Analgesic efficacy of pre-operative etoricoxib for termination of pregnancy in an ambulatory centre

W Liu, C C Loo, J W Chiu, H M Tan, H Z Ren, Y Lim

ABSTRACT

Introduction: Etoricoxib is a second generation cyclooxygenase-2 inhibitor with a rapid-onset time and a long duration of action. It is ideal for providing pre-emptive analgesia for ambulatory surgeries. We hypothesised that pre-operative etoricoxib can decrease the use of fentanyl post-operatively, when compared with placebo in patients undergoing termination of pregnancy. We also compared their pain scores, time to discharge, side effects and satisfaction with analgesia post-operatively.

Methods: After approval by the hospital research ethics committee and receipt of informed written consent, we recruited 40 American Society of Anesthesiologists Physical Status Classification I and II patients scheduled for elective first trimester termination of pregnancy. Patients were randomly allocated to receive either oral etoricoxib 120 mg (Group E, n=20) or placebo tablet (Group P, n=20) pre-operatively. A blinded observer evaluated the post-operative pain scores, need for supplementary analgesia, side effects and satisfaction scores. Sample size was calculated (power of 0.8 and α=0.05) to detect a 20% difference in fentanyl usage. Amount of fentanyl used, pain scores and satisfaction scores were analysed using non-parametric tests. The incidence of side effects was analysed using X^2 test.

Results: Etoricoxib 120 mg significantly decreased the amount of fentanyl required after termination of pregnancy compared to placebo (0 ug/patient, interquartile range [IQR] 0-25 versus 50 ug/patient, IQR 0-50, p-value is less than 0.05). Patients who received etoricoxib 120mg also had significantly lower pain scores than the placebo group at time of discharge (8 [±11] versus 1 [±3], p-value is less than 0.05) and at six hours post operation (8 [±12] versus 0 [±0], p-value is less than 0.01). There was no difference in their side effects, and time to discharge and overall satisfaction were similar in both groups.

Conclusion: Pre-operative administration of oral etoricoxib 120 mg decreased the use of fentanyl and pain scores after minor gynaecological surgery without significant side effects.

Keywords: ambulatory surgical procedures, analgesia, cyclooxygenase inhibitors, etoricoxib, non-steroidal anti-inflammatory drugs

Singapore Med J 2005; 46(8):397-400

Department of Anaesthesia
KK Women's and Children's Hospital
100 Bukit Timah Road
Singapore 229899

W Liu, MD
Registrar

C C Loo, MMed
Consultant

J W Chiu, MD
Consultant

H M Tan, MMed
Senior Consultant

Y Lim, MMed
Registrar

Department of Anaesthesia
Peking Union Medical College Hospital
Beijing
China

H Z Ren, MD
Consultant

Correspondence to:
Dr Yvonne Lim
Tel: (65) 6394 1081
Fax: (65) 6291 2661
Email: yve16@hotmail.com

INTRODUCTION

Termination of pregnancy (TOP) is a procedure frequently carried out in the ambulatory centre. Although most patients are discharged early, mild to moderate pain frequently delays discharge. It has been shown that the administration of non-steroidal anti-inflammatory drugs (NSAIDs) can significantly decrease post-operative pain, and reduce opioid consumption and opioid-related side effects after surgical procedures[1,2]. However, an association between NSAID use and gastrointestinal and operating site bleeding has been demonstrated, especially in elderly patients[3,4]. There have also been reports of severe complications such as death and renal failure requiring dialysis in otherwise healthy patients who received only one dose of ketorolac[5].

Cycloxygenase-2 (COX-2) is involved in the production of prostaglandins that are produced during inflammation. COX-2 selective inhibitors initially introduced for chronic pain management have been used for acute pain management[6]. They have been shown to provide effective pain relief in dental, orthopaedic and gynaecological surgery with fewer gastrointestinal adverse events compared to traditional non-selective NSAIDs[6-8].

First generation selective COX-2 inhibitors, such as celecoxib and rofecoxib, have been shown to be efficacious in providing post-operative pain relief[7,9]. Rofecoxib 50 mg has been demonstrated to provide analgesic effects similar to those of ibuprofen, and to reduce opioid consumption by 36%[10]. However, studies of second generation COX-2 inhibitors, such as etoricoxib, paracoxib and

valdecoxib, for use in managing post-operative pain have been limited.

Etoricoxib (Arcoxia, Merck & Co Inc, New Jersey, USA) is a second generation COX-2 inhibitor with 100-fold increase in selectivity for COX-2 over COX-1. Its analgesic efficacy is comparable to traditional NSAIDs, and this has been demonstrated in the management of chronic pain and in the acute management of patients with dysmenorrhoea or undergoing dental procedures[11-13]. Compared with first generation COX-2 inhibitors, such as rofecoxib and celecoxib, etoricoxib is more selective in-vitro than any COX-2 selective NSAIDs currently available[11]. Its rapid onset time (20 minutes) and long duration of action (half-life of approximately 25 hours) allows convenient once-daily dosing[14].

The aim of our study was to evaluate the analgesic efficacy of pre-operative administration of etoricoxib 120 mg when compared with placebo control in patients undergoing day-case TOP. We hypothesised that pre-operative use of etoricoxib can decrease the use of fentanyl post-operatively. We also compared their post-operative pain scores, side effects, time to discharge and satisfaction with analgesia.

METHODS

With the approval of the hospital research ethics committee and informed written consent, we recruited 40 American Society of Anesthesiologists Physical Status Classification (ASA) I and II patients who were scheduled to undergo elective first trimester TOP in our ambulatory surgical centre. This procedure is relatively non-invasive and is usually carried out with either minimal fentanyl and/or non-steroidal anti-inflammatory drugs peri-operatively at our centre. Our exclusion criteria included patients with history of asthma, gastritis, coagulation disorder, renal impairment and allergy to NSAIDs or COX-2 inhibitors. Patients with history of long-term analgesic use or any agents that may influence the analgesic response were also excluded.

Using sealed opaque envelopes, the patients were randomly allocated into two groups. The control group, Group P (n=20), received oral placebo tablets and Group E (n=20) received oral etoricoxib 120 mg with 20 ml plain water 30-60 minutes before operation. The primary anaesthetist who provided the anaesthesia and evaluated the post-operative pain scores was blinded to their group assignment. Every patient received a general anaesthetic with intravenous (IV) propofol 2.0-2.5 mg/kg given at induction. Anaesthesia was maintained with oxygen nitrous mixture (40:60) and Desflurane (end tidal) 1% at fresh gas flow of 3L/min.

Table I. Patients demographics and surgical duration.

	Placebo (n=20)	Etoricoxib (n=20)
Age (year)	27±7	24±5
Weight (kg)	53±7	54±9
Duration of surgery (min)	7±3	6±5

All values are mean ± standard deviation

Post-operative pain was assessed using a 100 mm verbal analogue score (VAS) (0=no pain and 100=the worst imaginable pain). The primary anaesthetist assessed the pain scores at emergence, 15 minutes, 30 minutes, and 60 minutes post-operatively, and at time of discharge (TimeD). Any patient who had a VAS>50mm or requested supplementary analgesia received boluses of IV fentanyl 25 μg every 15 minutes until she was comfortable or had a VAS<50mm. We also recorded their side effects (nausea, vomiting, gastric pain, heart burn, or dizziness), time to first drink (TimeF), time to step down (TimeS), and step-down time to discharge (TimeD).

Patients were discharged from day surgery when they met the discharge criteria. They were instructed to take rescue analgesia acetaminophen 1 g six hourly if needed at home. Follow-up assessment via the telephone was done to evaluate their pain scores at six hours and 24 hours post-operatively. The patient's requirement for rescue analgesia at home was also recorded. Patient's satisfaction with the pain management was assessed using a 100-point analogue scale (0 = very bad experience and 100 = excellent experience).

Sample size was calculated for a power of 0.8 and α=0.05 to detect a 20% difference in opioid usage between the two groups. We compared the amount of fentanyl used, pain scores and satisfaction scores using the Mann-Whitney test. Duration of procedure, time to first feed, time to step-down and time to discharge were analysed using non-parametric tests. The presence of side effects and the need for rescue analgesia (paracetamol) after discharge was analysed using the X^2 test.

RESULTS

The demographical characteristics of the two groups were similar, and there were no significant differences with respect to age, weight or duration of surgery (Table I). All patients were followed-up for 24 hours post-operatively and data of all 40 patients was analysed. The amount of IV fentanyl used during their recovery in the post-anaesthetic care unit (PACU) was significantly higher in Group P than in Group E (0 ug/patient, interquartile range [IQR]

Table II. Recovery profile and rescue analgesia needed in each group.

	Placebo (n=20)	Etoricoxib (n=20)	p-value
Time to 1st feed (min)	66±18	64±15	NS
Time to step-down(min)	80±20	83±17	NS
Time to discharge (min)	78±19	84±18	NS
Rescue fentanyl needed in PACU	12/20(60)	7/20(35)	NS
Rescue paracetamol needed after discharge	3/20(17)	1/20(0)	NS
Amount of fentanyl used (ug/patient)	50 (0-50)	0 (0-25)	<0.05
Overall satisfaction score	95 (90-100)	100 (90-100)	NS

All values are mean + standard deviation, proportion of patients (%) or median (interquartile range); NS: not significant.

Table III. Post-operative pain scores.

	Placebo (n=20)	Etoricoxib (n=20)	p-value
VAS ≥70mm at emergence	4/20 (20)	2/20 (10)	NS
Pain score at 15 min (0-100 VAS)	37±29	26±27	NS
Pain score at 30 min (0-100 VAS)	28±23	25±18	NS
Pain score at 60 min (0-100 VAS)	15±22	9±17	NS
Pain score at time of discharge (0-100 VAS)	8±11	1±3	<0.05
Pain score at 6 hours (0-100 VAS)	8±12	0±0	<0.01
Pain score at 24 hours (0-100 VAS)	0±0	0±0	NS

All values are proportion of patients (%) or mean + standard deviation; NS: not significant.

0-25 versus 50 ug/patient, IQR 0-50, p<0.05). More patients in the placebo group complained of pain post-operatively and requested supplementary analgesia but this did not reach statistical significance (12/20 or 60% versus 7/20 or 35% p>0.05) due to the small number of patients studied. None of the patients in the etoricoxib group and three patients in the placebo group required supplementary paracetamol after discharge; however, this did not reach statistical significance as our study was not powered to detect a difference (Table II).

The placebo group received more fentanyl in the PACU but their VAS scores were consistently higher post-operatively. The difference was statistically significantly at time of discharge (8 [±11] versus 1 [±3], p<0.05) and at six hours post-operation (8 [±12] versus 0 [±0], p<0.01) (Table III). All patients could perform normal routine activities. There was no increase in complications or side effects (e.g. nausea, vomiting, gastric pain, heart burn or dizziness) in either group although our study was not powered to detect this. There were no differences in their time to first feed, time to step down and time to discharge. Both groups were satisfied with their pain management (Table II).

DISCUSSION

TOP is usually associated with minimal post-operative pain. However, some patients may experience cramps and pain after the procedure, resulting in a delay in discharge. In ambulatory centres, the use of opioid is limited due to the need for early discharge, lack of monitoring at home as well as side effects associated with excessive opioid therapy (e.g. nausea, vomiting, urinary retention and sedation).

We showed that a single dose of oral etoricoxib 120 mg given pre-operatively significantly decreased the amount of fentanyl needed post-operatively, and improved the pain scores at time of discharge and six hours post-operation. In another study involving treatment of primary dysmenorrhoea, etoricoxib 120 mg demonstrated rapid and sustained analgesia which was superior to a placebo and similar to that of naproxen 550 mg[13]. Etoricoxib has a rapid onset time and this is especially useful when used for pre-emptive analgesia in the ambulatory surgery setting. The patients were given a single dose of etoricoxib when they arrived for surgery, and the rapid onset prevented delays in surgery and ensured that the drug is effective after the relatively short procedure. We were unable to show a significant decrease in the number of patients in Group E requesting analgesia as our study was not powered to do so. However, only 35% in Group E requested analgesia post-operatively, compared with 60% in Group P. This represented an absolute risk reduction of 25%.

A recent review of 18 randomised controlled studies on the use of NSAIDs showed only six studies (33%) demonstrated a pre-emptive analgesic effect[14]. Studies which failed to demonstrate pre-emptive analgesia attributed it to insufficient peri-operative nociceptive afferent blockade or the development of central sensitisation once the pharmacological action of the pre-emptive analgesia has worn off[15]. They recommended administering long-acting analgesics whose duration of action extends well into post-operative period. Etoricoxib with its long half-life and once-a-day dosing is ideal. This was seen in our study where only one patient in Group E required further analgesia (oral paracetamol) at home and this was taken only 14 hours after the surgical procedure.

In our study, time to discharge between the two groups was not significantly different, despite better VAS scores in the etoricoxib group. However, the discharge time was influenced by many factors,

such as the availability of a surgeon to review the patient prior to discharge and waiting for a relative to accompany the patient home. Furthermore, our study was not powered to detect a difference in discharge time. There was no increase in side effects among the patients in the etoricoxib group. Post-operative bleeding is a major concern among surgeons after gynaecological procedure and this is even more crucial in patients who are discharged home after the operation. Pre-clinical study of etoricoxib demonstrated that etoricoxib did not inhibit platelet aggregation and this was also validated by our study outcome[11].

The ideal analgesic agent for day-case surgery management should provide good peri-operative analgesia, allowing early discharge with minimal side effects. Pre-operative administration of oral etoricoxib 120 mg for TOP decreased the use of fentanyl post-operatively and decreased pain scores at discharge and six hours post-operatively without significant side effects.

REFERENCES

1. Claeys MA, Camu F, Maes V. Prophylactic diclofenac infusions in major orthopedic surgery: effects on analgesia and acute phase proteins. Acta Anaesthesiol Scand 1992; 36:270-5.
2. Gillies GWA, Kenny GN, Bullingham RE, et al. The morphine sparing effect of ketorolac tromethamine. A study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery. Anaesthesia 1987; 42:727-31.
3. Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative side bleeding. A postmarketing surveillance study. JAMA 1996; 275:376-82.
4. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999; 282:1929-33.
5. Smith K, Halliwell RM, Lawrence S, et al. Acute renal failure associated with intramuscular ketorolac. Anaesth Intensive Care 1993; 21:700-2.
6. Sinatra R. Role of COX-2 inhibitors in the evolution of acute pain management. J Pain Symptom Manage 2002; 24 (1 suppl):S18-27.
7. Malmstrom K, Fricke JR, Kotey P, et al. A comparison of rofecoxib versus celecoxib in treating pain after dental surgery: a single-center, randomized, double-blind, placebo- and active-comparator-controlled, parallel-group, single-dose study using the dental impaction pain model. Clin Ther 2002; 24:1549-60.
8. Morrison BW, Daniels SE, Kotey P, et al. Rofecoxib, a specific cyclooxygenase-2 inhibitor, in primary dysmenorrhea: a randomized controlled trial. Obstet Gynecol 1999; 94:504-8.
9. Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000; 91:1221-5.
10. Bekker A, Cooper PR, Frempong-Boadu A, et al. Evaluation of preoperative administration of the cyclooxygenase-2 inhibitor rofecoxib for the treatment of postoperative pain after lumbar disc surgery. Neurosurgery 2002; 50:1053-8.
11. Riendeau D, Percival MD, Brideau C, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J Pharmacol Exp Ther 2001; 296:558-66.
12. Chang DJ, Desjardins PJ, King TR, et al. The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial. Anesth Analg 2004; 99:807-15.
13. Malmstrom K, Kotey P, Cichanowitz N, et al. Analgesic efficacy of etoricoxib in primary dysmenorrhea: results of a randomized, controlled trial. Gynecol Obstet Invest 2003; 56:65-9.
14. Gottesdiener K, Schnitzer T, Fisher C, et al. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. Rheumatology (Oxford) 2002; 41:1052-61. Erratum in: Rheumatology (Oxford) 2003; 42:814.
15. Katz J. Pre-emptive analgesia: importance of timing. Can J Anaesth 2001; 48:105-14.
16. Kissin I. Preemptive analgesia. Why its effect is not always obvious. Anesthesiology 1996; 84:1015-9.