The effect of etoricoxib premedication on postoperative analgesia requirement in orthopedic and trauma patients

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ABSTRACT

الأهداف: تقييم كفاءة تأثير استخدام عقار الايتوريكوكسيب قبل جراحات العظام والإصابات على تسكين آلام المرضى بعد العمليات.

الطريقة: أجريت هذه الدراسة في مستشفى الملك فهد الجامعي – جامعة الملك فيصل – الدمام – المملكة العربية السعودية، في الفترة مابين أغسطس 2005م وحتى أكتوبر 2007م. شملت هذه الدراسة 200 مريض لإجراء عمليات جراحية في العظام وبعد الإصابات. تم تقسيمهم إلى مجموعتين، احتوت كل مجموعة على 100 مريض. تناول المرضى قرص من عقار الايتوريكوكسيب 120mg بالفم، أو عقار مموه (بلاسيبو)، وذلك قبل الجراحة بـ90 دقيقة في المجموعة الأولى والثانية على التوالي. تم توصيل جهاز حقن المورفين الذي يتحكم فيه المرضى وذلك بعد العملية الجراحية مباشرة. تم ملاحظة درجة الألم باستخدام المقياس المرئي التناظري، ومدى حاجة المريض إلى المسكنات الإضافية، وكمية المورفين المستخدمة بعد الجراحة خلال 24 ساعة، مع تسجيل أية مضاعفات إن وجدت.

النتائج: أكمل الدراسة في كل مجموعة مائة مريض. أدى إستخدام عقار الايتوريكوكسيب قبل جراحات العظام والإصابات الى تقليل واضح في كمية استهلاك عقار المروفين خلال 24 ساعة بعد الجراحة، حيث كانت كمية المورفين المستخدمة في مجموعة الايتوريكوكسيب هي35.1 (7.0) مقارنة ب44.2 (8.2) في مجموعة المناظرة ($p<0.001$)، كان معدل القيء والغثيان أقل في مجموعة الايتوريكوكسيب عنه في الجموعة الأخرى ($p=0.014$). لم يكن هناك اختلاف بين مجموعتي الدراسة في كمية الدم المفقود بعد الجراحة.

خاتمة: نستنتج من هذه الدراسة إن العلاج الإعدادي باستخدام عقار الايتوريكوكسيب طريقة فعالة لتسكين آلام المرضى بعد جراحات العظام والإصابات، ويقلل من الحاجة لإستخدام المورفين.

Objectives: We hypothesized that etoricoxib premedication would reduce the need for additional opioids following orthopedic trauma surgery.

Methods: A double blind, controlled study, conducted in King Fahd University Hospital, King Faisal University, Dammam, Kingdom of Saudi Arabia. After obtaining the approval of the Research and Ethics Committee and written consent, 200 American Society of Anesthesiology grade I & II patients that underwent elective upper limb or lower limb fracture fixation surgeries during the period from August 2005 to October 2007 were studied. Patients were randomly premedicated using 120 mg of etoricoxib or placebo (n=100, each). To alleviate postoperative pain, a patient controlled analgesia device was programmed to deliver one mg of morphine intravenously (lockout time, 6 minutes). Visual analog scale and total postoperative morphine consumption over 24 hours and the adverse effects were recorded.

Results: One hundred patients in each group completed the study period. Etoricoxib premedication provides a statistically significant postoperative morphine sparing effect over 24 hours postoperatively. Total morphine consumption was 44.2 (8.2) in the placebo and 35.1(7.0)mg in the etoricoxib groups ($p<0.001$). The incidence of nausea and vomiting requiring treatment was lower in the etoricoxib group, ($p=0.014$). The postoperative blood loss was similar in both groups.

Conclusion: Etoricoxib is a suitable premedication before traumatic orthopedic surgery as it enhanced postoperative analgesia and reduced the need for morphine

Saudi Med J 2008; Vol. 29 (7): 966-970

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Received 22nd February 2008. Accepted 2nd June 2008.

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Effective pain management is an essential component of postoperative care. Postoperative pain requires treatment not only to provide patients comfort, but also to reduce morbidity and mortality.[1] However, patients continue to suffer postoperative pain, cited as moderate to severe in over 70% of cases.[2] Monotherapy with non-opioids would not offer complete relief particularly in the first postoperative day.[3] Opioids provide a good analgesic effect, but their use is limited because of its adverse effects.[4] Therefore, multimodal pain strategies have been recommended to reduce the opioid doses by co-administering non-opioid analgesics such as non-steroid anti inflammatory drugs (NSAIDs).[5,6] The NSAIDs are associated with side effects such as increased perioperative bleeding, adverse renal and gastrointestinal effects.[7] The development of specific inhibitors, which selectively inhibit cyclooxygenase (COX)-2 without inhibiting COX-1 at therapeutic doses, has allowed effective treatment of pain, while reducing most side effects caused by NSAIDs.[7] Etoricoxib is a selective COX-2 inhibitor.[8] It has an advantage that a single oral dose provides pain relief for 24 hours.[9] Etoricoxib premedication has not been evaluated in the traumatic orthopedic patients as a component of multimodal analgesia to enhance postoperative pain relief and decrease opioid requirements with its undesirable effects. The present study was designed to study the efficacy of oral etoricoxib premedication in reducing opioid consumption in patients undergoing orthopedic and trauma surgeries.

Methods. This Study was conducted in King Fahd University Hospital, King Faisal University, Dammam, Saudi Arabia. After obtaining the approval of the Research and Ethics Committee of King Faisal University, Dammam and written consent from the patients, 200 American Society of Anesthesiology grade I & II patients undergoing elective open upper limb or lower limb fracture fixation surgeries in the period from August 2005 to October 2007 were studied. Exclusion criteria were known hypersensitivity to the study drugs, bronchial asthma, renal insufficiency, a history of peptic ulcer, a history of bleeding diathesis, pregnancy, history of alcohol or drug abuse, any analgesic premedication 12 hours period before the operation and inability to use the patient controlled analgesia (PCA) device. Patients were randomly allocated into 2 equal groups using an online research randomizer (htt://www.randomizer.org) with 100 patients in each arm. Patients were explained how to use the PCA pump and the visual analogue scale (VAS) in the preoperative visits. All patients were premedicated with 10 mg of oral diazepam preoperatively. In the etoricoxib group, each patient received an oral dose of etoricoxib 120 mg tablets (Arcoxia®, MSD Saudi Arabia), 90 minutes before surgery, while in the control group each patient received a placebo tablet orally at the same time. In the operating room, the baseline VAS for pain and scores for sedation, nausea, and vomiting were recorded. In addition, lactated Ringer's infusion was started and all the standard monitors were applied. Anesthesia was induced with IV propofol 2 mg/kg, fentanyl 2 μg/kg, and atracurium 0.5 mg/kg. Anesthesia was maintained by 1-2% sevoflurane in nitrous oxide and oxygen. All the patients were mechanically ventilated to maintain an end-tidal CO_2 between 30-36 mmHg. Intraoperative fentanyl supplement for maintenance of analgesia was according to the preference of the attending anesthesiologist. Following tracheal extubation, the patients were transferred to the post anesthesia care unit (PACU). Whenever possible in the PACU, the patient rated their pain on a 100 mm long VAS (0 mm = no pain and 100 mm worst pain imaginable). When the VAS pain score was ≥30 mm, intravenous morphine was titrated to effect. Patients could receive up to 5 mg of morphine initially. Patients then used a PCA delivery system for IV morphine. The PCA solution contained morphine one mg/ml. The administration variables were one mg demand dose with a lockout time of 6 minutes and 4 hours limit of 20 mg without basal infusion. The demand dose was increased to 2 mg if analgesia were inadequate. A team member unaware of patient's group allocation evaluated the VAS pain scores at rest and movement. As regard to morphine-related side effects, sedation, nausea, and vomiting scores were monitored. Degree of sedation was determined according to a sedation score (0 = alert, 1 = drowsy but arousable to voice, and 2 = very drowsy but arousable to shaking). Nausea and vomiting were recorded using a score (0 = no nausea or vomiting, 1 = nausea with no treatment, 2 = nausea and vomiting requiring treatment). Nausea and vomiting were treated with one mg of IV granisetron. The VAS scores at rest and movement, sedation and nausea and vomiting scores, mean arterial pressure (MAP), heart rate (HR), and pulse oximetry data (SPO_2) were assessed at one, 2, 4, 6, 8, 12, and 24 hours after surgery. Total and incremental morphine consumptions were recorded from the PCA device at these times. The surgical and anesthesia times were also assessed. Postoperative blood loss during the first 24 hours was recorded as the amount collected in a low-pressure closed drainage system. Before surgery and 24 hours postoperatively, urea and creatinine concentration were measured. Any complication related to the study drugs was reported.

Disclosure: This study is an independent study and not funded by the manufacturer of the drug involved.

Statistical analysis. The number of patients to include was based on the means and standard deviations of postoperative morphine consumption described by Du Manoir et al.[10] Data were tested for normal distribution using the Kolmogorov-Smirnov test. Student's t-test was used for comparison of normally distributed data, while Mann-Whitney U-test was used for data, which did not achieve normality. Repeated measures analysis of variance was used for morphine consumption, VAS, HR, MAP, and SPO_2. Categorical data were analyzed using X^2. Analysis was performed using Statistical software version 6.0 for windows (stat soft, Inc. Tulsa, USA). Data were presented as mean (SD) in the text and table, and as mean (95%) confidence intervals in the figure. A value of $p \leq 0.05$ was considered statistically significant.

Results. One hundred patients in each group completed the study. There were no significant differences between both groups with respect to the demographic data, baseline vital signs, types and duration of surgical procedures and anesthesia times. The average intraoperative fentanyl requirements were 375 µg in the placebo and 356.8 µg in the etoricoxib groups (**Table 1**). In the postoperative period, the analgesic requirements were observed in terms of the incremental PCA morphine consumption at the 1st and 2nd hour and at the end of 4th, 6th, 8th, 12th, and 24th hours (**Figure 1**). There were significant differences between the 2 groups in the morphine consumption at one, 2, 4, 6, and 8 hours. Thereafter, the analgesic requirements decreased in both groups. From postoperative 8 to 12 hours, the analgesic requirements were almost the same. There were insignificant differences in analgesic requirements in both groups in the last 12 hours. The total morphine requirements were 44.2±8.2 in the placebo and 35.1±7.0 mg in the etoricoxib groups (p=0.0001). A lower incidence of post-operative nausea and vomiting requiring treatment was observed in the etoricoxib group (9%) compared to 20% in the placebo group (p=0.014). No significant differences in the postoperative blood loss, urinary retention, pain, and sedation scores were detected. There were no adverse events related to excessive surgical bleeding, wound complications, renal dysfunction (no patient developed a creatinine concentration exceeding 1.2 mg/dl). Cardiovascular-related events or gastrointestinal bleeding were not recorded in any patient of both groups.

Discussion. The main finding in this study is that etoricoxib premedication reduced the need for supplemental analgesics after upper and lower limb orthopedic surgeries. An opioid-sparing effect throughout the study period with a lower incidence of nausea and vomiting requiring treatment was observed in the etoricoxib group. Postoperative blood loss was similar in both groups. Opioid sparing effects have been reported in several previous studies on selective COX-2 inhibitors used perioperatively. Puura et al[11] found that premedication with etoricoxib had a statistically significant fentanyl-sparing effect over 20 hours after laparoscopic cholecystectomy.[11] In another study of acute pain associated with removal of third molars,

Table 1 - Patient characteristics (n=100 in each group) data are mean (SD).

Parameters	Placebo group	Etoricoxib group	*P*-value
Age (yr)	32.3 (13.6)	31.4 (13.2)	0.62
Weight (kg)	77.6 (11.1)	74.1 (15.6)	0.08
Gender (M/F)	85/15	79/21	0.36
ASA status (I/II)	90/10	85/15	0.39
Surgical time (minutes)	129.3 (44.4)	119.7 (37.0)	0.10
Anesthesia time (minutes)	139.4 (44.2)	130.3 (37.8)	0.12
Fentanyl requirement (µg)	375 (61.5)	356.8 (74.3)	0.06

M - Male, F - Female, ASA - American Society of Anesthesia

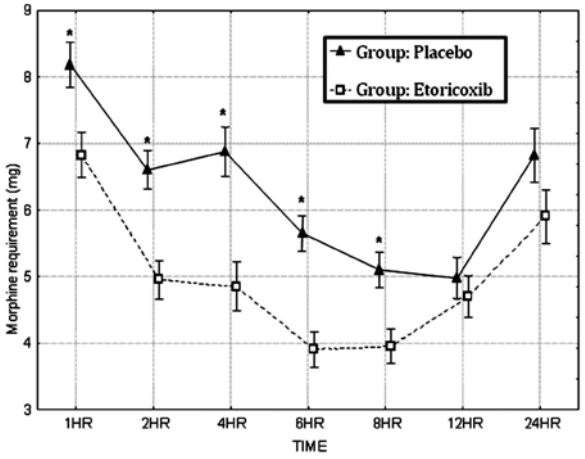

Figure 1 - Incremental morphine requirements during the 1st hour (1hr), 2nd hour (2hrs), from 2-4 hours (4hrs), from 4-6 hours (6hrs), from 6-8 hours (8hrs), from 8-12 hours (12 hrs) and from 12-24 hours postoperatively (24hrs). Vertical bars denote 0.95 confidence intervals. *A significance difference in comparison to the etoricoxib group.

etoricoxib 120 mg provided rapid onset of analgesia that was maintained over 24 hours.[12] Rasmussen et al[13] proved that oral etoricoxib improved postoperative analgesia and reduced morphine consumption after hip and knee arthroplasty. In addition, etoricoxib 120 mg premedication reduced postoperative pain following thyroidectomy in the period between 7-24 hours.[14] Moreover, in patients undergoing arthroscopic surgery under general anesthesia combined with intraoperative subacromial regional analgesia, etoricoxib enhanced early and late postoperative analgesia and facilitated early postoperative discharge.[15]

In the present study, the higher opioid requirement in the placebo group was also associated with an increased incidence of nausea and vomiting. There is some evidence that opioid sparing by COX-2 inhibitors also reduce these opioid-related side effects.[16] Nonselective NSAIDs produce its analgesic and anti-inflammatory effects by inhibiting the synthesis of prostaglandins through the inhibition of both isoforms of cyclooxygenase (COX-1 and -2).[17,18] The COX-1 has a homeostatic role in platelet aggregation, gastrointestinal mucosal integrity, and renal function, while COX-2 is inducible and mediates pain and inflammation.[8] Etoricoxib is a COX-2 inhibitor with a higher COX-1 to COX-2 selectivity ratio than other COX-2 inhibitors.[9] After the oral administration of etoricoxib, the maximum concentration is achieved in one hour and the bioavailability is almost 100%, with a half-life of 22 hours.[19]

Several limitations of the present study should be considered before recommending the use of etoricoxib as a routine premedication preoperatively. First, although our results demonstrated that etoricoxib administration was not associated with a significant increase in perioperative bleeding inferred from similar operation times and postoperative blood loss in both groups. There is a casual relationship between the bleeding criteria and the operation time.[11] However, intraoperative blood loss was not measured since most of the surgical procedures were performed under the surgical tourniquet. This may limit the power of this finding. Previous studies have shown that using the COX-2 selective drugs was associated with a reduced blood loss compared to the nonselective NSAIDs and a similar blood loss to the control.[11,20,21]

Second, safety concerns regarding the perioperative use of COX-2 inhibitors remain conflicting.[22] The COX-2 inhibitors, although less than nonselective NSAIDs effect, inhibit or delay bone healing in animal fracture models.[23,24] However, Reuben and Ekman[25] demonstrated no effect on the rate of nonunion after one year follow up when perioperative celecoxib was administered in patients undergoing spinal fusion surgery. The use of COX-2 inhibitors may be also associated with cardiovascular adverse effects.[26] However, the thrombotic cardiovascular events of etoricoxib were reported to be similar to diclofenac.[27] In addition, the incidence of such complications is related to the prolonged administration of these drugs or its use in certain patients at risk of cardiovascular problems.[28] There were no recorded adverse effects related to non-union or impaired healing, wound complications, adverse cardiovascular events, renal dysfunction or gastrointestinal bleeding in any patient of both groups during the study period.

In conclusion, etoricoxib can be safely used as a component of multimodal analgesia regimen in patients undergoing traumatic orthopedic surgery. A single preoperative dose of etoricoxib 120 mg decreased patients' morphine consumption with a lower incidence of postoperative nausea and vomiting.

References

1. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. ***Br J Anaesth*** 2001; 87: 62-72.
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be under managed. ***Anesth Analg*** 2003; 97: 534-540.
3. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. ***Anesthesiology*** 2005; 102: 822-831.
4. Ben-David B, Swanson J, Nelson JB, Chelly JE. Multimodal analgesia for radical prostatectomy provides better analgesia and shortens hospital stay. ***J Clin Anesth*** 2007; 19: 264-268.
5. Hartrick CT. Multimodal postoperative pain management. ***Am J Health Syst Pharm*** 2004; 61 Suppl 1: S4-S10.
6. White PF. Multimodal analgesia: its role in preventing postoperative pain. ***Curr Opin Investig Drugs*** 2008; 9: 76-82.
7. Myles PS, Power I. Clinical update: postoperative analgesia. ***Lancet*** 2007; 369: 810-812.
8. Gajraj NM. Cyclooxygenase-2 inhibitors. ***Anesth Analg*** 2003; 96: 1720-1738.
9. Cochrane DJ, Jarvis B, Keating GM. Etoricoxib. ***Drugs*** 2002; 62: 2637-2651.
10. Du Manoir B, Aubrun F, Langlois M, Le Guern ME, Alquier C, Chauvin M, et al. Randomized prospective study of the analgesic effect of nefopam after orthopaedic surgery. ***Br J Anaesth*** 2003; 91: 836-841.
11. Puura A, Puolakka P, Rorarius M, Salmelin R, Lindgren L. Etoricoxib pre-medication for post-operative pain after laparoscopic cholecystectomy. ***Acta Anaesthesiol Scand*** 2006; 50: 688-693.
12. Malmstrom K, Kotey P, Coughlin H, Desjardin PJ. A randomized, double-blind, parallel group study comparing the analgesic effect of etoricoxib to placebo, naproxen sodium, and acetaminophen with codeine using the dental impacted pain model. ***Clin J Pain*** 2004; 20: 147-155.

13. Rasmussen GL, Malmstrom K, Bourne MH, Jove M, Rhondeau SM, Kotey P, et al. Etoricoxib provides analgesic efficiency to patients after knee hip or hip replacement surgery: A randomized, double blind, placebo-controlled study. ***Anesth Analg*** 2005; 101: 1104-1111.
14. Smirnov G, Terävä M, Tuomilehto H, Hujala K, Seppänen M, Kokki H. Etoricoxib for pain management during thyroid surgery--a prospective, placebo-controlled study. ***Otolaryngol Head Neck Surg*** 2008; 138: 92-97.
15. Toivonen J, Pitko VM, Rosenberg PH. Etoricoxib premedication combined with intra-operative subacromial block for pain after arthroscopic acromioplasty. ***Acta Anaesthesiol Scand*** 2007; 51: 316-321.
16. Malan TP Jr, Marsh G, Hakki SI, Grossman E, Traylor L, Hubbard RC. Parecoxib sodium, a parenteral cyclooxygenase-2 selective inhibitor, improves morphine analgesia and is opioid sparing following total hip arthroplasty. ***Anesthesiology*** 2003; 98: 950-956.
17. Rainsford KD. Anti-inflammatory drugs in the 21st century. ***Subcell Biochem*** 2007; 42: 3-27.
18. Smith WL, Garavito RM, DeWitt DL. Prostaglandin endoperoxide H synthases (cyclooxygenases)-1 and -2. ***J Biol Chem*** 1996; 271: 33157-33160.
19. Dallob A, Hawkey CJ, Greenberg H, Wight N, De Schepper P, Waldman S, et al. Characterization of etoricoxib, a novel, selective COX-2 Inhibitor. ***J Clin Pharmacol*** 2003; 43: 573-585.
20. Martinez V, Belbachir A, Jaber A, Cherif K, Jamal A, Ozier Y, et al. The influence of timing of administration on the analgesic efficacy of paracoxib in orthopedic surgery. ***Anesth Analg*** 2007; 104: 1521-1527.
21. Leese PT, Recker DP, Kent JD. The COX-2 selective inhibitor, valdecoxib, does not impair platelet function in elderly: result of a randomized control trial. ***J Clin Pharmacol*** 2003; 43: 504-513.
22. Simon LS, Smolen JS, Abramson SB, Appel G, Bombardier C, Brater DC, et al. Controversies in COX-2 selective inhibitors. ***J Rheumatol*** 2002; 29: 1501-1533.
23. Gerstenfeld LC, Thiede M, Seibert K, Mielke C, Phippard D, Svagr B, et al. Differential inhibition of fracture healing by non-selective and cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs. ***J Orthop Res*** 2003; 21: 670-675.
24. Simon AM, O'Connor JP. Dose and timing-dependent effects of cyclooxygenase-2 inhibition on fracture-healing. ***J Bone Joint Surg Am*** 2007; 89: 500-511.
25. Reuben SS, Ekman EF. The effect of cyclooxygenase-2 inhibition on analgesia and spinal fusion. ***J Bone Joint Surg Am*** 2005; 87: 536-542.
26. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. ***JAMA*** 2001; 286: 954-959.
27. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. ***Lancet*** 2006; 368: 1771-1711.
28. Ott E, Nussmeier NA, Duke PC, Feneck RO, Alston RP, Snabes MC, et al. Efficacy and safety of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. ***J Thorac Cardiovasc Surg*** 2003; 125: 1481-1492.

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