Postoperative naproxen after coronary artery bypass surgery: a double-blind randomized controlled trial

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Abstract

Objective: Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely used after coronary artery bypass surgery (CABG), yet their effects have seldom been evaluated in randomized controlled settings. The aim of this study was to examine the efficacy and safety of a commonly used NSAID, naproxen. We hypothesized that naproxen would reduce postoperative pain following CABG without increasing complications.

Methods: Patients (N=98) undergoing primary CABG were randomized to receive naproxen (500 mg q12h for 5 doses via suppository started 1 h after operation, followed by oral 250 mg q8h for 6 doses) or placebo. Standard analgesic and anti-emetic regimens were available to both patient groups. Interventions were double-blinded. Primary end-points were postoperative pain measured before and after chest physiotherapy by visual analog scale and pulmonary slow vital capacity (SVC).

Results: Baseline characteristics were equivalent between the two groups. Over the first 4 postoperative days, naproxen decreased pain by 47% on average before chest physiotherapy (P=0.034), and 44% after chest physiotherapy (P=0.0092). Patients who received naproxen also had better preservation of SVC over the first 4 postoperative days (mean loss of SVC from baseline: 2.1 ± 0.1 vs. 2.5 ± 0.1 l, naproxen vs. placebo, P=0.0032). This was concomitant with a lower white blood cell count observed in naproxen patients (9.2 ± 0.3 vs. 12.7 ± 1.5 x 10^9/l, naproxen vs. placebo, P=0.03). Patients who received naproxen had more chest tube drainage after 4 h postoperatively, but there was no difference in the incidence or amount of transfusions. There was no difference in medication use, length of stay, or in the incidence of atrial fibrillation, azotemia, and other complications.

Conclusions: Naproxen is an effective and low-cost adjunct for optimization of pain control and lung recovery after CABG. Its use may result in increased chest tube drainage, but no apparent increase in other complications.

Keywords: Coronary artery bypass surgery; Anesthesia; Postoperative care; Lung physiology

1. Introduction

Inadequate postoperative analgesia has been recognized as a common problem associated with suboptimal patient outcomes [1]. Postoperative pain results in autonomic nervous system stimulation and the release of catecholamines. This can lead to adverse physiologic consequences, such as an increase in myocardial oxygen consumption and a higher likelihood of myocardial ischemia [2]. Furthermore, immobilization and poor inspiratory effort as a result of inadequately controlled pain may increase the risk of thromboembolic [3] and pulmonary complications [4]. Adequate pain control following cardiac surgery is therefore essential not only with respect to patient comfort, but also because of important physiologic benefits.

While opioids provide excellent analgesia, undesirable side effects such as respiratory depression, sedation and nausea constitute major limitations. As a result, many surgical centers use non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen, as analgesic adjuvants. The short-term use of NSAIDs in the perioperative period has been demonstrated to be reliable and safe in carefully
selected patients [5,6]. Compared to other NSAIDs, naproxen has a low cost, may be administered orally or as a suppository in the anesthetized patient, and has been shown to have an acceptable side effect profile in the outpatient setting [7,8].

Although several studies have reported on the use of NSAIDs after cardiac surgery [9–13], their effects have seldom been evaluated in randomized controlled settings, and none have examined the use of naproxen. Therefore, the aim of this study was to examine the efficacy and safety of naproxen in a prospective, double-blind, randomized, controlled trial comparing early naproxen administration with placebo as an adjunct to opioids following coronary artery bypass graft surgery (CABG). The primary end-points of the study focused on postoperative pain and pulmonary function, while the secondary end-points related to safety. We hypothesized that naproxen would reduce postoperative pain following CABG without increasing postoperative complications.

2. Materials and methods

2.1. Patients

This study was approved by the Human Research Ethics Board, and written consent was obtained from each participating patient. Eligible subjects consisted of patients undergoing non-emergency primary multi-vessel CABG on cardiopulmonary bypass, during which the non-skeletonized left internal mammary artery (LIMA) was grafted to the left anterior descending artery and saphenous vein segments were used for other coronary targets. The left pleural space was routinely opened in order to ensure a lateral lie of the LIMA. Exclusion criteria were the following: left ventricle ejection fraction <20%; serum creatinine >130 μmol/l; preoperative use of H2 antagonists, proton pump inhibitors, steroids, NSAIDs (with the exception of ASA), narcotics or illicit drugs; a history of peptic ulcer, liver disease or NSAID allergy; or the inability to provide informed consent for the study. Patients were excluded from further study drug administration in the presence of: low cardiac output syndrome with inotrope and/or intra-aortic balloon pump support for greater than 24 h, recurrent ventricular arrhythmias, intubation for more than 24 h, or a postoperative rise in serum creatinine of more than 25 μmol/l from baseline.

2.2. Anesthesia

All patients enrolled in the study received a standardized anesthesia regimen. Two milligrams of oral lorazepam were administered 2 h preoperatively, followed by 10 mg of intramuscular morphine 1 h before surgery. Anesthesia was induced with 2–5 mg of intravenous midazolam, 0.5–1.0 μg/kg of intravenous sufentanil, 0.6–1.2 mg/kg of intravenous rocuronium, and inhaled isoflurane. Maintenance of anesthesia was achieved with 0.5 μg/kg per h of intravenous sufentanil, 0.5 μg/kg per min of intravenous midazolam, inhaled isoflurane, and intravenous rocuronium as needed. Anti-fibrinolytics were not used.

2.3. Study protocol

Study patients were randomized preoperatively to receive either naproxen or placebo after surgery. An unrestricted randomization schedule was generated using SAS 6.0 software (SAS, Cary, NC). The placebo and naproxen medications were prepared by the hospital pharmacy and appeared identical. Medication administration and data collection was performed in a double-blind manner, such that neither the patient nor the healthcare personnel were aware of the medication assignment. Following surgery, patients received either placebo or naproxen 500 mg rectal suppository within 1 h after arrival in the recovery room. The suppository was repeated every 12 h for a total of five doses. Patients then received oral therapy of either placebo or naproxen 250 mg three times a day for 2 days (total six doses).

In addition to the study medication, a standard analgesic regimen was available to all patients. This included 0.5–4.0 mg/h of intravenous morphine, titrated to effect by the attending intensive care unit (ICU) nurse. Oral analgesia was initiated at the end of postoperative day (POD) one with 1–2 oral tablets of acetaminophen 325 mg plus 30 mg codeine phosphate every 4 h as needed. In patients with codeine sensitivities, oral anileridine 25–50 mg every 6 h was substituted. Peptic ulcer prophylaxis was not used in order to fully evaluate potential gastrointestinal side effects of the study drug. Standard anti-emetic regimens were available to both patient groups.

Packed red blood cells were transfused postoperatively to anemic patients with evidence of hemodynamic instability, poor organ perfusion, or hemoglobin levels below 80 g/l. Platelets in aliquots of 5 units were transfused postoperatively to patients with platelet counts below 60,000/μl, or to patients with active bleeding and platelet counts below 100,000/μl. Fresh frozen plasma, at a dose of 15 ml/kg, was transfused to bleeding patients with an INR > 2.5 regardless of bleeding. Cryoprecipitate, at a dose of 0.25 units/kg, was transfused to bleeding patients with fibrinogen levels less than 1.0 g/l.

2.4. Study endpoints

The primary endpoints of the study were postoperative pain and pulmonary function. Postoperative pain was evaluated using a standard 10-cm visual analog scale (VAS) [14]. Patients were familiarized with the scale preoperatively, and postoperatively, pain was assessed using this scale on days 1–4 at 10:00 h. Pain was assessed prior to the administration of analgesia, both at rest and...
following chest physiotherapy. Postoperative analgesia requirements were recorded, and total opioid consumption was determined by converting oral narcotics to parenteral morphine equivalents (i.e. 10 mg of parenteral morphine being equivalent to 75 mg of oral anileridine and 300 mg of oral codeine).

Pulmonary function was assessed using slow vital capacity (SVC), measured preoperatively and daily after surgery at 10:00 h on postoperative days 1–4 using a Respiradyne® II Plus flow spirometer (Davis and Geck, Markham, Canada). Arterial oxygen saturations on room air were measured with pulse oximetry and recorded daily.

Secondary study endpoints related to safety, including chest tube blood loss, blood product transfusions, wound infection, renal dysfunction and gastrointestinal complications. Other postoperative data collected included inotrope use, the duration of intubation, the incidence of atrial fibrillation, and the use of anti-emetics. Daily postoperative blood work was also obtained including serum creatinine, hemoglobin concentration and white blood cell (WBC) count.

2.5. Statistical analysis

The sample size was determined by considering that a mean difference in VAS pain score of at least 1 point would be clinically important, and that ±1 would correspond to the maximum standard deviation of the VAS scale. Setting a Bonferroni-adjusted α value of 0.0125 (i.e. 0.05/4) to account for repeated measures and a β value of 0.10, a minimum of 42 subjects per group were needed.

Data were imported and analyzed in Intercooled Stata 8 (Stata, College Station, TX). Continuous data are presented as a mean ± standard error of the mean and were compared between groups using a two-sided Student’s t test or a two-sample Wilcoxon rank-sum test for variables determined to be skewed by a 1-sample Kolmogorov–Smirnov test. A Pearson χ² test was used for categorical data. VAS scores and SVC were compared between groups using a two-sided Student’s t test and a one-way analysis of variance (ANOVA) with a Bonferroni multiple-comparison test for overall effect estimates. Statistical significance was set at a P value of <0.05. Analyses were conducted on an intention-to-treat basis. All patients who had received at least one dose of study drug were included in the analysis.

3. Results

3.1. Patients

Ninety-eight patients were randomized (50 naproxen, 48 placebo). Preoperative characteristics and intraoperative data showed no statistical differences between the groups, with the exception of the mean number of grafts performed (Table 1). Nine patients from the placebo group and seven patients from the naproxen group were withdrawn from the study prematurely (Fig. 1). Within the placebo group, patients were withdrawn for the following reasons: one patient suffered a cardiac arrest in the recovery room, one patient experienced a perioperative myocardial infarction, one patient had an elevated baseline creatinine level (115 µmol/l), two patients had excessive chest tube output in the recovery room, and four patients had protocol violations. Of the naproxen patients that were withdrawn, one patient had a prolonged cardiopulmonary bypass time, one patient had a perioperative cerebrovascular accident, one patient had severe anorexia, and four patients had protocol violations.

3.2. Postoperative pain

Patients who received naproxen had significantly less pain before chest physiotherapy over the first 4 postoperative days (mean VAS 1.6 ± 0.1 vs. 3.0 ± 0.6, naproxen vs. placebo respectively, P = 0.034) (Fig. 2). Similarly, after chest physiotherapy, patients who received naproxen had significantly less pain during the first 4 postoperative days (mean VAS 2.2 ± 0.1 vs. 3.9 ± 0.6, naproxen vs. placebo respectively, P = 0.009) (Fig. 3). However, there was no significant difference in pain on POD 4 between patients who received naproxen or placebo (P = 0.76 before chest physiotherapy, P = 0.49 after chest physiotherapy). There was also no significant difference between the two groups in terms of daily opioid consumption or cumulative opioid intake (63.7 ± 4.0 vs. 64.1 ± 4.9 total morphine equivalents in milligrams, naproxen vs. placebo respectively, P = 0.96).

3.3. Pulmonary function

Patients who received naproxen had better preservation of SVC over the first 4 postoperative days (mean loss of
SVC from baseline: 2.1 ± 0.1 vs. 2.5 ± 0.1 L, naproxen vs. placebo respectively, \( P = 0.0032 \) (Fig. 4). This was associated with a significantly lower WBC count on POD 2 (9.2 ± 0.3 vs. 12.7 ± 1.5 \times 10^9/l, naproxen vs. placebo respectively, \( P = 0.03 \)). There was no difference observed in postoperative oxygen saturations between the two groups.

### 3.4. Blood loss and transfusion

Naproxen use was associated with increased chest tube drainage during the initial four postoperative hours (1035 ± 88 vs. 732 ± 107 ml, naproxen vs. placebo respectively, \( P = 0.04 \)). There was however no difference in the incidence of transfusion, or in the amount of blood products administered (Table 2). Patients who received naproxen had a trend towards receiving less platelet concentrates than those who received placebo (0.1 ± 0.1 vs. 1.3 ± 0.6 units, naproxen vs. placebo respectively, \( P = 0.08 \)).

### 3.5. Postoperative complications

There was no difference in the rate of gastrointestinal or renal complications between the placebo and naproxen groups (Table 3). Two patients in each group developed a postoperative upper gastrointestinal bleed (\( P = 0.93 \)). A moderate reduction in serum creatinine was seen postoperatively in both groups compared to preoperative values (\(-7.6 ± 2.4 \text{ vs. } -8.0 ± 2.2 \mu mol/l, \) naproxen vs. placebo, \( P = 0.90 \)). A creatinine rise of 25 \( \mu mol/l \) was noted in five patients in the naproxen group and seven in the placebo group (\( P = 0.44 \)). There was no difference in medication use, infection, hospital length of stay, or in the incidence of atrial fibrillation between the naproxen and placebo groups.

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**Fig. 1.** Flow diagram following randomization of enrolled study patients.

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**Fig. 2.** Postoperative pain before chest physiotherapy assessed with the visual analog scale (VAS).

**Fig. 3.** Postoperative pain after chest physiotherapy assessed with the visual analog scale (VAS).
4. Discussion

Postoperative pain control is important to patients and clinicians alike. The physiological consequences of suboptimal analgesia following cardiac surgery can be harmful, contributing to mobility limitations and the impairment of the hematologic, immune, cardiovascular, and respiratory systems. Furthermore, a direct relationship has been demonstrated between poorly controlled pain and the cost of medical care, time spent in an intensive care unit and hospital length of stay [15].

In this randomized controlled trial comparing naproxen to placebo as an adjunct to opioids following CABG, naproxen significantly reduced postoperative pain and improved pulmonary function compared to placebo. The present data add to that of other studies which have also illustrated the analgesic effects of NSAIDs after cardiac surgery. A significant reduction in postoperative pain was demonstrated with the use of ketorolac [9,10], diclofenac [11] and rectal indomethacin after CABG [12]. However, unlike previous trials, this is the first to date to demonstrate an improvement in both pain control and lung function following CABG using a low-cost NSAID such as naproxen.

Postoperative pain following CABG occurs as a result of surgical trauma and inflammation to the thoracic cage and parietal pleura. Pain is normally transient, and has been reported to be maximal up to POD 3 [16]. Our results are consistent with this description, and interestingly, in our study, naproxen was not associated with a reduction in postoperative pain after POD 3. This data indicate that NSAIDs have the greatest impact in relieving postoperative pain early in recovery after cardiac surgery. Although inflammation has been implicated as a possible etiology of postoperative atrial fibrillation, our results and that of others have not shown any effect of NSAIDs on the incidence of postoperative atrial fibrillation [11,17].

Significant changes in pulmonary function occur following cardiac surgery. After median sternotomy, vital capacity is significantly reduced, resulting in secretion retention, lobar collapse, and a predisposition to infection. In this study, naproxen significantly improved pulmonary SVC postoperatively, consistent with a previous study using ketorolac [10]. Patients who received naproxen also had a significantly lower WBC count postoperatively. This suggests that naproxen, as an adjunct to opioids, may potentially reduce postoperative lung atelectasis, in accordance with previous work by Gust et al. [17].

NSAIDs have traditionally been avoided in cardiac surgery because of the older patient population and the fear of untoward side effects on the gastric, renal and coagulation systems. By inhibiting prostaglandin secretion, NSAID use can contribute to gastroduodenal mucosal ulceration. In carefully selected patients however, the short-term use of NSAIDs in the postoperative period appears safe, without an increased incidence of gastrointestinal bleeding or peptic ulceration [5,6]. Routine peptic ulcer prophylaxis is advocated by most surgeons that prescribe NSAIDs postoperatively. However, our study illustrated that even in the absence of peptic ulcer prophylaxis, an increased risk of gastrointestinal events was not demonstrable. Recently, the use of higher-cost selective cyclooxygenase-2 inhibitors (COX-2) has been promoted due to the lower incidence of gastrointestinal events compared to non-selective...
cyclooxygenase inhibitors such as naproxen [18]. However, increasing evidence indicates that COX-2 inhibitors may also be associated with acute gastrointestinal events [19]. Furthermore, no significant benefits were demonstrated in a recent randomized study comparing the use of etodolac (COX-2 inhibitor) versus diclofenac (non-selective inhibitor) after CABG [11].

Concerns remain regarding postoperative renal impairment with the use of NSAIDs after cardiac surgery. However, the incidence of acute renal failure following exposure to NSAIDs is very uncommon in adults without underlying kidney disease [20]. Our study suggests that in patients free of preoperative renal insufficiency, short-term postoperative naproxen use is not associated with an increased incidence of renal dysfunction following CABG. This is in agreement with other studies that have also found no increased risk of postoperative renal impairment after cardiac surgery in carefully selected patients [12,13].

Through the inhibition of platelet cyclooxygenase, NSAIDs block the formation of thromboxane-A2 and impair platelet aggregation, thereby producing a systemic bleeding tendency. Although the use of NSAIDs may predispose to an increase in perioperative blood loss, previous trials of NSAIDs after cardiac surgery have failed to demonstrate this effect [12]. In this study, naproxen use was associated with increased chest tube drainage during the initial four postoperative hours. However, this was not associated with an increased rate of transfusion, and in the current era of routine anti-fibrinolytic use, it is uncertain whether this effect would be observed or not. Although it is biologically plausible that delaying the administration of naproxen for several hours after surgery may reduce perioperative blood loss, this question cannot be answered within the realm of this study. Also, it is unclear whether such a delayed approach would affect the early postoperative pain relief associated with naproxen. Patients who received naproxen in this study had a trend towards receiving less platelet concentrates than those who received placebo. Previous work has shown that NSAIDs can interfere with the anti-platelet effect of aspirin [21]. Through the antagonism of aspirin-induced platelet dysfunction, naproxen administration may lead to less perioperative platelet transfusion requirements. Alternatively, the increase in platelet transfusions in the placebo group may have been coincidental, contributing to less blood loss in these patients.

The opioid-sparing effect of NSAIDs has been consistently described in the cardiac surgery literature. Rapanos and colleagues [12] illustrated a reduction in morphine consumption in the first 24 h after administration of rectal indomethacin. Hynninen et al. [13] showed an opioid-sparing effect with diclofenac, but neither indomethacin nor ketoprofen decreased opioid consumption in their trial. Our study failed to demonstrate an opioid-sparing effect, with no significant difference between the naproxen and placebo groups in terms of postoperative opioid consumption. This may have been due to our institution’s aggressive management of postoperative pain, as illustrated by the relatively low VAS scores. Not infrequently, patients are administered narcotics around-the-clock as prophylaxis before pain progresses.

Our study was limited by the absence of a strict nursing protocol for narcotic administration, impairing our ability to detect an opioid-sparing effect of naproxen. Because patients undergoing CABG with cardiopulmonary bypass were selected for this study, our results may not necessarily be generalizable to all patients undergoing cardiac surgery. Furthermore, with the advent of COX-2 inhibitors, the applicability of this study to modern postoperative pain regimens may be questioned. However, COX-2 inhibitors have not been demonstrated to be safer, more efficacious [11] or cost effective than standard NSAIDs in the cardiac surgery literature. Irrespective of these potential limitations, the strengths of this study rest in its randomized placebo-controlled design, intention-to-treat analysis, and use of a simple regimen with an inexpensive medication.

In conclusion, the benefits of early naproxen use in combination with opioids for postoperative analgesia after cardiac surgery appear to outweigh the risks in carefully selected patients. Naproxen results in less postoperative pain and faster recovery of lung function without producing significant side effects. Our findings support the routine inclusion of an NSAID in the postoperative pain regimen in all patients in whom specific contraindications do not exist.

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