EFFECTS OF PREOPERATIVE SINGLE DOSE ETORICOXIB ON POSTOPERATIVE PAIN AND SLEEP AFTER LUMBAR DISKECTOMY: PROSPECTIVE RANDOMIZED DOUBLE BLIND CONTROLLED STUDY

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Abstract

Background: Etoricoxib, a selective Cox-2 inhibitor has been found to be effective in the management of acute pain. This study evaluates the effect of preoperative use of oral Etoricoxib on post operative pain relief and sleep in patients undergoing single level diskectomy.

Methods: In this prospective, randomized, controlled study, forty four patient (ASA 1&2,age 18-60 years) scheduled to undergo single level lumber diskectomy were given either placebo (control group) or Etoricoxib 120 mg orally one hour before surgery. Post operatively fentanyl intravenous (IV) PCA pump was started. Visual analog score (VAS) was assessed at 0, 6, 12, 18 and 24 hours at rest and movement. Primary end point was total pain relief over 24 hours. Sleep overnight, total fentanyl consumption, incidence of nausea and vomiting, intra-operative blood loss and patient satisfaction were noted.

Results: Forty three patients completed the study. Reductions in VAS at rest and on movement were observed in the Etoricoxib group when compared with the Control group at all the intervals till 24 hours postoperatively, except on movement at 24 hours postoperative ($P<0.05$). Total fentanyl consumption (μg/kg/hr) was higher in Control group ($P=0.007$). More patients in Etoricoxib group had a contented facial expression ($p=0.003$), relaxed body language ($p=0.00$) and better sleep at night than control group ($p=0.0004$).

Conclusion: Single preoperative oral dose (120 mg) of Etoricoxib, given one hour before surgery, has significantly reduced the post operative pain at rest and movement and improved sleep in patients undergoing single level diskectomy without any side effects and with good patient satisfaction.

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Introduction

Acute postoperative pain is an important part of anesthesia management, on a day to day basis. It causes distress to the patient, and may lead to hemodynamic disturbances, myocardial ischemia, respiratory dysfunction, patient dissatisfaction and may lead to chronic pain if not promptly treated. Acute postoperative pain is usually treated with opioids and non steroidal anti- inflammatory agents (NSAIDS). Opioids are associated with side effects like sedation, respiratory depression, nausea and vomiting[1] whereas nonselective NSAIDS are associated with increased risk of perioperative bleeding, renal dysfunction and gastrointestinal disturbances[2-3].

Among the NSAIDs, is the new generation of COX 2 inhibitors, of which Etoricoxib is a member. COX-2 selective inhibitor is a form of NSAID that directly targets cyclooxygenase-2, an enzyme responsible for inflammation and pain and devoid of side effect of COX-1 enzyme inhibition.

Etoricoxib, has been effective in providing analgesia in ambulatory surgeries, dental procedures, laparoscopic cholecystectomy and knee repair[4-5]. It is a safe and effective agent in controlling post-operative pain with minimal side effects.

However there is no existing literature with regards to its use as a preoperative analgesic to relieve postoperative pain in spinal surgery. Pain in patients with spine pathology is different from other types of pain, because these people have chronic pain issues and this may flair up in the acute post-operative period due to sensitization of the receptor. Furthermore, it is poorly studied entity.

Sleep disturbances are common in post operative patients, particularly in the first two nights after surgery[6]. Sleep in the post-operative period is of poor quality and is due to many factors, and adds to the discomfort of the paitient[7].

Hence, this study was formulated to effects of preoperative use of Etoricoxib to decrease postoperative pain and improve sleep after lumbar disc surgery.

Method

This prospective randomized, double blind, placebo controlled study was conducted after institute ethical committee approval and written informed consent from the patients. Forty four patients were enrolled from ASA physical status 1 & 2, age between 18-60 years of either sex scheduled to undergo single level lumbar diskectomy from January 2009 to February 2010.

Patients with history of asthma, gastritis, coagulation disorders, hepatic and renal impairment, and allergy to NSAIDS were excluded from the study. Patients on long term analgesics and patients unable to handle PCA pumps were also excluded from the study. Patients who were re-explored within 24 hours of surgery, or in whom surgery was extended more than one level, were dropped from the study and were not subjected to final statistical analysis.

Presuming that following surgery incidence of postoperative analgesic requirement would differ by 20% between the groups, for result to be significant with alpha = 0.05 and power beta = 0.08, one needed to recruit 20 patients in each group. We enrolled 22 cases to take care of any drop outs (if any).

Patients were assessed for eligibility during the pre anesthetic checkup and were explained about study protocol and use of patient controlled analgesia (PCA) pumps. All the patients were premedicated with tablet lorazepam 1mg in the night before and morning of surgery. Using sealed envelopes, the patients were randomly allocated into two groups by anesthesia assistant. The control group (Group C), received oral placebo tablets and Etoricoxib group received oral Etoricoxib (Group E) 120 mg with sips of water 60 minutes before surgery. Study medication and the placebo were identical. Patients were taken as a first case on the operation list to, avoid circadian rhythm related bias. Anesthesia was induced with fentanyl 3 µg/kg and propofol 2mg/kg. Tracheal intubation was facilitated with vecuronium bromide 0.1mg/kg. Anesthesia was maintained with propofol infusion 100-200 µg/kg/min and mixture 70% nitrous oxide in oxygen. Intermittent boluses of fentanyl 50 µg and vecuronium were given to maintain adequate depth. Extubation was done after reversal of neuromuscular block with injection neostigmine 0.04mg/kg and

glycopyrrolate 0.01mg/kg, on completion of surgery. Patients were shifted to post anesthesia care unit and connected to intravenous (IV) PCA pump. On IV PCA pump they received demand bolus of fentanyl 20 µg with a lockout interval of 10 minutes and maximum hourly fentanyl limit being 2µg/kg/hr.

Primary outcomes were the severity of postoperative pain both at rest and on movement, sleep at night and total consumption of fentanyl postoperatively. Secondary outcomes were intra-operative blood loss, facial expression, body language and incidence of nausea, vomiting, and pruritus.

An anesthesiologist, who was blinded to the study group, assessed the pain score at time points 0, 6, 12, 18, 24 hours on VAS scale (0-100 mm) at rest (static) and on movement (Dynamic). Total fentanyl consumption and incidence of side effects as nausea, vomiting during the study period were noted. Facial expression, body language and sleep at night were assessed in the morning following surgery, by the same anesthetist as in the following manner. Sleep at night was assessed subjectively as 1 = good, 2 = interrupted and 3 = no sleep; facial expression as 1 = contended, 2 = sad and 3 = frightened; and body language as 1 = relaxed, 2 = tensed and 3 = unhappy.

The method of analysis was decided prospectively and incorporated the intention-to-treat principle. Demographic data were analyzed with one way ANOVA for continuous variables and chi square test for categorical variables. Pain was measured as Median (interquartile range) VAS and was analyzed using the Mann-Whitney test. Total consumption of fentanyl was analyzed with student t test. The incidences of side effects were analyzed with Fisher's exact test. SPSS 14.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. $P<0.05$ was considered as significant.

Results

A total of 50 patients were evaluated out of which six patients were excluded from the study on account of preoperative history of asthma (2), use of prolonged NSAID medication (3), gastritis (1). Therefore 44 patients were included in this study and grouped according to randomization. One patient was dropped from the study as the incision needed to be extended to two more level. Therefore this patient was not subjected to further statistical analysis and only 43 patients completed the study (22 and 21 in control and Etoricoxib group, respectively) (Fig 1). There was no difference amongst the groups as regard to age, sex, weight, height, duration of anesthesia and intra-operative blood loss ($P>0.05$) (Table 1).

Table 2:
Postoperative Pain Score: Pain was assessed by 100 mm visual analogue scale (VAS); 0 = none, 100 = worst imaginable pain and expressed as median VAS scores (inter-quartile range). Pain was analyzed by Mann Whitney test and total fentanyl consumption with one way ANOVA.

Variables \ Groups		Control (n=22)	Etoricoxib (n=21)	P value
0 hr	Static	55(12.5)	20(32.5)	0.000
	Dynamic	55(10)	30(52.5)	0.003
6 hr	Static	45(10)	22.5(40)	0.008
	Dynamic	50(7.5)	27.5(40)	0.003
12 hr	Static	40(7.5)	20(30)	0.000
	Dynamic	45(10)	27.5(31.3)	0.006
18 hr	Static	35(5)	20(31.3)	0.06
	Dynamic	40(7.5)	30(20)	0.02
24 hr	Static	30(5)	15(30)	0.012
	Dynamic	35(5)	20(30)	0.33
Total postoperative fentanyl consumption (µg)		675.00	461.81	0.007

Table 1:
Demographic data presented either as mean ± SD or numbers. No significant differences between the groups by one way ANOVA for continuous variables and chi square test for categorical variables (P>0.05).

Groups / Variables	Control (n=22)	Etoricoxib (n=22)
Age (yrs)	39.6± 11.5	39.9± 11.1
Sex (M/F)	12/8	15/5
Weight (kg)	62.4±11.3	60.3±13.3
Height (cm)	166.1±5.2	168.7±7.1
Duration of Anaesthesia (min)	160.4±30.0	152±38.4
Intraoperative Blood Loss	**188.10+49.76**	**190.91+52.64**

Reduction in VAS static (at rest) and dynamic (on movement) were observed in Etoricoxib group compared with Control group at all the point of time till 24 hours postoperatively, with the exception where VAS dynamic between two groups was similar at 24 hours postoperatively. Total fentanyl consumption (µg/kg/hr) was higher in Control group compared to Etoricoxib group (P<0.05) (Table 2).

More patients in Etoricoxib group had a contented facial expression and relaxed body language than control group. (P<0.05) (Table 3) Sleep at night was better in Etoricoxib group compared to control group. (P<0.05) (Table3). None of the patients in both the groups complained of nausea, vomiting, headache or any other side effect, although our study was not powered to detect this (P>0.05). Intraoperative blood loss was equal in the both the groups (P>0.05) (Table 1). There were no episodes of sedation or respiratory depression requiring any intervention.

Table 3:
Sleep Facial expression and Body language; data are presented as numbers and analyzed by Fisher's exact test.

Groups / Parameters		Control (n=22)	Etoricoxib (n=21)
Sleep (p=0.00)	Good	6	14
	Interrupted	13	7
	No sleep	3	0
Facial expression (p=0.003)	Contended	5	14
	Sad	12	6
	Frightened	5	1
Body language (p=0.004)	Relaxed	7	16
	Tensed	11	4
	Unhappy.	4	1

Discussion

Our results demonstrated that preoperative use of oral Etoricoxib, 120 mg one hour before surgery has reduced the post operative pain score both at rest and movement; and postoperative fentanyl requirement after single level lumbar diskectomy. Sleep at night, facial expression and body language were better with the use of Etoricoxib whereas there was no increase in intra-operative blood loss and side effect.

Etoricoxib is a second generation COX-2 inhibitor with 100 fold increases in selectivity for COX-2 over COX-1. This reduces prostaglandins (PGs) generation from arachidonic acid. It has been found to be safe and effective in the management of acute pain in different surgical conditions[8-10].

NSAIDs (nonselective COX) also have pain relieving and an opiate sparing effect and proven to be effective after major surgery however gastrointestinal bleeding and bleeding from operative site are the major concern with its use. A review of 18 randomized controlled trials on the use of NSAIDs, showed only six (33%) studies demonstrated a preemptive analgesic effect. Studies which failed to demonstrate preemptive analgesia ascribed it to the short duration of action of these agents and recommended a long acting analgesic which can provide analgesia in the post operative period also[11].

Etoricoxib with its convenient single daily dosing and long half life (24.8 hours) was found to be superior in the relief of post operative pain. Cochrane database of five studies observed that Etoricoxib in the dose of 120 mg gives high levels of good quality pain relief after dental surgery as effective as or better than, other commonly used analgesics[12]. Etoricoxib due to its short onset and long duration of action was also proved to be useful as a preemptive analgesic, in ambulatory gynecological surgeries[4]. The maximum plasma drug concentration occurs after approximately 1 hour of oral dose and the extent of absorption is similar with oral and intravenous doses. The elimination half-life of approximately 20 hours in healthy subjects enables once-daily dosing[13]. Preoperative use of Etoricoxib 120 mg was found to be equally effective with Etoricoxib and paracetamol combination for postoperative pain relief after laparoscopic cholecystectomy, when pain intensity and opioid sparing effects were compared[5].

Preoperative use of Etoricoxib 120 mg in patients undergoing ambulatory, laparoscopic gynecological surgery was found to be equally effective in controlling pain compared with iv ketorolac 30 mg at 24 and 48 hours though immediate pain relief was better with ketorolac[14]. Kitti J et al, also showed that parecoxib reduces post-operative pain in spinal surgery patients and this study is comparable with our study[15].

There has been growing interest in the assessment of patient satisfaction with health care. Studies have shown that adequate postoperative pain control may be an important determinant of patient satisfaction[16-17]. Better satisfaction expressed as contented facial expression and relaxed body language might be translated into superior postoperative pain relief in the patient of Etoricoxib group in our study.

Post-operative sleep disturbance seems to be related to the magnitude of trauma and thereby to the surgical stress response. Post-operative sleep disturbance may contribute to the development of episodic hypoxemia, haemodynamic instability and altered mental status, all of which have an influence on post-operative morbidity and mortality. Prevention or reduction of the post-operative sleep disturbance may be achieved by minimizing surgical trauma, changing the conventional nursing procedures, avoiding opioids and treating pain with non-opioid analgesics. Multifactorial nature of post-operative sleep disturbance indicates that it may be difficult to prevent. However in our study we found that the group which received Etoricoxib had better quality of sleep. This may be due to, decreased pain, reduced stress response and less need for opioids, which inhibit Random Eye Movement (REM) sleep and Slow Wave Sleep (SWS)[18].

COX-2 inhibitors are known to decrease opioid consumption by 30–50%, yet the effects of perioperative Coxibs on opioid-related side effects (PONV) are still uncertain[19]. However, there were no differences in PONV incidence between control and Etoricoxib group in present study. Further evaluation, using a larger sample, is called for. Possible common side effects of COX-2 inhibitors and other NSAIDS are fluid retention, hypertension and renal damage, particularly in the elderly. None of such problems have been encountered in any of our cases.

The major limitation of our study was the limited period of pain evaluation (24 hours) postoperatively and since Etoricoxib has a long half life of 20 hours, we should have observed the long term effects of Etoricoxib beyond 24 hours.

Thus preoperative use of oral Etoricoxib, 120 mg one hour before surgery has significantly reduced the post operative pain score both at rest and movement and post operative opioid requirement with good sleep and patient satisfaction after single level lumber diskectomy therefore looking at the benefits we recommend its use in these patients.

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