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PREOPERATIVE CELECOXIB EFFECT ON POSTOPERATIVE PAIN MANAGEMENT IN PATIENTS UNDERGOING LEG SURGERY: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background: Preoperative pain management is an important aspect for anesthetists. Using analgesics before the surgery can delay pain feeling and analgesic request by patients. We compared the effectiveness and priority of single dose 400 mg celecoxib, over two doses of 200 mg celecoxib in patients undergoing leg surgery.
Methods: We performed a double blind randomized controlled trial on 60 undergoing elective leg surgery. The patients were randomly classified into three groups of A: 400 mg celecoxib in two divided doses (200 mg each dose), B: 400 mg celecoxib single dose, and C: placebo. Pain after the surgery was scored according to visual analogue rating scale, on recovery and in 2 – 4 - 6 hours after recovery. The time to ask rescue medication was also recorded.
Results: There were not any significant difference between the studied groups regarding age, gender, surgical duration and VAS in 1st, 2nd, 4th, and 6th hours after surgery. The time lag for opium demand after surgery was longest (18.1 ± 15.8 vs. 20.4 ± 10.8 and 21.5 ± 8.4), and the used opium was lowest in the one dose 400 mg celecoxib group (196.5 ± 121 vs. 127.5 ± 68 and 122.7 ± 44) than in others (P value= 0.023).
Conclusion: We used tolerability and clinical significant of single dose 400 mg celecoxib in the postoperative pain management in leg surgery. It was more effective than two doses celecoxib 200 mg in postoperative pain control and postponing the time for rescue medicine need by the patients.

INTRODUCTION

Post operative pain control is an essential part of surgery (Joshi *et al*., 1994; Kehlet *et al*., 2003). Surgical procedures should be performed with minimum stress, maximum comfort and the optimal chance of early discharge. Improving day surgery rates is a win-win situation, with both clinical and financial benefits (Kehlet *et al*., 2006). It is in eternally managed with opium containing compounds and non steroidal anti inflammatory drugs (NSAID) (Lunn *et al*., 2011; Mao *et al*., 1995). Many studies have shown the beneficial effect of NSAID in pain management (Malmstrom *et al*., 2004; Zelenakas *et al*., 2004). NSAID have been shown to have opium sparing effect. Studies have shown that preoperative NSAID improve postoperative pain management of leg, knee and hip fracture or spinal fusion surgery (Reuben *et al*., 2000; Reuben *et al*., 2006; Roy *et al*., 2010). Celecoxib is a selective cyclooxygenase (COX-2) inhibitor prescribed for the relief of chronic pain in osteoarthritis and rheumatoid arthritis (Parsa *et al*., 2009). The drug is believed to be associated with fewer adverse effects than conventional non-steroidal anti-inflammatory drugs (NSAIDs) especially in antiplatelates activities (Reuben *et al*., 2006). Despite risk of bleeding in NSAIDs use, celecoxib has no effect on serum thromboxane or platelets function. Although celecoxib has some other useful effects on prevention of heterotopic ossification after hip surgeries (Cicirello *et al*., 2011), but some important complications such as risk of myocardial infarction has been reported after long time administration of celecoxib (De Vecchis *et al*., 2014). Studies have shown a similar analgesic effect of celecoxib 400 mg (one dose) with conventional non selective NSAID (Huang *et al*., 2008). Also 200 and 400 milligram celecoxib in different times after surgery have been

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Table 1. Primary characteristics and the studied variables between the studied groups

	Placebo (N=20)	Celecoxib (200 MG, 2 DOSE)	Celecoxib (400 MG, 1 DOSE)	P Value
Age (years)	29.4±7.7	25.5±6.2	29.2±6.9	0.154
Female (N, %)	3 (15%)	2 (10%)	3 (15%)	0.800
Surgical Duration	123±41	126±44	126±55	0.981

Table 2. Finding about pain and rescue medication compared between the studied groups

	Placebo (N=20)	CELECOXIB (200 MG, 2 DOSE)	CELECOXIB (400 MG, 1 DOSE)	P Value
VAS in 1st hour	0.9±0.6	0.8±0.6	0.7±1	0.76
VAS in 2nd hour	2.8±1.1	2.8±1.1	2.9±1.9	0.945
VAS in 4th hour	2.9±0.9	3.1±0.9	3.8±1.8	0.066
VAS in 6th hour	2.8±0.9	2.9±0.9	3.5±1.5	0.119
Time to use of rescue medication (min)	122.7±44	127.5±68	196.5±121	***0.023***
Amount of used opium (mg)	21.5±8.4	20.4±10.8	18.1±15.8	0.662

used to obtain which of them is more useful. Up to now, all studies assessed and compared the efficacy of pain killing after surgery after using celecoxib 200mg, celecoxib 400mg or placebo. Here we aimed to assess the 200 mg celecoxib (2 doses), in the management of postoperative pain comparing with single dose (400 mg).

MATERIALS AND METHODS

The local ethics review committee of Iran University of Medical Sciences approved the study protocol and written informed consent was obtained from all patients before participation in the study. The trial has been registered at IRCT (Iranian Registry of Clinical Trials) (code number: IRCT201010194969N1) According to previous studies and consultant epidemiologist, sample size was considered about 56 (Reuben *et al*., 2000). We performed a double blind randomized controlled trial on 68 patients undergoing elective leg surgery in 2011, Firoozgar Hospital (educational hospital, Iran University of Medical Sciences) Tehran, Iran. Eight patients (3 in group A, 4 in group B, 1 in control group) were excluded from the study due to different reasons. The patients were randomly allocated into three groups of A: 400 mg celecoxib (Darou Pakksh Mfg. Co., Iran) in two doses (200 mg the night before operation and 200mg in the morning of surgery, two hours before starting the surgery), B: 400 mg celecoxib in one dose (the night before), and c: control group which received placebo (empty capsule with the same size and the same color as the main drug). Patient recruitment was from the surgical ward of Firoozgar Hospital, affiliated with Iran University of Medical Sciences.

ASA I, II patients between 20 and 40 years old candidate for elective leg surgery were included. Exclusion criteria were ASA ≥ III, pregnancy, oral contraceptive or hormone replacement therapy (in women), congestive heart failure, any underlying disease, drug addiction, multiple trauma, height lower than 150 centimeters and surgery longer than 3 hours. Demographic and anthropometric data including age, sex, and duration of surgery, height, and pain score after operation and more analgesic request by patients were recorded. All patients received 5 ml/kg normal saline before procedure. After noninvasive blood pressure and EKG monitoring, all were anesthetized intrathecaly by 3 ml bupivacaine 0.5%. Pain after the surgery was scored according to visual analogue rating scale (VAS), on recovery and in 2-4-6 hours after recovery.

In the case of complaining from pain by the patients, 0.3 mg/kg Pethidine was injected intravenously. The time to use for rescue medication was also recorded. The times of going away of anesthesia is when the numbness limit is lower than T10, and if it already was lower than T10, when it reached lower than L1. After allocation, none of the patients were excluded for analysis from the study.

Statistical analysis

The statistical package SPSS 17 for windows (Chicago, Illinois, USA), was used for analysis. Variables distributed normally are presented as mean and standard deviation (SD). Chi2 and One way ANOVAs test was used to compare variables, between the

RESULTS

Primary characteristics of the groups and demographic results are presented in Table 1. There were not any significant difference between the studied groups regarding age, gender, surgical duration and VAS in 1st, 2nd, 4th, and 6th hours after surgery. The time to ask for rescue medication after surgery was longest, and the used opium was lowest in the one dose 400 mg celecoxib group. The only significant difference have been found in this study was the time of analgesic request after surgery between the control group and 400 mg celecoxib Table 2.

DISCUSSION

Our findings showed that patients in the one dose celecoxib 400 mg group had the longest time lag for opium demand and the least used opium compared to the other groups. We did not found any significant difference in the pain scale between the groups, and hence VAS would not be an effective measure for pain assessment. It should be taken into account that all the patients received analgesics prior to demand. It seems as if the amounts of used opium as well as the time for rescue medication demand are more important measures of celecoxib effectiveness. These findings confirm those of previous studies. In consistent with our findings, many studies have shown the effectiveness of single dose 400 mg celecoxib in the management of postoperative pain. Barden *et al*. (2003) reviewed two randomized controlled trials of adults prescribed any dose of oral celecoxib or placebo for acute postoperative

pain. They found that for every 4.5 patients experiencing moderate to severe acute pain treated with celecoxib 200 mg one more will experience at least 50% pain relief. The median time to remedication over 24 hours in their review was 5.1 hours with celecoxib 200 mg and 1.5 hours with placebo. They concluded single dose oral celecoxib is an effective means of postoperative pain relief, similar in efficacy to single dose of aspirin and paracetamol. In all of those studies they assessed, Just one dose of celecoxib used for pain relief. However to date we are unaware of any study demonstrating the effectiveness of 200mg celecoxib, two times a day, in the management of postoperative surgical pain in leg surgery. In postsurgical dental pain study, patients who received celecoxib 400 mg as a single dose had a significantly longer time to use of rescue medication and had higher pain relief scores later in the study than those who received ibuprofen 400 mg. Cheung *et al*. (2007) concluded that Mean times to onset of analgesia with celecoxib 400 mg and ibuprofen 400 mg were rapid and comparable and were significantly shorter than with placebo. They found patients who received celecoxib 400 mg as a single dose had a significantly longer time to use of rescue medication and had higher pain relief scores later in the study than those who received ibuprofen 400 mg. Celecoxib was well tolerated compared with placebo but they reported 3 most common adverse events experienced in the patients received celecoxib (headache, nausea and dizziness).

Derry and collaborators (Derry *et al*., 2008), also showed the effectiveness of single dose oral celecoxib in the management of postoperative pain. They reviewed Eight studies (1380 participants) and concluded median time to use of rescue medication was 6.6 hours with celecoxib 200 mg, 8.4 with celecoxib 400 mg, and 2.3 hours with placebo and the percents of patients requiring rescue medication over 24 hours was 74% with celecoxib 200 mg, 63% for celecoxib 400 mg, and 91% for placebo. Celecoxib 400 mg was as effective as ibuprofen 400 mg and was more effective than celecoxib 200 mg in pain relief. Most of their findings, especially about the time for rescue drug request, are similar to our study. Similarly, single dose oral etoricoxib produces high levels of good quality pain relief after surgery. Clarke *et al*. (2009) assessed five trials about Etoricoxib (another selective cyclo-oxygenase-2 inhibitor). At least 50% pain relief was reported by 64-79% with different doses of etoricoxib and 10-12% with placebo. Significantly fewer participants used rescue medication when taking etoricoxib than those taking placebo.

On the other hand, studies have shown the efficacy, superior analgesia and tolerability of oral doses of celecoxib 200 mg taken 3 times a day over hydrocodone 10 mg/acetaminophen 1000 mg taken 3 times a day. Moreover most of their studied population required no more than 2 daily doses of celecoxib 200 mg for the control of their post orthopedic surgical pain. Gimbel *et al*. (2001) reviewed 2 trials (418 patients) who received celecoxib, hydrocodone/acetaminophen, or placebo. They analyzed the findings and found that celecoxib group had significantly lower maximum pain intensity scores, required fewer doses of study medication and had superior scores on a modified American Pain Society Patient Outcome Questionnaire. Over 8 hours, patients with moderate to severe pain after orthopedic surgery experienced comparable analgesia with single doses of celecoxib and hydrocodone/ acetaminophen. Over a 5-day period, oral doses of celecoxib 200 mg taken 3 times a day demonstrated superior analgesia and tolerability compared with hydrocodone 10 mg/ acetaminophen 1000 mg taken 3 times a day. Most patients required no more than 2 daily doses of celecoxib 200 mg for the control of their post orthopedic surgical pain. In another dose study about celecoxib, Recart *et al*. (2003) found that oral premedication with celecoxib 400 mg was more effective than 200 mg in reducing postoperative pain and the need for rescue analgesic medication in the early postoperative period. They compared oral celecoxib 200 mg to 400 mg when administered for premedication of outpatients undergoing minor ear-nose-throat surgery. In their study drug was given orally 30-45 min before surgery, all patients received a standardized general anesthetic technique, and during the postoperative period, pain scores were assessed. Both celecoxib 200 mg and 400 mg were more effective than placebo in reducing the postoperative fentanyl requirement and Celecoxib 400 mg was significantly more effective than 200 mg (and placebo) in reducing postoperative pain. Our finding also confirms the effectiveness of higher dose of celecoxib in postoperative pain management.

Here we showed the efficacy and tolerability of single dose 400 mg celecoxib in pain management in patients undergoing leg surgery. We did not found any similar study demonstrating the impact of celecoxib in the management of leg surgery. The main important finding of our study was effectiveness of 400 mg celecoxib as preemptive analgesia for postoperative pain control and postponing the patients need for more analgesic drugs. The principal limitation of the present study is its short term follow up duration, which precludes the determination of the direction of causality. However, we took advantage of a relatively large sample size and close similarity between groups in most of the potentially confounding variables. It also could be recommended to design another studies with different doses of this drug or different prescription times before or after the operation and analyze the efficacy of pain control after the surgery.

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