Outcome after Percutaneous Coronary Intervention (PCI)

Is a shortened (14-day) course of clopidogrel after successful coronary artery stenting appropriate?

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ABSTRACT

This study aimed to retrospectively investigate the outcome of 1000 patients after a successful coronary artery intervention and evaluate the appropriateness of a 14-day clopidogrel therapy after the procedure. Participants' data was obtained using two hospital databases, 'Oracare' and 'Cardiobase' and analysed using Microsoft Access and Excel. This study found that there was not a significant increase in clinical event occurrence after a 14-day clopidogrel therapy. As part of this study, a database containing demographic and clinical details of 1000 patients who had PCI with stenting was created. This database will provide the base or comparison for future research.

Ever since the first percutaneous coronary intervention (PCI) was done in 1977, there have been many advances in PCI technology and it was postulated that one day it might extinguish the need for coronary artery bypass surgery. PCI is a minimally invasive interventional procedure that unblocks narrowed coronary arteries through balloon dilatation or other instruments in the artery. While interventional treatment will vary from patient to patient, currently the majority of PCI procedures involve coronary artery stenting. During stenting a small, latticed, metal tube is placed against the artery wall by balloon expansion to scaffold it open following plaque disruption. Stents substantially increase procedural safety and success and reduce the need for emergency coronary artery bypass surgery by reducing restenosis to very low rates (with the latest generation of drug-eluting stents).[1]

The coronary plaque disruption, which follows PCI, activates platelets and coagulation pathways, which play an integral and complex role in the process of thrombosis. Platelets adhere to collagen and von Willebrand Factor at the site of disruption and result in an initial platelet monolayer. After activation, secondary agonists like thromboxane A2 (TXA2) and adenosine diphosphate (ADP) are released. Combined with thrombin generated from the coagulation cascade, these molecules mediate the stimulation and recruitment of more platelets. Because of this, it is not surprising that anti-platelet therapy is vital to the management of patients undergoing PCI.[2]

Aspirin is an anti-platelet agent which inhibits the production of TXA2 by irreversibly acetylating cyclooxygenase (COX). Despite the efficiency of aspirin in reducing adverse events in a variety of ischemic heart disease states, many patients still experience adverse events. Thus, more potent anti-platelet agents have been developed and used. Clopidogrel is an oral anti-platelet agent of the thienopyridine class, which selectively and irreversibly inhibits the platelet ADP receptor. By blocking this receptor, clopidogrel interferes with platelet activation, degranulation and aggregation. When it is given with aspirin, the anti-platelet effect is synergistic.[3,4] A proportion of these patients, for whom clopidogrel did not achieve its pharmacological effect, are classified as having 'clopidogrel resistance'. Patients who are resistant to clopidogrel are more likely to develop complications after PCI.[5]

Following PCI, continuation of dual anti-platelet therapy (aspirin and clopidogrel treatment) for at least nine months instead of two to four weeks, leads to a reduction in major thrombotic events. [4,6] Apart from that, further platelet inhibition can be achieved by increasing clopidogrel dosage beyond currently recommended loading and maintenance doses.[7] These findings may be useful in the management of diabetic patients, who have a higher mortality and adverse event rate following PCI compared to non-diabetic patients.[8]

Worldwide, four weeks of clopidogrel treatment has been accepted as the mainstream management of patients who had a successful PCI with stenting. However, this costly drug is not funded in New Zealand. In Dunedin, the local health board subsidises the use of clopidogrel for two weeks following PCI. While the proposed study was observational and does not compare outcomes following four weeks of clopidogrel treatment with two weeks' treatment, our aim was to retrospectively explore whether there is a significant increase in event occurrence rates after two weeks of clopidogrel therapy in patients who have had a successful stent implantation. We hypothesised that there will be an increased event occurrence rate two weeks after PCI. Since no literature to date documents the outcome of patients who went through a successful PCI with stenting in New Zealand,

we also hoped to create a database through our analysis, which future research can be based on or compared with.

METHODS

The outcome of 1000 consecutive patients who had a successful PCI with stenting done in Dunedin Public Hospital from February 2000 to October 2003 were reviewed. The participants resided in Otago and Southland and were under the care of the Cardiac Department of Dunedin Public Hospital. They came forward for PCI due to problems with coronary artery disease.

Utilizing the clinical database system Cardiobase used in the Department of Cardiology in Dunedin Public Hospital, a list of patients who had a PCI from 2000 to 2004 was generated. From the list, the first 1000 patients who had a successful PCI were selected. To be included in the analysis, participants had to have one or more successful stent implantations in the PCI procedure. However, it did not have to be the patient's first stent implantation or PCI procedure. An additional hospital patient management database, Oracare, was used to find out more about the participants' demographics and readmission details after their PCI procedure. Patients were not identified through their name but through their National Health Index (NHI) number.

From the Oracare database, information about the gender and ethnicity of the 1000 participants was collected. The Oracare database was also used to ascertain whether the participants were deceased, had risk factors (hypertension, diabetes, hyperlipidaemia and smoking), had an event following PCI (time of event and what it was) and whether they had a previous myocardial infarction (MI) or coronary artery bypass surgery (CABG). An event is classified as cardiovascular-related death, myocardial infarction, sub-acute stent thrombosis or urgent target-vessel revascularisation through a repeated PCI or CABG. The Cardiobase database was used to identify the participants' primary indication for the PCI procedure, body mass index (BMI), procedural details (number of diseased vessels, number of treated vessels, complications), drug regimes (dosage of clopidogrel, heparin and Gp IIb/IIIa receptor antagonist), time from the PCI procedure to November 2004 and whether they had clinical restenosis.

The information collected about the 1000 participants from the Oracare and Cardiobase databases was recorded using Microsoft Office Access 2003. Microsoft Office Excel 2003 was used to analyse the data. The angiographic data for patients who had an event within the first 70 days was reviewed to exclude database errors and to establish further information (detailed clinical outcome and coronary vessel details).

Table 1: Baseline demographic, clinical and procedural characteristic

	Timing of event (days after PCI) (n=1000)				
	Group 1 (0-14) n=17	**Group 2** (15-35) n=3	**Group 3** (36-70) n=11	**Group 4** (>70) n=169	**Group 5** (None) n=800
Age (years)	67.8 ±'b1 12.8	64.1 ±'b1 10.9	62.1 ±'b1 8.8	68.9 ±'b1 11.9	66.1 ±'b1 11.2
Men	13 (76.5%)	1 (33.3%)	7 (63.6%)	114 (67.5%)	552 (69.0%)
White	16 (94.1%)	3 (100.0%)	11 (100.0%)	160 (94.7%)	759 (94.9%)
Previous CABG	3 (17.6%)	0 (0.0%)	4 (36.3%)	27 (16.0%)	70 (8.8%)
Previous MI	2 (11.8%)	0 (0.0%)	6 (54.5%)	53 (31.5%) (n=168)	244 (30.5%)
Systemic Hypertension	7 (41.2%)	1 (33.3%)	8 (66.7%)	98 (58.0%)	423 (52.9%)
Diabetes	2 (11.8%)	0 (0.0%)	2 (18.1%)	36 (21.3%)	103 (12.9%)
Smoking - Current	1 (0.1%)	0 (0.0%)	3 (27.2%)	24 (14.2%)	188 (23.5%)
- Ex-Smoker	11 (64.7%)	0 (0.0%)	5 (45.4%)	79 (46.7%)	333 (41.6%)
Hyperlipidaemia	7 (41.2%)	2 (66.6%)	9 (81.8%)	109 (64.5%)	524 (65.5%)
BMI	28.9±'b14.1 (n=10)	28.1±'b10.6 (n=2)	31.9±'b16.1 (n=6)	27.9±'b14.8 (n=105)	29.4±'b111.7 (n=407)
GP IIa/IIIb Inhibitor use	10 (58.8%)	3 (100%)	5 (45.4%)	75 (44.6%) (n=168)	304(38.1%)(n=798)
Heparin Units (1000's)	7.6±'b12.4 (n=16)	6.6±'b12.1	6.4±'b12.3 (n=10)	7.7±'b12.3 (n=166)	7.4±'b12.2 (n=798)
Clopidogrel (weeks)	1.9 ±'b1 0.4	2.0 ±'b1 0.0	2.1 ±'b1 0.3	2.1 ±'b1 0.8	2.1 ±'b1 1.1
Later CABG	2 (11.7%)	0 (0.0%)	4 (36.3%)	35 (20.7%)	0 (0.0%)
Clinical Restenosis	2 (11.8%)	2 (66.6%)	5 (45.4%)	72 (42.6%)	18 (2.3%)
Years from PCI to Nov 05	3.3 ±'b1 1.3	3.9 ±'b1 0.6	3.3 ±'b1 1.2	3.2 ±'b1 1.0	3.0 ±'b1 1.0
No. Deceased at Nov 05	7 (30.4%)	1 (33.3%)	5 (45.4%)	43 (25.4%)	0 (0.0%)

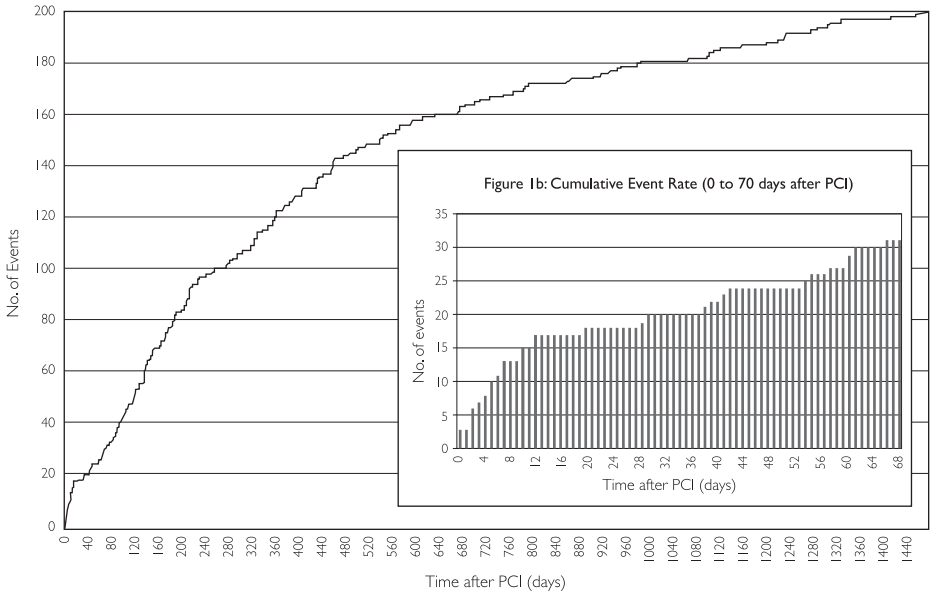
RESULTS

After the demographic and procedural data of the 1000 participants was obtained, it was sorted into five groups: patients who had an event in the first two weeks, an event in the third to fifth weeks, an event in the sixth to tenth weeks, an event after the tenth week and patients who had no event following PCI. The demographic and procedural characteristics of the participants are listed in Table 1 according to their groups.

Of the 1000 patients included in the study, 31 (3.1 per cent) had an event within the first ten weeks. 800 (80 per cent) of the patients did not

Since clopidogrel is a costly drug, more resources could potentially be allocated to other services to provide better patient care if a 14-day therapy is sufficient after PCI.

Figure 1a: Cumulative Event Rate (0 to 1470 days after PCI)



have an event after their PCI procedure. 68.7 per cent of the patients were men and 94.9 per cent were of European descent. The mean BMI of the study participants was 29.1 (n=530). The mean time between the participants' PCI procedure and the time of data collection was three years. All of the participants were given aspirin therapy indefinitely and clopidogrel therapy for at least two weeks after their PCI procedure. Some of the patients had more than two weeks of clopidogrel because they were in another study or were privately funded. Statistical analyses comparing the different groups were not carried out because of insufficient patient numbers in groups 1, 2 and 3. All the patients underwent PCI with stent implantation following initial angiogram.

Originally, 39 patients were found to have had an event in the first 70 days. However, after revision using angiographic data, it was discovered that eight out of the 39 patients did not have an event. Thus, they were transferred to Group 5. All the events within the first 70 days were either death, myocardial infarction or an acute coronary syndrome. There were 12 deaths in the first 70 days (nine deaths caused by cardiovascular factors, one because of chronic renal failure and two patients did not have an identifiable cause of death). In the first 70 days, nine patients had a myocardial infarction and ten patients had an acute coronary syndrome. Six out of the 31 patients (19.4%) had later coronary artery bypass surgery done on them.

Based on Figure 1a, patients were more likely to have an event within the first few days following their PCI procedure. The risk of them having an event diminishes as time goes by. Figure 1b shows that there is an increase in event occurrence in the first 14 days, which reduces after that for the remainder of the 70 days following PCI. Clopidogrel therapy for most patients ends at 14 days after their PCI procedure. However, no significant increase in event occurrence was documented 15-35 days (n=3 in Group 2) after PCI.

DISCUSSION

The results of the study failed to support the hypothesis that there will be a significant increase in clinical event occurrence after a 14-day clopidogrel therapy. Only three participants (Group 2) had an event 15 to 35 days after their PCI procedure. The initial sharp rise in occurrence rate displayed in the first 14 days following PCI (Figure 1b) suggests that most events resulted from complications after PCI (thrombosis, dissection) or possibly resistance to clopidogrel or aspirin therapy.[2,5]

In the present study, 20 (two per cent) had an event between 0 to 35 days after PCI (Table 1). The CREDO trial, which compared a clopidogrel loading dose versus placebo prior to PCI, showed that at 28 days, 6.8 per cent of patients in the clopidogrel pre-treatment group had an event (death, MI or urgent revascularization) and 8.3 per cent of patients in the placebo group had an event. Patients enrolled in the CREDO trial had 28 days of dual anti-platelet therapy (aspirin and clopidogrel) after PCI.[6]

While it is recognisable that the event occurrence rate is lower in the present study, it is important to note that the CREDO trial was a randomised controlled trial and thus is more conclusive than the present study. It is also important to note the limitations of hospital databases such as Oracare and especially Cardiobase. The information recorded in the Cardiobase database in the Cardiac Department was not complete, not entirely accurate and not reviewed by cardiologists. Angiographic and clinical outcome review showed that 8 out of 39 (20.5 per cent) events in the initial analysis were false. This mistake was corrected.

The present study showed that a 14-day clopidogrel therapy after PCI did not result in a significant increase in event occurrence rate 15 to 35 days after PCI, which supports the decision by the local health board to only subsidise a 14-day clopidogrel therapy following PCI with stent implantation. However, further prospective studies must be done to confirm this finding, such as a randomised control trial comparing the outcome of patients on a 14-day clopidogrel therapy versus a 28-day clopidogrel therapy after PCI. Since clopidogrel is a costly drug, more resources could potentially be allocated to other services to provide better patient care if a 14-day therapy is sufficient after PCI.

By doing the present study, a database containing demographic and clinical details of 1000 patients who went through PCI with stenting was created. Using this database, we can determine the platelet response to clopidogrel treatment in the patients who had an event in the first 35 days through platelet function assays. By doing so, we hope to provide better care to patients who do not respond well to clopidogrel by using other anti-platelet agents, such as oral Glycoprotein IIb/IIIa inhibitors, with the hope that event occurrence rate following PCI will be reduced.

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