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Full Length Research Paper

Effect of perioperative administration of parecoxib on post-tonsillectomy pain in adults

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Post-tonsillectomy pain is one of the most difficult pain states to manage in otolaryngology. In this study, we investigated the analgesic effect of parecoxib in adults undergoing tonsillectomy. Eighty-eight patients that underwent tonsillectomy were randomly allocated to two groups to receive either intravenous 80 mg 24 h^{-1} parecoxib (group P) or saline as control (group C) at two medical center of university. Anesthesia was induced using intravenous sufentanil and propofol, while endotracheal intubation was facilitated with rocuronium and maintenance was accomplished using sevoflurane. Pain scores, the rescue analgesic consumption, the frequency of postoperative complications including bleeding, nausea and vomiting and other major event were recorded 1, 2, 4, 12 and 24 h after the operation. P<0.05 was considered statistically significant. In total, 80 patients successfully completed the study. Intravenous parecoxib (40 mg Bid), significantly reduced pain intensity both at rest and during swallowing in the first 24 h after tonsillectomy. The median pain score was reduced from moderate (4.5) to light pain (3) at rest and from severe pain (6.5) to moderated pain (4-5) during swallowing. Forty-four (43%) patients received paracetamol in the ward [22 (55%) in the control group and 12 (30%) in the parecoxib group; *P*<0.05]. Re-operation for bleeding, postoperative nausea and vomiting (PONV) and other major adverse events were not different between groups. In conclusion, perioperative administration of parecoxib (40 mg, Bid) was effective for postoperative pain at rest relief in adults undergoing tonsillectomy.

Key words: Tonsillectomy, pain, parecoxib, analgesia.

INTRODUCTION

Adult chronic tonsillitis is a common disease. Tonsillectomy is a frequently performed procedure in adults. Post-tonsillectomy pain can be severe, which is one of the most difficult pain states to manage in otolaryngology (Husband and Davis, 1996; Mathiesen et al., 2011). Opioids such as morphine have been widely used in moderate to severe pain, but these may depress respiration. Furthermore, opioids are possibly associated with an increased risk of airway obstruction after tonsillectomy. Therefore, pain management in tonsillectomy patients is challenging. Many medicinal plants are used in developing countries for the management of pain and inflammatory conditions (Musa et al., 2009; Rafiq et al., 2009), which could be an alternative therapy. But herbal medicine on analgesia should be further research.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the enzymes cyclooxygenase (COX) -1 and -2, which are non-opioid analgesics with a well-documented efficacy after different surgical procedures. However, only the inhibition of COX-2 is involved in analgesic, anti-inflammatory, and antipyretic effects of NSAIDs. The reduced activity of COX-1 is associated with adverse events of NSAIDs as platelet dysfunction, which may increase the risk of post-tonsillectomy hemorrhage

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(Marret et al., 2003; Moiniche et al., 2003). In consequence, selective inhibition of COX-2 might have therapeutic actions similar to those of traditional NSAIDs, but cause fewer unwanted drug effects. Thus, parecoxib, a specific COX-2 inhibitor, may be suitable for use in post-tonsillectomy pain. Systematic reviews support that intravenous administration of parecoxib reduces postoperative pain after various types of surgery, and the need for postoperative rescue pain medication (Nikanne et al., 2005). However, few studies to date have evaluated the efficacy of parecoxib for postoperative pain following tonsillectomy.

In this study, we hypothesized that perioperative intravenous administration of parecoxib would provide postoperative analgesia without increasing bleeding after tonsillectomy in adults. We aimed to compare the difference in the pain scores at rest and swallowing, bleeding, postoperative nausea and vomiting (PONV) and postoperative rescue pain medication.

METHODOLOGY

Study object

This study was conducted at two medical centers (Sir Run Run Shaw Hospital and Second affiliated Hospital) in Zhejiang University in China, and it was approved by the research Ethics Committee at Sir Run Run Shaw Hospital and the Second Affiliated Hospital, School of Medicine, Zhejiang University. Between November 2009 and March 2011, patients were enrolled in the study if they were scheduled to receive general anesthesia for elective bilateral tonsillectomy due to chronic tonsillitis, ASA I – III aged between 18 and 35 years, and they provided informed consent. Meanwhile, all operations were performed by two designated attending doctors (one in Sir Run Run Shaw Hospital and the other in 2nd affiliated hospital). Patients undergoing day-case surgery, with a history of ischemic heart disease, cerebrovascular disease, asthma, renal impairment (serum creatinine concentration >100 $\mu mol \cdot L^{-1}$) or hematologic disease, body mass index <19 or >35, chronic drug or alcohol abuse, chronic pain, angiotensin-converting enzyme inhibitor use, allergy to any of the drugs used in the study were excluded. And in pregnant female, patients unable to cooperate or operation time more than 90 min were also excluded.

Study procedure

Anesthesia management

The day before surgery, the patients gave informed written consent to the study. The verbal rating scale for pain (VRSP) (0-10) was explained to patients. Patients also were introduced to the documentation of postoperative nausea and vomiting (PONV) on numerical analogue scale. No pre-anaesthetic medication was administered. Baseline patient characteristic data were collected before induction. Routine monitoring included electrocardiography (ECG), non-invasive blood pressure, peripheral pulse oximetry (SpO_2). Patients were mechanically ventilated to maintain end-tidal carbon dioxide concentration ($ETCO_2$) between 35-40 mmHg. Induction, maintenance of general anaesthesia and also PONV prophylaxis were standardized in all participants. We induced general anaesthesia with intravenous midazolam 2 - 3 mg, sufentanil 0.4 - 0.5 $\mu g\ kg^{-1}$ bodyweight up to 50 µg, and propofol 1 $mg\ kg^{-1}$. Tracheal intubation was facilitated with rocuronium 0.6 $mg\ kg^{-1}$. We maintained anaesthesia with sevoflurane 2 - 3 vol% and remifentanil 0.1 - 0.4 $\mu g\ kg^{-1}\ min^{-1}$. Patient received an infusion of Ringer's acetate solution 10 ml/h. In addition, all patients received ondansetron 4 mg at the end of surgery for PONV prophylaxis. Upon completion of surgery, sevoflurane and remifentanil were discontinued, and the neuromuscular block was reversed with neostigmine 2 mg and atropine 1 mg. The trachea was extubated upon emergency from anesthesia (spontaneous eye opening, cough, or purposeful movement). Patients were then transferred to the post-anesthesia care unit (PACU).

Patients were randomized to receive either 40 mg parecoxib (Dynastat®, Pfizer, British) or saline intravenously after induction. The allocation sequence was obtained by a computed randomization list. The randomization was stratified by gender. The study medication was prepared by an anesthesia resident who was not involved in the perioperative care of the patient. Patients and researchers were not aware of the study medication. Study medications were clear, colorless fluids avoiding visible differences between the study drugs. Postoperative pain was initially treated with nurse-administered intravenous (i.v) fentanyl when a VRSP was ≥5 in the PACU. Patients with VRSP ≥ 5 received intravenous fentanyl 0.2 µg/kg at 10-min intervals until the score was <5 (maximum 0.1 mg). And postoperative pain occurred in the ward, was treated with paracetamol, 0.5 g i.v. (q6h, maximum daily dose not more than 2 g). Ten hours after surgery, the participants received 40 mg parecoxib or normal saline (Table 1). No other analgesic drugs or glucocorticoids were administered.

Observation item

Intraoperative blood loss was assessed by visual estimation of the blood volume in swabs and suction bottle, and re-operation for bleeding was also recorded. Total rescue analgesics dose was measured at PACU discharge and 24 h after surgery. Pain (rest and swallowing) scores on a 11-point verbal rating scale (0, no pain; 10, worst pain imaginable), PONV scores on a 4-point scale (0, absent; 1, nausea not requiring treatment; 2, nausea requiring treatment; and 3, vomiting), sedation scores on a 4-point scale (0, awake and alert; 1, easy to rouse with verbal commands; 2, drowsy, roused only by touch; 3, somnolent, roused only by pain), mean arterial pressures, heart rates, respiratory rates and SpO_2 were recorded at 0, 1, 2, 4, 8 and 24 h.

Study outcome

The primary outcome was pain during swallowing at 2 h postoperatively using the verbal rating scale for pain. The following variables were defined as secondary outcomes: VRSP scores during swallowing at other time points and at rest, number of rescue analgesia requests and incidence of side-effects such as re-operation for bleeding, PONV, cardiovascular adverse event at 24 h postoperatively.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS, Chicago, IL). Nikanne and colleagues reported that the VAS-pain score (0-100 mm) during swallowing at 2 h postoperatively was 46 mm (SD 24) (Nikanne et al., 2005). The likely 40% reduction in pain score was thought to be of clinical relevance. The sample size required for each group therefore was 38 patients ($\alpha = 0.05$; power = 0.8). To account for dropouts, we planned a total inclusion of 88 patients in the study. Demographic and anesthetic data were analyzed and compared with the

Table 1. Study design.

Study group	Control	Parecoxib
After induction	Normal saline 2 ml	Parecoxib 40 mg/2 ml
10 h after surgery	Normal saline 2 ml	Parecoxib 40 mg/2 ml

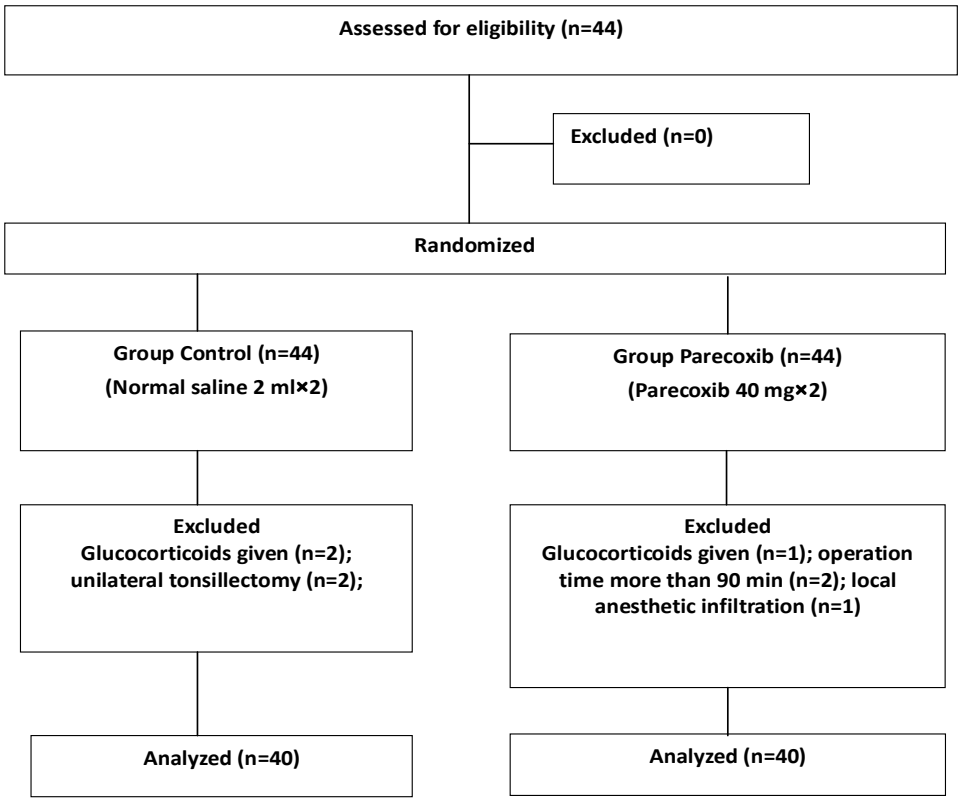

Figure 1. Study protocol.

Wilcoxon's rank sum test and Fisher exact test. Pain scores were analyzed with the Mann-Whitney *U* test and because of the existence of repeated measures, the Bonferroni correction was performed. The 95% confidence interval was calculated by the Hodges-Lehmann method. Friedman's test was used to compare PONV scores, sedation scores between the two groups. A *P* value <0.05 was considered statistically significant in all cases except when the Bonferroni correction was performed for pain scores, in which case a *P* value <0.01 was considered significant (this value represents 0.05 divided by the number of repeated measures: 5).

RESULTS

Participant characteristics and perioperative data

The study was carried out from December 2009 to March 2011. Eighty-eight patients were included and randomized. Because three patients were administered glucocorticoids, two patients were performed unilateral tonsillectomy, two patients' operation time was more than 90 min, and one patient was given ropivacaine infiltration, these eight patients were excluded after randomization. Eighty patients successfully completed the study (Figure 1). There were no significant differences between groups for patient characteristics and perioperative data (Table 2).

Pain outcome

The median VRSP score during swallowing at 2 h was significantly lower in the parecoxib group (median 5, interquartile range: 4 - 5) compared with the control group (median 6.5, interquartile range: 6 - 7) (Figure 2B). Similarly, the VRSP scores during swallowing at 1, 4, 12 and 24 h were lower in the parecoxib group than in the

Table 2. Baseline characteristics.

Patients' characteristic / preoperative data	Control	Parecoxib
Number of patients	40	40
Age (yr)	22 (18 - 29)	24 (19 - 31)
Weight (kg)	65 (58 - 71)	62 (58 - 67)
male/female	18/22	16/24
Duration of surgery (min)	48 (43 - 54)	47 (41 - 52)
Intraoperative dose of sufentanil (μg)	40 (35 - 45)	40 (35 - 45)

Age, weight, duration of surgery, intraoperative sufentanil dosage and perioperative bleeding are expressed as mean (95%CI).

control group. The VRSP scores at rest during 24 h after surgery all were lower in the parecoxib group (Figure 2A).The rescue analgesic demand was the same in both groups at PACU; in the control group (1/40, 2.5%) and in the parecoxib group (1/40, 2.5%). Thirty-four (43%) patients received paracetamol in the ward [22 (55%) in the control group and 12 (30%) in the parecoxib group; $P<0.05$].

Side effects

There was no significant difference in median intra-operative bleeding amount between the two groups [20 (interquartile range: 15-25) vs. 20 (interquartile range: 15-25)] ml (Table 3). One patient was re-operated for bleeding in the parecoxib group, the same occurred in the control group. There were no difference between groups in PONV scores and sedation scores (Table 3). No major morbidity or death was recorded.

DISCUSSION

In this study, we found that i.v. parecoxib (40 mg Bid) reduced pain intensity both at rest and during swallowing in the first 24 h after tonsillectomy. These reduced pain scores may be of clinical relevance for the patients as the median VRSP score was reduced from moderate (4.5) to light pain (3) at rest and from severe pain (6.5) to moderated pain (4-5) during swallowing. Fentanyl consumption was the same in the PACU. This may be as a result of the good analgesic effect of sufentanil and the short operation duration. Paracetamol consumption was reduced in the first 24 h postoperatively. In addition, a reduced number of patients requiring paracetamol in ward in the first 24 h after operation were observed in the parecoxib group. Perioperative administration of parecoxib did not increase perioperative bleeding. And other adverse effects, such as PONV, cardiovascular affairs, were also not increased.

Nikanne's study on celecoxib showed that COX-2 inhibitor alleviated post-tonsillectomy pain (Nikanne et al., 2005). However, to the best of our knowledge, the literature lacks a review of perioperative parecoxib for pain management in tonsillectomy patient. Many studies have demonstrated that parecoxib is an effective analgesic for post-operative pain (Lloyd et al., 2009; Langford et al., 2009; Gehling et al., 2010; Pandazi et al., 2010) and our result is consistent with them. In contrast, some studies have shown that parecoxib has no clinical benefit for post-surgical pain, such as post-craniotomy pain (Williams et al., 2011; Jones et al., 2009). The reason for the different results may be related to different operation.

NSAID therapy has been reported to provide effective pain control without opioids after tonsillectomy (Gunter et al., 1995; Jeyakumar et al., 2008; Yaman et al., 2011; Mowafi et al., 2011). However, the ability of NSAIDs to inhibit platelet cyclooxygenase (COX) may be associated with a risk of increased bleeding after tonsillectomy. But the evidence of a substantial increased bleeding effect of NSAIDs after tonsillectomy has been questioned. A meta-analysis on the effects of NSAIDs on bleeding after tonsillectomy show that postoperative use of conventional NSAIDs such as ketorolac, ibuprofen or ketoprofen increases the risk reoperation for hemostasis after operation (Marret et al., 2003). The meta-analysis included 20 randomized controlled trials of the 243 patients who did not receive NSAID therapy; 13 had primary or secondary postoperative bleeding, 2 patients of them required reoperation for hemostasis and of 263 patients who received NSAID therapy, 24 had postoperative bleeding, 11 of them required reoperation for hemostasis.

Additionally, Møiniche analyses of twenty-five studies with data from 970 patients receiving a NSAID and 883 receiving a non-NSAID treatment or a placebo showed that reoperation happened significantly more often with NSAIDs. Therefore, there is some evidence for an increased likelihood of reoperation because of bleeding (Moiniche et al., 2003). In contrast, Krishna's meta-analysis on 1368 patients demonstrated that there appears to be no significant increased risk of bleeding for nonaspirin NSAIDs (Krishna et al., 2003). Cardwell also analyzed 13 trials involving 955 children and concluded that NSAIDs did not cause any increase in bleeding requiring a return to theatre (Cardwell et al., 2005). Thus,

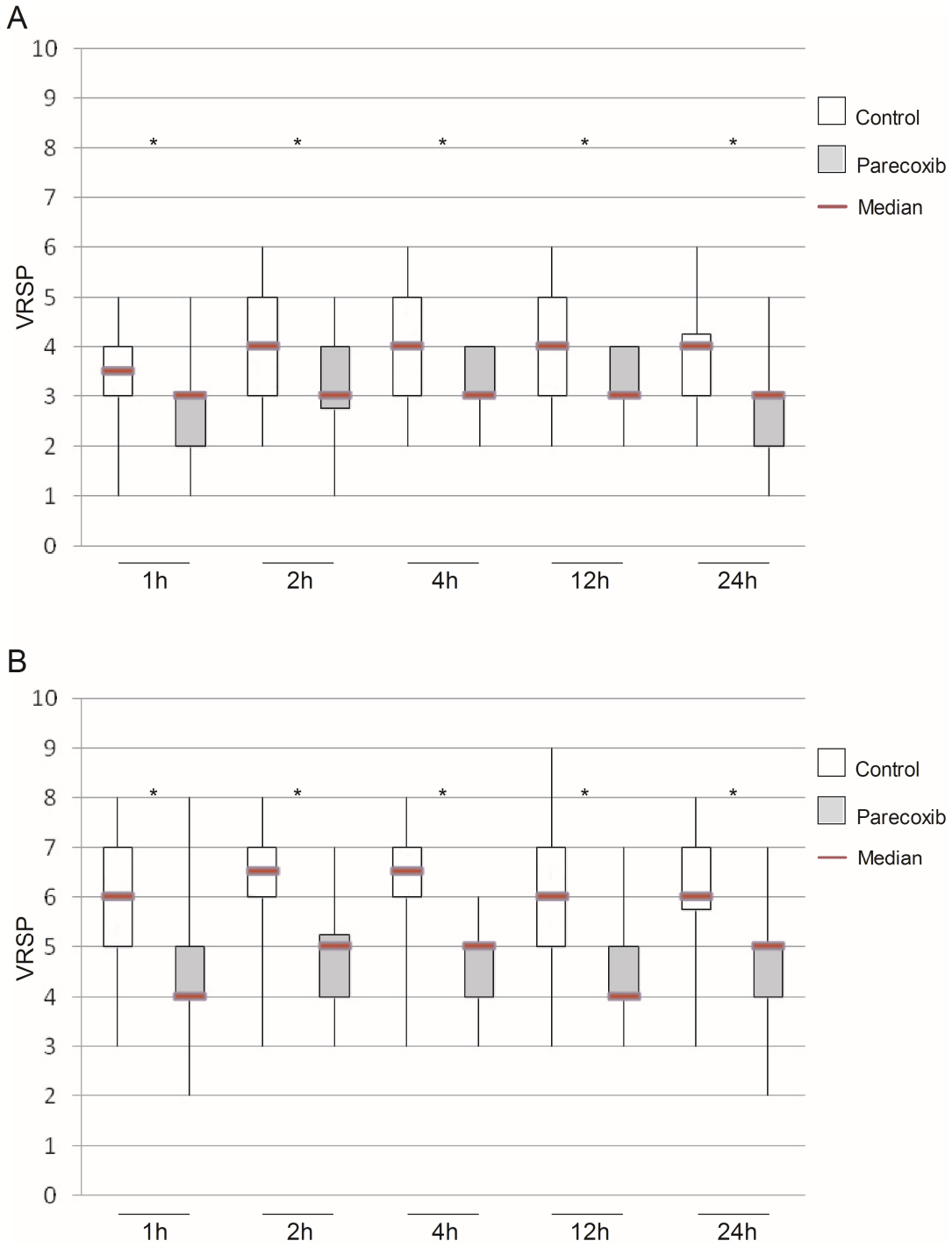

Figure 2. Pain scores at 1, 2, 4, 12, 24 h after surgery. Results are median (horizontal solid line) with interquartile range (box limits) and minimum and maximum values (whiskers). A, Resting pain scores; B, swallowing pain scores.*Corrected *P* values <0.001. VRPS = Verbal rating pain scale.

the effect of NSAID on bleeding after tonsillectomy is controversial and needs further research. It has been confirmed that parecoxib 40 mg have an equipotent analgesic efficacy relative to traditional NSAIDs in post-operative pain after minor and major surgical procedures (Rømsing and Møniche, 2004), while selective COX-2 inhibitors have less anti-platelet effects than conventional non-selective NSAIDs (Klein et al., 1994). Our study has

Table 3. Postoperative characteristics.

Characteristics		Postoperative time (h)						*P*-value
		0	1	2	4	12	24	
Perioperative bleeding	Control	20(15-25)	—	—	—	—	—	
	Parecoxib	20(15-25)	—	—	—	—	—	1.0*
PONV score	Control	—	1(1 - 2)	1(1 - 2)	1(1 - 2)	1(1 - 1)	1(1 - 1)	
	Parecoxib	—	1(1 - 1)	1(1 - 2)	1(1 - 2)	1(1 - 1)	1(1 - 1)	1.0**
Sedation score	Control	—	1(1 - 2)	1(1 - 3)	1(1 - 3)	1(1 - 3)	1(1 - 1)	
	Parecoxib	—	1(1 - 2)	1(1 - 3)	1(1 - 3)	1(1 - 3)	1(1 - 1)	1.0**

Results are presented as median (inter-quartile range). PONV, Postoperative nausea and vomiting; PONV was rated by patients as: 0, absent; 1, nausea not requiring treatment; 2, nausea requiring treatment; and 3, vomiting. Sedation was rated by attending nurses as: 1, awake and alert; 2, easy to rouse with verbal commands; 3, drowsy, roused only by touch; and 4, somnolent, roused only by pain. *Wilcoxon's rank sum test; **Friedman test.

demonstrated that perioperative parecoxib did not increase the risk of bleeding. It is consistent with previous studies on COX-2 inhibitor, such as celecoxib and rofecoxib on post-tonsillectomy (Pandazi et al., 2010; Vallée et al., 2007; Sheeran et al., 2004; Joshi et al., 2003).

Due to an increased risk of major cardiovascular events, the cyclogenase-2 (COX-2) inhibitor rofecoxib was withdrawn (Jüni et al., 2004). Whether this risk is a class effect or limited to rofecoxib is still unclear. As the only COX-2 inhibitor which can be given intravenously, parecoxib has been confirmed to be associated with an increased incidence of cardiovascular adverse (Aldington et al., 2005). Therefore, parecoxib was forbidden to be used in patients with cardiovascular disease. This study excluded the patient with such disease and as no cardiovascular adverse event occurred in the study.

Meanwhile, our study has several limitations. First, we only observed post-surgical pain and the recovery of patient during 24 h postoperatively. In a study of post-tonsillectomy pain, all of the patients experienced moderate or severe pain during the first 48 h after surgery (Sutters et al., 2004). Secondly, even though we were restricting the operators to two designated doctors at two medical centers of university respectively, this still allowed a variety of operations to be included that undoubtedly produced a range of postoperative pain (Ozkırış, 2011). In this study, both monopolar and bipolar cautery dissection were included. Thirdly, our study was too small to identify the risk of rare but important adverse effects such as bleeding, myocardial infarction and renal failure. Systematic review may be the only way to establish these risks firmly.

Conclusion

Perioperative administration of parecoxib twice daily reduced post-tonsillectomy pain scores during swallowing and at rest. Paracetamol in the ward was reduced in the first 24 h postoperatively. Therefore, in patients with tonsillectomy, parecoxib (40 mg Bid) provided a good analgesic efficacy at rest during the first 24 h after surgery. Other analgesic therapy should be added for post-tonsillectomy pain during swallowing.

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