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A Multimodal Analgesia of Cyclooxygenase-2 for Postoperative Pain

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ABSTRACT

Recently, Interest to multimodal analgesia, using of two or more analgesics and modalities to treatment of postoperative pain is rising. The aim of this study was to assess the effect of celecoxib on pain and associated complications after lumbar disc surgery. In a randomized, double- blind, placebo- controlled trial, 76 patients scheduled for elective laminectomy divided into two groups. Group A : celecoxib group (n=38, received celecoxib 400 mg 2hrs before surgery and 200 mg 6 hrs after surgery, along with morphine), Group B : control group (n=38, received placebo tablets at the same time along with morphine). Visual Analog Scale (VAS) was used to determine the severity of pain. Complications after surgery, anxiety scores before surgery and patient's satisfaction 24 h after surgery were recorded. The mean pain severity score and morphine consumption in the celecoxib group were less compared to the control group at various intervals (P < 0.001). The mean anxiety score(2.2 vs 3), shivering (23.6% vs 42.1%), nausea (18.4% vs 44.7%), vomiting (13.1% vs 39.5%) and Pruritus (18.4% vs 44.7%) in the celecoxib group were significantly lower compared to the control groups, respectively (P < 0.001, P < 0.05). Not significantly differences were observed between groups in relation to blood loss (331.12 vs 335.17), drowsiness (13.2% vs 5.3%) ,dizziness (26.3% vs 21.1%) and headache (13.2% vs 10.5%), respectively (p> 0.05). In the celecoxib group patient satisfaction was significantly higher compared to the control group (p< 0.001). Celecoxib 400 mg 2 hrs before surgery and 200 mg 6 hrs after surgery is a good alternative in multimodal analgesia, effective in pain control with lesser side effects seen with morphine alone in patients' pain management following lumbar disc surgery.

Keywords: Multimodal Therapy, Analgesia, Lumbar Spine Surgery, Celecoxib, Trial
IRCT Number: (IRCT2015071222870N3).

INTRODUCTION

Postoperative pain is one of the most common challenges in surgical patients that affects a various types of physiological functions. According to researches, 57% of patients reported that postoperative pain is their primary preoperative concern [1,2]. Literature shows that 80% of patients undergoing surgery experience postoperative pain [3,4]. The majority (more than 80%) of these patients reported the intensity as moderate to severe [5]. Pain after surgery with several complications include decreased wound healing, increased infections, longer hospitalization, development of chronic pain, readmission after discharge, increase morbidity and costs of hospital is a major challenge in postoperative care [6]. Therefore management of postsurgical pain play a critical role in quality of the care plan [7]. Patients who experienced postoperative pain are exposed to decreased pulmonary function and the risk

of developing thromboembolism due to immobility and suffer from nausea and vomiting .Also cardiac workload, systemic vascular resistance, and myocardial oxygen consumption increase due to catecholamine release [8].

Laminectomy following lumbar herniation is one of the most common surgeries with an incidence of 10 to 40% in neurosurgery. Annually, between 300,000 to 400,000 lumbar surgery was done. In the United States alone $ 2.5 billion will spent lumbar surgery. In addition annually, back pain causes loss of about 150 million days of work [9,10]. The first choice for the management of postoperative pain is opioid. The use of opioids due to a number of adverse effects such as respiratory depression, nausea, vomiting, excessive sedation, dizziness, drowsiness, pruritus, and urinary retention is limited [11,12,13]. The use of NSAIDs is one of the most common nonopioid analgesic techniques for postoperative pain management [14]. In multimodal *analgesia*, nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX-2 inhibitors) are effective in pain management [15].

Celecoxib is a selective cyclooxygenase (COX-2) inhibitor as an effective analgesic for postoperative pain, decreasing pain scores and morphine consumption after surgery [16,17]. Recently there has been emphasis on the use of non opioid analgesic drugs , the use of two or more analgesics, and multimodal therapy [18,19]. One of these multimodal analgesia methods is the use of NSAID's such as celecoxib. Although previous studies have evaluated the analgesic efficacy of NSAID's, few studies to date have evaluated the efficacy of celecoxib for Laminectomy.

To the best of our knowledge and importance of economic and physical aspects of postoperative pain, due to the lack of comprehensive studies of the efficacy of celecoxib in laminectomy patients, investigation in this field is necessary. The purpose of this study was to assess the effect of celecoxib on pain and associated complications after laminectomy. In this study, we hypothesized that celecoxib provides better efficacy than the use of morphine, which is currently the standard therapy in spinal surgery.

MATERIALS AND METHODS

This was an experimental study that was carried out at the Imam Khomeini hospital affiliated with Ilam University of Medical Sciences, Ilam, IR, during the April - September 2015. The statistical population included all the patients that due to laminectomy were referred to our department.

Sample Collections

The sample size was calculated according to information obtained from a pilot study with 10 patients and following formula.

$n= (Z_1+Z_2)^2 (2S^2) /d^2 = 38$

$Z_1 = 95\%= 1.96$

$Z_2 = 80\%= 0.84$ (test power)

S (an estimate of the standard deviation of VAS in the groups; 1.67 was obtained in a pilot study).

d (The minimum of the mean difference of VAS between the groups which showed a significant difference and was obtained 1.1.)

In a randomized, double-blind, placebo -controlled trial, 76 patient American society of Anesthesiologists (ASA) grade I or II, aged 20-60 years, scheduled for elective laminectomy under general anesthesia were enrolled in this study. Patients were divided into two groups. In each group, there were 38 patients. group A : celecoxib group (subjects received 400 mg celecoxib 2hrs before surgery and 200 mg 6 hrs after surgery, along with morphine in the postoperative period .Group B: control group (subjects received placebo tablets at the same time points along with morphine in the postoperative period). The administration of morphine in both groups was according to patient needs in the postoperative period. In order to achieve the same VAS scores after surgery in the groups we used the extra morphine in Patients that suffering from pain in the placebo group.

A simple random sampling design was used (Table/Fig 1: flow chart). Sampling with a sealed envelopes technique and coding was done. Coded as: code 1= celecoxib, code 2= control. Coding and sealed envelopes technique was prepared by a nurse who was not participating in the study. The patients with drug abuse, history of allergic reaction to the study drug, on non-steroidal anti-inflammatory analgesic, pregnancy, cardiovascular, metabolic, respiratory, peptic ulcer and renal failure, or coagulation abnormalities were excluded from the study. Neurosurgeon and

anesthesiologist were same in all patients. Anesthesia was given with inj. Thiopentone (5 mg/ kg IV) and inj. Atracurium (0.5 mg/ kg IV), and maintained with Isoflurane (1-1.5%) and Nitrous Oxide (50%) in Oxygen. Fentanyl was given in the operation room according to patient need and clinical discretion. Patients were reversed with 0.05 mg/kg Neostigmine combined with 0.02mg/kg Atropine. Standard monitoring included electrocardiogram, noninvasive blood pressure, and pulse oximetry.

Measurements

We used the VAS to determine severity of pain. The pain severity was assessed 2, 4, 6, 8, 12 and 24 hrs after surgery. The patient's mean blood pressure (BP), heart rate (HR), blood loss during surgery , respiratory rate (RR), saturation (SPO2), urine retention, vomiting, shivering , headache , dizziness , nausea , drowsiness, pruritus , and morphine consumption were recorded. Anxiety scores before surgery and patient's satisfaction 24 h after surgery were recorded. Preoperative anxiety was assessed according to a seven-point scale (1 = relaxed, 2 = apprehension, 3 = mild anxiety, 4 = moderate anxiety, 5 = manifest anxiety, 6 = severe anxiety, 7 = very severe anxiety). The patient's satisfaction with pain management was assessed on a 5-point scale; 0 = poor, 1 = fair average, 2 = moderate, 3 = good and 4 = excellent) during postoperative periods was recorded. Shivering was assessed on a scale with 0 = no shivering observed, 1 = shivering observed [1]. [3].

Validity and Reliability

VAS rating is a standard tool for evaluating of pain severity having ratings from 0 to 10. 0 [0 means no pain and 10 means the maximum pain in this scale]. To determine the validity of the Questionnaire, content validity was used. The questionnaire was given to 10 faculty members of Ilam University of Medical Sciences and was used after revision. To determine the reliability of questionnaire, Cronbach's alpha test was used. The reliability of the questionnaire was 0.83.

Ethical consideration

The study was approved by the Institutional Ethics Committee at the Ilam University of Medical Sciences, Ilam, IR, (EC: 94/H/269) and informed consent was obtained from all samples. This study was registered at the Iranian Registry of Clinical Trials (IRCT2015071222870N3).

Statistical analysis

Collected data were analyzed using the statistical software SPSS, Ver.16. (SPSS Inc, Chicago, IL, USA). Descriptive statistics, Chi-square test, independent T test and Repeated Measurement were performed to analyze the results. $P<0.05$ was considered significant.

RESULTS

Baseline characteristics of the patients are shown in Table 1. None of the 76 enrolled patients was withdrawn for any reason. In the quantitative data according to Kolmogorov-Smirnov test, data distribution was normal and we used the parametric methods ($P > 0.05$)

Samples characteristics were not different among the groups ($P > 0.5$) (Table 1). independent T test showed that the mean pain severity score in the celecoxib group were less than the control group at various intervals ($P < 0.001$) (Table 2).

Repeated measurement analysis showed that the mean pain score in the celecoxib group ($P < 0.001$), and control group ($P < 0.05$) were significantly different in various intervals.

The mean morphine consumption, anxiety score, shivering, nausea, vomiting and pruritus in the celecoxib group were significantly lower than the control group ($P < 0.001$, $P < 0.05$) (Table 2,3/ Fig 2).

No significantly statically difference was observed between groups in relation to blood loss, drowsiness, headache, Urine Retention and dizziness ($p> 0.05$) (Table 1,3). In the celecoxib group patient satisfaction was significantly higher than those in the control group ($p< 0.001$). (Table 2).

DISCUSSION

Postoperative pain result to decreases quality of postoperative recovery, readmissions, causing chronic pain after surgery and increasing morbidity and costs [5]. Although opioids are the first choice for postoperative pain management but they are associated with side effects [20].Studies emphasized on the use of nonopioid analgesic drugs and multimodal therapy for preventing pain in the preoperative period. Several benefits of multimodal therapy include improved pain relief, reduction in preoperative stress response, shorter hospital stays, decreased hospital costs, improved patient satisfaction, and a reduction in postoperative morbidity and mortality [11].

Recently, Interest to multimodal analgesia , using of two or more analgesics and modalities with multi mechanisms to treatment of analgesia and decreases the prevalence of complication is rising [3].Meta-analysis studies highlighted the importance using of NSAIDs and COX-2 inhibitors in the multimodal analgesic approach [21]. Therefore, the multimodal analgesic approach has been recommended as an alternative treatment for the management of postoperative pain [22].

Our results showed that celecoxib significantly reduced pain, overall morphine consumption, preoperative anxiety, pruritus , postoperative shivering, nausea and vomiting in patients following laminectomy under general anesthesia. In the celecoxib group patient satisfaction was significantly higher compare to the control group. This finding was consistent with the previous studies on the effects of celecoxib on postoperative pain and complications [16, 23-29].

Huang et al (2008) concluded following total knee arthroplasty, 400 mg of celecoxib, 1 hour before surgery, and 200 mg every 12 hours along with morphine for five days significantly decreases postoperative pain scores at 48 and 72 hrs and opioid consumption without increasing the risks of bleeding [16]. In another study Reuben and Connelly (2000) found that perioperative use of celecoxib (200 mg) and rofecoxib (50 mg) for spinal fusion surgery significantly improve postoperative pain and decrease morphine consumption [26].

In follow-up study with these researchers preoperative celecoxib 400 mg significantly reduce morphine consumption than a single 200 mg dose of celecoxib [23]. Bekker et al demonstrated that rofecoxib significantly decreases use of morphine consumption in lumbar disc surgery [30]. Sieper et al (2008) shows celecoxib 200 mg once a day and 200 mg twice a day significantly reduce pain score than diclofenac 75 mg twice a day in active ankylosing Spondylitis [31]. In Ishiguro et al (2015) research celecoxib is superior compared to placebo and etodolac for controlling acute postoperative pain [32].

Rouhani et al (2014) conclude celecoxib (400mg/daily) started 48 hours before surgery and continued for 10 days after operation is effective analgesia in patients' pain management following arthroscopic rotator cuff repair surgery [33]. Matsota et al (2013) found a single dose of 200 mg of celecoxib significantly improved pain score in parturients under patient-controlled epidural analgesia, and reduce supplemental analgesics with increasing patient satisfaction [34].

Previous research found celecoxib (1200 mg daily) has no effects on platelet functions or serum thromboxane [16]. It seem consistent with our study, further dose of 400 mg of celecoxib is more optimal than 200 mg in controlling acute postoperative pain [35,36]. In Reuben et al study (2008) nausea and vomiting in the celecoxib group were less than the placebo group [37]. Similar result of our study with the aforementioned study indicates to significant effect of celecoxib in reducing nausea and vomiting in patients underwent lumbar disc surgery.

The cardiovascular side effects of COX-2 inhibitors widely accepted. Several studies of long-term use of selective COX-2 inhibitors suggested an increased risk of incident atrial fibrillation, myocardial infarction, stroke, and heart failure [38,39]. Although conventional non-selective NSAIDs increase bleeding risks but researches suggested selective COX-2 inhibitors have less antiplatelet effects [16] gastrointestinal toxicity [40] and cardiovascular risk [41] than conventional non-selective NSAIDs.

Celecoxib is a selective COX-2 inhibitor, with an inhibitory effect on COX-2 that is 375 times stronger than on COX-1 [32]. The mechanism of action of NSAIDs to reduce postoperative pain by suppressing cyclooxygenase-mediated production of prostaglandin E2 [14]. The limitations of our study include relatively small sample size and

the subjective perception of pain by patients. All patients enrolled in this study were operated upon by a single surgeon and data collected from a single center that was the strength of this study.

Table1. Baseline Characteristics of the patients

Characteristic	Control group (n=38)	Celecoxib group (n=38)	P value
Age (year) [mean± sd]	50.2±7.2	50.2±4.2	0.881*
Sex [(M/F) n%]	[28(73.7%), 10(26.3%)]	[29(76.3%), 9(23.7%)]	0.467*
Married (n%)	34 (89.5%)	36 (94.7%)	0.871*
Mean duration of surgery ± SD (hr)	2.11 ± 0.23	2.17± 0.35	0.654*
Mean duration of anesthesia ± SD (hr)	2.35 ± 0.14	2.49± 0.25	0.537*
Blood loss ^{cc}	335.17±45	331.12± 38	0.246*
BP (mm/Hg)	132± 3.2	126±3.1	0.863*
PR (per/min)	72.8± 3.4	74.4± 5.4	0.736*
Spo_2	95± 3.4	96± 2.7	0.741*

** P > 0.05*

Table 2: Severity of pain, Morphine consumption and Anxiety score in groups

Characteristic	Control group(n=38)	Celecoxib group (n=38)	**P value**
Pain score by VAS at various intervals (hours)	M±SD	M±SD	
2 h after intervention	7.6±1	5±1	0.000*
4 h after intervention	6.6± 0.9	3.8± 0.5	0.000*
6 h after intervention	5.4± 0.5	3.1± 0.7	0.000*
8 h after intervention	4.5±0.6	2.4± 1	0.000*
12 h after intervention	3.9±0.7	1.8±0.4	0.000*
24 h after intervention	2.4± 0.4	1± 0.4	0.000*
Morphine consumption (mg)	30.1 ± 0.6	10.8± 6.8	0.000*
Anxiety score	2.2± 0.7	3± 0.9	0.000*
Patient Satisfaction			
Good	4(10.5%)	22 (57.8%)	0.000*
Excellent	0 (0)	13 (34.2%)	0.000**

** P <0.001 ** P < 0.05*

Table 3: frequencies of adverse effects between groups

Outcome parameters	Control group (n%)	Celecoxib group (n %)	P value
Vomiting	15 (39.5%)	5(13.1%)	0.02*
Shivering	16 (42.1%)	9 (23.6%)	0.01*
Headache	4 (10.5%)	5 (13.2%)	0.930***
Dizziness	8 (21.1%)	10 (26.3%)	0.519***
Nausea	17 (44.7%)	7 (18.4%)	0.01*
Drowsiness	2 (5.3%)	5 (13.2%)	0.03*
Pruritus	17 (44.7%)	7 (18.4%)	0.02*
Urine Retention	9 (23.7%)	8(21%)	0.637***

** P <0.05 ** P< 0.001 *** P> 0.05*

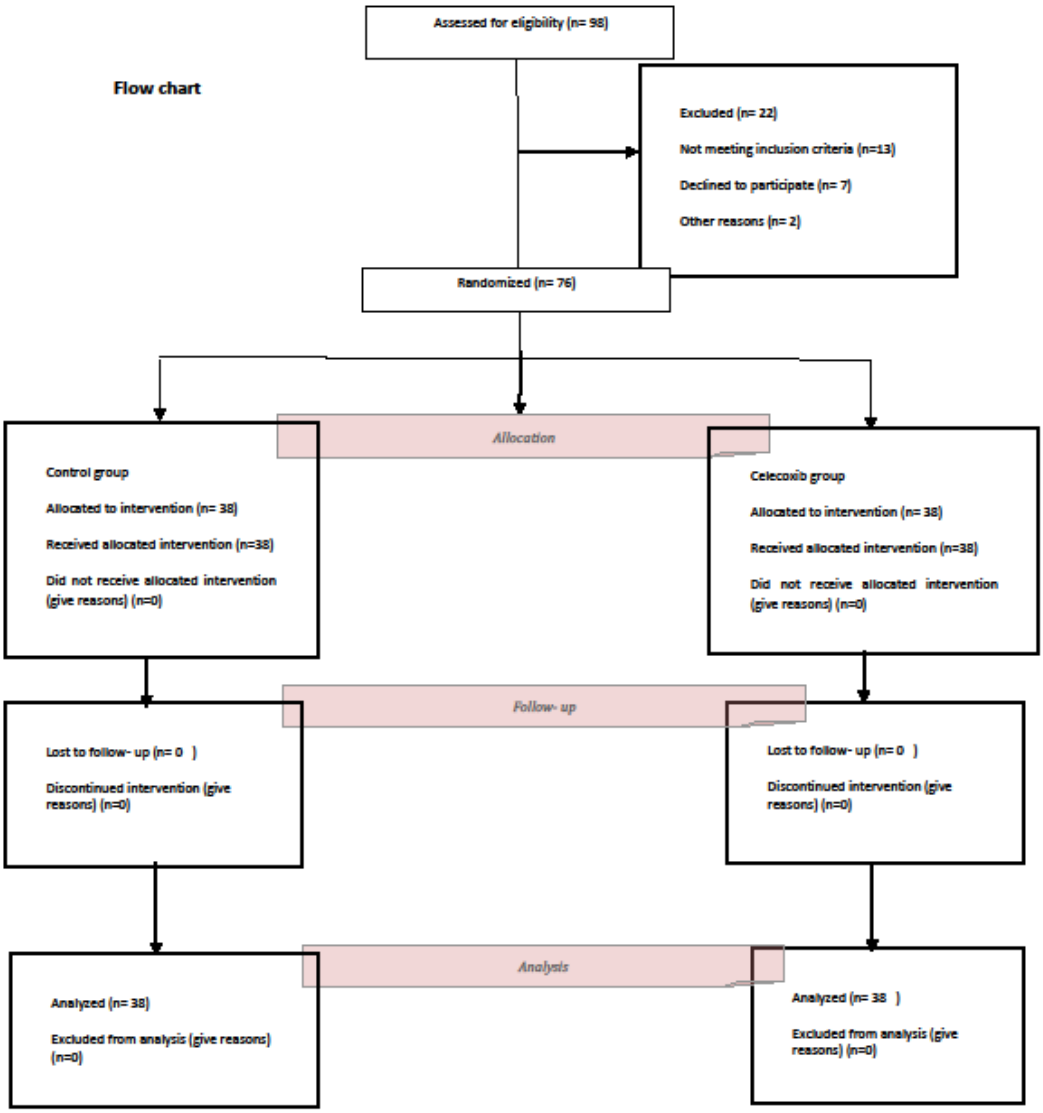

Fig 1: CONSORT diagram of participant in the clinical trial

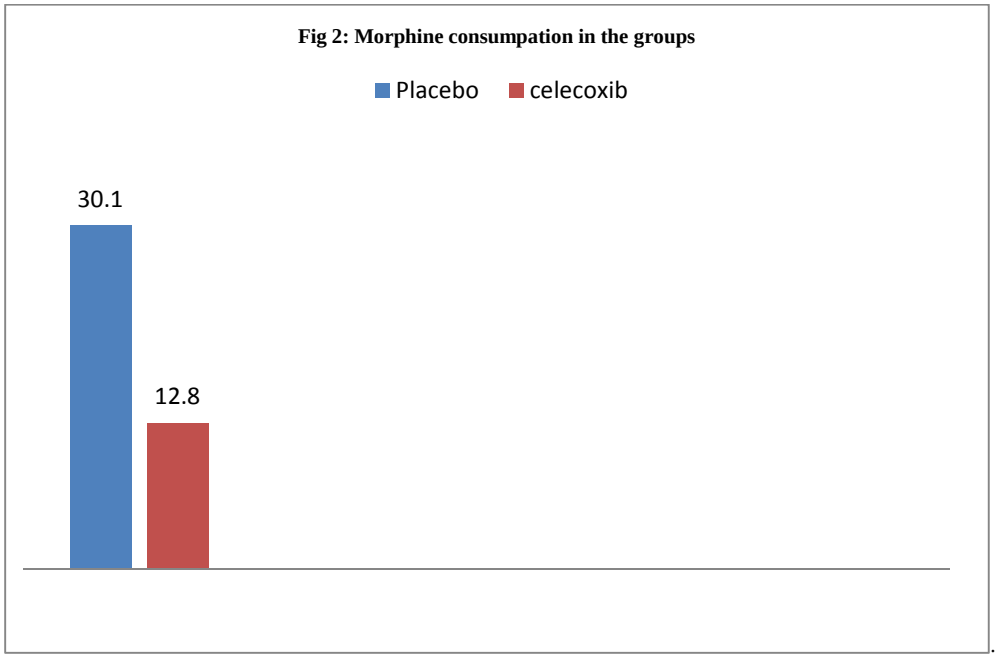

Fig 2: Morphine consumpation in the groups

CONCLUSION

To conclude, the use of celecoxib, 400 mg 2 hrs before surgery and 200 mg 6 hrs after surgery ,along with morphine is effective analgesia in patients' pain management following laminectomy and significantly reduce pain score. The adverse effects of celecoxib were found to be less. It also decreases the amount of morphine consumption for postoperative pain management as well as increased patient satisfaction in celecoxib group. So celecoxib is a good alternative in multimodal analgesia.

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