A randomized, double-blind, placebo-controlled trial of a COX-2 inhibitor (Rofecoxib) in patients undergoing coronary artery bypass surgery

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Abstract

The endothelium of patients with coronary artery disease shows increased expression of cyclooxygenase-2 (COX-2) during coronary artery bypass graft surgery (CABG) using cardiopulmonary bypass. This, together with serotonin, may lead to coronary microvessel spasm, which potentially, can contribute to myocardial ischemia and injury after surgery. We performed a randomized, double-blind, placebo-controlled trial in patients undergoing isolated CABG to determine whether short-term treatment with a selective COX-2 inhibitor, Rofecoxib (25 mg), given preoperatively and for 5 days after operation, can offer better myocardial protection in patients undergoing CABG by measuring serial cardiac troponin T (cTnT) levels. The study was powered to recruit 150 consecutive patients undergoing isolated CABG but the study was terminated prematurely by the worldwide withdrawal of rofecoxib. There were highly statistically significant increases in cTnT in both groups at each time point (1, 6, 24 and 48 h after onset of cardiopulmonary bypass) compared to preoperative levels. cTnT levels were similar at all post-operative time points between the 2 groups. There is no evidence that short-term treatment with rofecoxib has a myocardial protective effect in patients undergoing CABG. There is also no evidence that its effect is deleterious to the myocardium in patients undergoing CABG.

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1. Introduction

Specific biochemical markers demonstrate that some degree of myocardial injury is an inevitable consequence of cardiac operations [1]. The pathophysiology of operative myocardial injury is complex and results from a combination of direct trauma from surgical manipulation and myocardial ischemia due to inadequacies in cardioprotection and coronary thrombosis, ischemia-reperfusion injury [2], the systemic inflammatory response syndrome [3] and altered vasomotor regulation [4] and coronary artery spasm [5]. Platelet activation occurs at the sites of coronary stenoses and endothelial injury and may be associated with serotonin release [6], which has been implicated in contributing to vasoconstriction in patients with coronary artery disease. Cyclooxygenase (COX)-2 is expressed in the endothelium of patients with coronary artery disease. This expression is enhanced in the reperfusion phase following blood cardioplegia during coronary artery bypass graft surgery (CABG). Consequently, prostaglandin release (likely thromboxane A₂) is stimulated which then activates the contractile response of coronary arterioles to serotonin. This may lead to coronary microvessel spasm, which potentially, can contribute to myocardial ischemia and injury after surgery [7].

The aim of this study was to examine whether short-term treatment with a selective COX-2 inhibitor, Rofecoxib, has a protective effect on the myocardium during CABG by assessing serial measurements of cardiac troponin T (cTnT).

2. Patients and methods

The Hospital Ethics Committee approved this study, and written informed consent was obtained from all patients. This was a prospective, randomized, double blind, placebo-controlled trial performed at the Heart Institute at National University Hospital, Singapore between October 2002 and October 2004. Patients were randomized according to a list of random treatment codes generated by a biostatistician (Y.H.C.) using a block design. Patients were sequentially assigned to pre-packed treatments (Rofecoxib 25 mg or placebo) to be administered orally at least 4 h before CABG and daily thereafter for 5 days.

The inclusion criteria for the study included patients undergoing first-time isolated coronary artery bypass grafting. Exclusion criteria included allergy to COX-2 inhibitors, patients with renal impairment (serum creatinine > 120 μmol/l) or a previous history of peptic ulcer disease.
Our aim was to assess serial measurements of cTnT preoperatively and at 1, 6, 24, and 48 h after the onset of cardiopulmonary bypass. Additionally, postoperative complications were also analyzed. In this study, cTnT levels higher than 3.4 \( \mu \text{g/l} \) 48 h was used to diagnose perioperative myocardial infarction (PMI) [9]. Electrocardiographic criteria for the diagnosis of PMI were based on new Q wave formation, loss of R wave progression or new permanent ST elevation [9]. Associations of categorical outcomes with treatments will be assessed using Chi-square or Fisher’s exact tests with odds ratios presented where applicable. Statistical significance was set at P < 0.05 and Bonferroni adjustment for type I error was performed when multiple comparisons (for each post-operative time point) were carried out. Anticipating a mean (S.D.) clinical difference of 0.1 (0.2) \( \mu \text{g/l} \) for cTnT, 150 subjects (to be randomized equally to placebo or rofecoxib) will be required for a power of 80% and a 2-sided test 5% to achieve a significant result.

3. Result

Between October 2002 and October 2004, there were 264 isolated CABG performed. The trial recruitment process is outlined in Fig. 1. One hundred and fifty-seven patients were not enrolled because of refusal to participate (n = 80 patients), renal impairment (n = 39) and history of peptic ulcer disease (n = 38 patients). One hundred and seven subjects were randomized (53 rofecoxib, 54 placebo). Twelve patients did not complete the study (Fig. 1). A further 19 patients who had undergone coronary endarterectomy and had elevated preoperative cTnT levels were also excluded from further analysis.

As shown in both Tables 1 and 2, the 2 groups were well matched with respect to the characteristics shown. There was 1 death within 7 days in the active group. The patient died of sudden hemorrhage from the proximal anastomotic site of the aorto-saphenous vein graft from sudden severe hypotension on the second postoperative day after an uneventful CABG. The mean number of grafts, internal mammary artery usage rate, cardiopulmonary bypass time, myocardial ischemia time, duration of postoperative ventilation and postoperative hospital stay were not significantly different in the 2 groups. There were also no significant differences in postoperative complications listed in Table 2.

There were highly statistically significant (\( P < 0.001 \)) elevations in cTnT levels in both groups at each time point.
compared to pre-operative levels. However, cTnT levels were similar at all post-operative time points between the 2 groups (Fig. 2). The peak increase in cTnT was at 6 h after onset of cardiopulmonary bypass.

4. Discussion

The use of COX-2 inhibitors in cardiovascular disease has been highly controversial and its safety has been questioned [10]. Rofecoxib, a selective COX-2 inhibitor, has recently been withdrawn after the trial APPROVe (Adenomatous Polyp Prevention on Vioxx) showed an adverse cardiovascular side-effect profile. Another study comparing several pain-relief regimes following CABG noted that adverse cardiovascular events were significantly more common among parecoxib/valdecoxib recipients than among double-placebo recipients [11].

COX-2 is expressed in atherosclerotic vessels but not in normal arteries [12]. Enhanced COX-2 expression by endothelial cells increases the production of prostaglandin I2 (PGI2) over thromboxane A2 (TXA2). Thus, inhibition of COX-2 blocks PGI2 formation without inhibiting platelet-derived TXA2, thereby increasing platelet activation, adhesion, and aggregation with a resultant possibility for thrombosis and ischemic events [13].

Conversely, there is emerging evidence that selective COX-2 inhibition may have a beneficial effect on cardiovascular events in atherosclerosis. There is increased COX-2 expression in atherosclerotic vessels that is localized to macrophages, endothelial cells, and vascular smooth muscles within the atherosclerotic plaque, which play a key role in the development and progression of atherosclerosis. Thus, it has been speculated that selective COX-2 inhibition may reduce vascular inflammation and atherosclerotic progression [12].

During the conception of this study, there were no reports of the ability of Rofecoxib to reduce myocardial injury in CABG. Rofecoxib was chosen in view of its favorable pharmacokinetic profile and, at that time, the only major reported side effects were renal impairment and peptic ulcer disease. Although our trial comprised dataset from only 76 patients, both the groups of rofecoxib and placebo patients are well matched. This, we feel, carries more weight towards the validity of this study. Cardiac troponin T (cTnT) is superior compared to CK-MB for the prediction of myocardial infarction after cardiac surgical procedures [1]. The results of this study show that the profile and magnitude of the responses of cTnT is similar to those described previously in patients undergoing myocardial revascularization with cardioplegia [1]. The most surprising observation in the current study, in view of the recent safety concerns of COX-2 inhibitors, was that rofecoxib did not result in an elevation in biochemical markers of myocardial injury as judged at individual time points, compared to placebo. This is despite the fact that the group receiving rofecoxib comprised more patients who required urgent and emergency operations (Table 1), although this did not reach statistical significance.

Two patients in the rofecoxib group had ECG criteria of PMI whilst there was none in the placebo group. This, however, did not reach statistical significance. These patients had cTnT profiles that were within normal limits in the first 48 h. Both patients had small caliber coronary

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Table 2
Operative and postoperative patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Active group (n=43)</th>
<th>Placebo group (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of grafts</td>
<td>3.7 (1.0)</td>
<td>3.6 (1.0)</td>
<td>0.948</td>
</tr>
<tr>
<td>IMA usage n (%)</td>
<td>36 (83.7%)</td>
<td>27 (81.8%)</td>
<td>0.497</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (min)</td>
<td>115.8 (35.7)</td>
<td>116.8 (28.0)</td>
<td>0.893</td>
</tr>
<tr>
<td>Myocardial ischemic time (min)</td>
<td>65.6 (21.2)</td>
<td>70.0 (21.9)</td>
<td>0.381</td>
</tr>
<tr>
<td>Postoperative ventilation (hrs)</td>
<td>11.3 (6.2)</td>
<td>15.1 (23.6)</td>
<td>0.323</td>
</tr>
<tr>
<td>Reoperation for bleeding n (%)</td>
<td>1 (2.3%)</td>
<td>1 (3.0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Deep sternal infection n (%)</td>
<td>1 (2.3%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stroke n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pulmonary prolonged ventilation n (%)</td>
<td>1 (2.3%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>ECG perioperative MI n (%)</td>
<td>2 (4.65%)</td>
<td>0 (0%)</td>
<td>0.502</td>
</tr>
<tr>
<td>Biochemical perioperative MI n (%)</td>
<td>1 (2.3%)</td>
<td>1 (3.0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Atrial arrhythmia n (%)</td>
<td>6 (14%)</td>
<td>4 (2.1%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Postoperative hospital stay (days)</td>
<td>7.1 (4.0)</td>
<td>7.7 (4.7)</td>
<td>0.258</td>
</tr>
<tr>
<td>Mortality n (%)</td>
<td>1 (2.3%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values are mean (S.D.) for quantitative variables.
IMA=Internal mammary artery.
MI=Myocardial infarction.
arteries with diffuse disease and there were intraoperative technical difficulties. This was identified as a possible contributing factor for the PMI. A further two patients (1 rofecoxib and 1 placebo) with elevated cTnT levels of >3. 4 μg/l at 48 h did not have ECG changes of PMI. One patient required revision of a proximal aorto-saphenous anastomosis 2 h after surgery, which may explain the rise in cTnT. There were no ECG changes of PMI possibly as a result of the subsequent improved coronary blood flow following the revision. The second patient underwent an emergency CABG for unstable angina with severe left main stem and triple vessel coronary artery disease. He required intra-aortic balloon pump support for 24 h after surgery and made an uneventful recovery.

A target of 150 patients would have made the data more robust and compelling. We were unable to achieve this because recruitment was low in the year 2003 because of the SARS crisis and the recent withdrawal of Rofecoxib from the market meant that the study had to be terminated. Furthermore, a significant number of patients were unable to complete the study. Due to relatively small patient numbers, any conclusions drawn from our study must be interpreted cautiously because of the possibility that the statistical power may be too small to detect clinically important differences between the groups.

In conclusion, our study found no evidence that short-term treatment with rofecoxib has a myocardial protective effect in patients undergoing CABG. There is also no evidence that its effect is deleterious to the myocardium in patients undergoing CABG.

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References