrel (2.1 versus 1.3 per cent;  $P < 0.001$ ).

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study examined the effect of addition of clopidogrel to standard therapy, including aspirin, in patients with non-ST segment elevation acute coronary syndrome (10). The risk of stroke, myocardial infarction or vascular death was 9.3 per cent in the dual-therapy group and 11.4 per cent in the aspirin group (RR reduction 20). However, this was at the small cost of significantly increased major bleeding in the clopidogrel group compared with aspirin alone (3.7 versus 2.7 per cent;  $P = 0.001$ ).

The above is evidence to the higher risk of bleeding associated with clopidogrel use. It is beyond the scope of this article to suggest that aspirin is better than clopidogrel, except to say, that prescription of clopidogrel should be done with responsibility and with properly laid down protocols. But the participating surgeons were more in favour of aspirin as they felt that aspirin induced bleeding was less severe and manageable.

The duration of cessation of clopidogrel, like aspirin, depends on the antiplatelet effect of the drug which persists until new platelets are produced and aggregatory responses return to normal. This usually takes about 7 days (2). The recommendation in the formularies is to stop clopidogrel about 5 days prior to the intervention. But the majority of the surgeons were of the opinion that clopidogrel should be omitted at least for 2 weeks.

## **Conclusion**

Clopidogrel was associated with haemorrhagic complications in 65 patients in this limited survey of surgeries from the years 2006 to 2007. The mortality associated with such haemorrhage is likely to be around 9%. The recommendations for patients using clopidogrel in the perioperative period would be withdrawal of therapy, use of platelet function studies to assess suitable timing of surgical or radiological intervention, to be aware of the need of platelet transfusions to facilitate clotting in the perioperative period and in high risk patients, to consider alternative anticoagulants such as low molecular weight heparin.

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