

Postoperative Analgesic Effect of Rofecoxib after Transabdominal Hysterectomy

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Introduction

Postoperative pain affects a variety of physiological functions and can adversely influence surgical outcome¹. Effective postoperative pain management has been demonstrated to improve clinical outcome² and patient satisfaction. Nonsteroidal antiinflammatory drugs (NSAIDs) are currently recommended as part of multimodal therapy for perioperative pain management. Several studies showed that NSAIDs were effective in reducing postoperative pain and opioid consumption.³⁻⁷ However, use of nonselective NSAIDs, which inhibit prostaglandin synthesis at both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) sites is associated with gastrointestinal, platelet-related, renal, and other adverse side effects.⁸⁻⁹ COX-1 is active and present at a constant concentration in most tissues and COX-2 is induced peripherally under conditions of inflammation.¹⁰ It is believed that the therapeutic activity of NSAIDs is from the inhibition of COX-2, whereas the adverse effects result from the inhibition of COX-1.

Recently, selective COX-2 inhibitors have been introduced as alternatives to nonselective NSAIDs in pain management and claimed that they have comparable analgesia with less adverse effects. Previous studies found that rofecoxib, an oral COX-2 inhibitor, provided effective postoperative analgesia after dental, orthopedic and otolaryngologic surgery³⁻⁷ but not in patients after radical prostatectomy.¹¹ Its efficacy may be partly dependent on type of surgery. This randomized, double-blinded, placebo-controlled study was designed to evaluate postoperative analgesic effect of administering preoperative rofecoxib for transabdominal hysterectomy.

Patients and Methods

After obtaining approval from the Hospital Ethics in Human Research Committee and written informed consent, 20 patients undergoing elective transabdominal hysterectomy under general anesthesia were studied. Inclusion criteria were patients with ASA physical status I – II and aged between 20-60 years. Exclusion criteria were known allergy to morphine or any NSAIDs, history of chronic pain or chronic use of analgesic medication, clinically significant neurologic, renal or gastrointestinal disease and unable to operate a patient-controlled analgesia (PCA) device. All patients were randomized to receive either an oral placebo (control group, n = 20) or rofecoxib 50 mg (rofecoxib group, n = 20) or rofecoxib 50 mg (rofecoxib group, n = 20) along with diazepam 0.2 mg/kg 1 hour before anesthetic induction. The patients, observers, and those involved in direct patient care were blinded to the group. Anesthesia was induced with propofol (1.25 mg/kg) and

fentanyl (1g/kg) and tracheal intubation was facilitated with pancuronium, atracurium or vecuronium. Anesthesia was maintained with halothane and 70% nitrous oxide in oxygen.

At postanesthesia care unit (PACU), when patients were awake and complained of pain, they would be treated with bolus intravenous morphine 0.05 mg/kg and connected to a PCA pump. All patients then received PCA morphine for postoperative pain management for the next 24 hours. The PCA solution contained morphine 1 mg/ml. Settings were as follows: incremental dose, 1 ml ; lock out interval, 3 min ; and 1 hour limit, 8 mg. Patients were asked to quantify their pain on verbal rating scale (VRS) between 0 and 10 with 0 representing no pain and 10 the worst imaginable pain at 4, 8 and 24 postoperative hour. Morphine consumptions after bolus dose were recorded at 4 hour interval at first and second evaluation periods at 4 hour interval at first and second evaluation periods and at 8 hour interval at third and fourth evaluation periods.

Statistical Analysis

Data analysis was performed using SPSS for windows version 7.5. Demographic data (age, height and weight) and morphine consumption were assessed by the unpaired t- test. Pain scores were analyzed by the Mann-Whitney U test. A p value of less than 0.05 was considered statistically significant. Sample size required in each group was calculated, based on the following assumptions: 1) mean and standard deviation of morphine dose after 24 hours in previous study ; 2) type I error = 0.05 ; 3) power of test = 80%

Results

Demographic data in the both groups were not different (Table 1). The interval doses of morphine at 8, 16 and 24 hour were significantly less in rofecoxib group than in control group (Table 2, Figure 1). The total morphine consumption was significantly greater in control group than in rofecoxib group (Table 2). There was no significant difference between groups with regard to VRS at 4, 8 and 24 postoperative hour (Table 3).

Discussion

Effective postoperative pain control has a large impact on the recovery process and patient satisfaction. A multimodal therapy including use of an opioid together with NSAID is currently recommended for postoperative pain management. However, the efficacy of nonselective NSAIDs is limited by their side effect.⁸⁻⁹ COX-2 specific NSAIDs appear to have advantages over nonselective NSAIDs in terms of improved side effect profiles. Recently, an oral COX-2 inhibitor, rofecoxib, has been available in Thailand

Several studies have examined the analgesic

Table 1 Demographic data, data shown are mean (SD).

Group	No.of patients	Age (yr)	Height (cm)	Weight (kg)
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Control	20	45.25 (5.22)	157.85 (4.89)	57.50 (9.77)
Rofecoxib	20	45.20 (5.24)	156.40 (4.45)	56.00 (8.39)

Table 2 Interval dose of morphine (mg) for the 4 time periods and total dose at 24 hours, data shown are mean (SD).

Evaluation period (hour)	Morphine consumption (mg)	
	Control group	Rofecoxib group
0-4	11.70 (6.38)	9.90 (6.50)
4-8	4.85 (4.07)	2.35 (2.13)*
8-16	6.60 (4.35)	2.75 (2.26)*
16-24	6.05 (6.09)	2.80 (2.35)*
0-24 (total)	29.70 (16.40)	18.45 (8.67)*

*P<0.05

Table 3 Verbal rating scale (VRS) at 4, 8 and 24 postoperative hour, data shown are mean (SD).

	Postoperative VRS	
	Control group	Rofecoxib group
at 4 th hour	5.20 (2.48)	4.10 (1.86)
at 8 th hour	3.65 (1.84)	3.00 (1.21)
at 24 th hour	2.25 (1.21)	1.80 (1.36)

efficacy of rofecoxib for postoperative pain relief. In dental, orthopedic and otolaryngologic procedures with mild to moderate pain, rofecoxib demonstrated greater analgesic efficacy than placebo.³⁻⁷ However, it failed to reduce pain or opioid requirement in more severe pain after radical prostatectomy.¹¹ Our study in transabdominal hysterectomy demonstrated significant reductions in total morphine consumption at 24 postoperative hour. Although both transabdominal hysterectomy and radical prostatectomy are intraabdominal operations, transabdominal hysterectomy is less extensive than radical prostatectomy, which is likely to cause less severity of pain.

Furthermore, the interval doses of morphine were significantly less in rofecoxib group than in control group at 8, 16 and 24 hour but not at first 4 hour. The ineffective analgesia of rofecoxib in early postoperative period may be from the greater severity of pain than late postoperative period. The VRS was slightly less in rofecoxib group than in control group, however there was no statistical significance. Previous data and our results suggest that rofecoxib may not be effective in severe pain especially immediate postoperative period. Later in the postoperative period as pain begins to subside, it could provide significant opioid sparing effect.

The analgesic dose-response studies showed that 50 mg of rofecoxib was significantly more efficacious than 7.5, 12.5 and 25 mg. No difference was noted between 50 mg and 100 or 200 mg, suggesting an analgesic ceiling at approximately 50 mg. Therefore, rofecoxib administered in our study appeared to be full therapeutic dosage. In addition, Reuben et al. showed that 50 mg rofecoxib given 1 hour preoperatively was more effective in reducing postoperative pain than the same dose given 15 min postoperative¹². These suggest that rofecoxib may have preemptive analgesic effects.

We also observed the incidence of nausea and vomiting in this study and found no difference between groups. One previous study¹³ investigating side effect profiles of rofecoxib in gynecological and breast surgery compared with diclofenac showed smaller effect on platelet aggregation, less use of antiemetics and less surgical blood loss in rofecoxib group. However, more studies are needed to determine its safety in patients with renal and cardiovascular problems.