COMPARISON OF PRE-EMPTIVE EFFECT OF MELOXICAM AND CELECOXCIB ON POST-OPERATIVE ANALGESIA: A DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL

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Introduction: Pre-emptive analgesia may reduce pain, accelerate recovery and shorten the duration of hospitalization. The present study aims to compare the preemptive analgesic effects of meloxicam and celecoxib in patients undergoing lower limb surgery.

Method: In this double blind randomized clinical trial, 70 patients, undergoing lower extremity surgery, entered in the study; thirty five patients were randomly allocated to either group using random allocation software. Meloxicam (15mg) was administered orally to one group two hours before the surgical onset. The other group was treated with oral celecoxib (400 mg) two hours before the operation. Pain severity was compared between the two groups.

Results: Upon admission to Recovery Room, the mean pain severity was not significantly different between the two groups. At one and two hours following surgery the mean pain severity was significantly higher in celecoxib group. However, 6 hours following surgery mean pain severity was higher with meloxicam administration. Pain severity was not significantly different in the two groups, 12 and 24 hours following surgery.

Conclusion: The analgesic effect of celecoxib seems to cover longer duration than meloxicam; but, meloxicam appears to be a stronger analgesic in shorter time interval.

Keywords: postoperative pain, preemptive analgesia, celecoxib, meloxicam.

Introduction

Pain can deeply influence the level of satisfaction and quality of life. Diverse measures have been taken to reduce pain through quick, cheap, accessible and safe methods[1].

Post-operative uncontrolled pain has different acute and chronic adverse effects on patients. Pre-emptive analgesia may reduce pain, accelerate recovery and shorten the duration of hospitalization which eventually diminishes the overall cost and burden, and increases the level of satisfaction[2-5]. One aim is to decrease the need for analgesic medications, and therefore, to lower analgesic induced side effects[6].

Preemptive analgesia requires pre-operative administration of analgesic medication, which yields reduced post-operative pain and less need for post-operative analgesic administration[7-9]. There is growing tendency towards the use of new agents without narcotic properties resulting in respiratory depression, cardiac and urinary side effects[10,11]. Some studies have shown that

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efficacy of such agents are similar to that of narcotics. Moreover, combination of these agents with narcotic analgesics is far more effective than narcotic analgesics alone[12,13].

Surgical procedures damage the tissue which leads to prostaglandin secretion by means of cyclooxygenase enzyme (COX), and increases inflammation and the sensitivity of nociceptors. By blocking COX activity, non-steroid anti inflammatory drugs (NSAIDs) inhibit the production of prostaglandins[14]. Specific COX-2 inhibitors can also lead to same effect while causing fewer side effects[15]. Celecoxib is a COX-2 inhibitor agent that has been shown to be effective in post-operative analgesia[16,17]. Meloxicam is an NSAID which selectively inhibits COX-2 over COX-1 at low therapeutic doses and has been used to manage pain in human and animals[18,19]. Meloxicam and robenacoxib, which have similar pharmacologic profiles, have been used in veterinary medicine to reduce pain in cats, and robenacoxib has been shown to be more effective[20]. The aim of the current study is to compare the pre-operative analgesic effects of meloxicam and celecoxib in patients undergoing lower limb surgeries.

Materials and Methods

This is a double blind randomized clinical trial, conducted in 2014 at Alzahra Hospital, Isfahan, Iran. It was approved by the ethics committee of Isfahan University of Medical Sciences (IUMS). Written informed consents were obtained from all patients.

The sample was randomly selected among patients undergoing lower limb surgery under general anesthesia.

Inclusion criteria were patients of age 18-65 years, ASA-I and II, candidates of lower extremity surgery, with absence of coagulopathy, not having any history of peptic ulcer disease, gastrointestinal bleeding, substance dependence or seizure disorder. Patients were excluded from the study if there were deviations in their surgical or anesthetic plan or they received treatment for dysrhythmias, or had an un expected decline in blood pressure. Using a random allocation software 70 patients were randomly allocated to receive either meloxicam (n=35) or celecoxib (n=35). Meloxicam (15mg) in water (5cc) was administered orally to one group two hours before the operation. The other group received oral celecoxib (400 mg) in water (5cc) two hours before the operation. To ensure the blinding process, both celecoxib and meloxicam were identically packed and alphabetically labeled by the pharmaceutical laboratory. Neither the patients nor the clinician who evaluated the patients and collected the data was aware of the patient group allocation. Standard monitoring, including blood pressure, electrocardiogram, pulse rate and O2 saturation, was performed for all patient before, during and after the surgery. Following pre-oxygenation, induction of anesthesia was similarly performed in groups using identical doses of intravenous sodium thiopental (6mg/kg), atracurium0.6 mg/kg, and fentanyl (100 µg). Maintenance of anesthesia was achieved with isoflurane (1.2%), O2 50% and N2O 50%. After induction, intravenous morphine (0.15 mg/kg) was administered to provide analgesia. Extubation and recovery time was registered for each patient. Patients were discharged from recovery room based on Aldrete score and assessment of consciousness level.

Pain severity was assessed and registered, using Visual Analogue Scale (VAS), on admission to recovery, and at 1, 2, 6, 12 and 24 hours post-operatively. In case of VAS score ≥4, intravenous pethidine (0.5 mg/kg) was administered. Consciousness was evaluated and registered at 1, 2, 6, 12 and 24 hours following surgery. The dosage of medication and side effects were registered for each patient. Time and dosage of first additional analgesic were also registered.

A power analysis considering a confident interval (CI) of 0.95, a power of 80%, a standard deviation of 1.17 for post-operative pain score and a minimum significant clinical difference of 0.8 in the VAS showed that 70 patients will be needed (35 patients in each group). Data were analyzed with Chi-square, Student t-test and repeated measure ANOVA by SPSS 16.0.2. (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0.2 Chicago, SPSS Inc.). Level of significance was considered at $p < 0.05$.

Results

Baseline data are presented in table 1 and showed no significant differences between the two groups.

Table 1
Demographic data presented as mean±SD

	Meloxicam (n=33)	Celecoxib (n=35)	p-value
Age (yrs)	37.8±14.0	36.9±10.5	0.76
Body weight (kg)	71.7±6.7	69.3±8.3	0.2
Gender (M/F)	27/8	26/9	0.78

SD: Standard Deviation.

Comparison of mean intra-operative hemodynamic parameters revealed that mean systolic and diastolic blood pressure in both groups was not significantly different. However, pulse rate was significantly higher in patients receiving meloxicam (p = 0.01). Also, O2 saturation was significantly higher in patients receiving celecoxib (p = 0.035) (Table 2).

There was no difference in the mean extubation time between the two groups (Table 2). Frequency of confusion, vomiting, and additional analgesic administration in recovery room and in the first postoperative 24 hours are presented in table 3. There was no significant difference in incidence of confusion between the two groups in the 1st hour following surgery. However, in patients receiving meloxicam the incidence of confusion was significantly higher two hours post-operatively. All patients in both groups were completely oriented six to 24 hours following surgery (Table 3).

Frequency of vomiting was not significantly different between the two groups in the recovery room and in the 1st, 2nd, 6th, 12th and 24th hours following the operation (Table 3). During the study, two patients in the celecoxib group and none of the patients in the meloxicam required intravenous metoclopramide.

Frequency of additional analgesic administration in the first two hours after the operation was significantly higher in participants receiving celecoxib

Table2
Comparison of intra-operative hemodynamic parameters as mean±SD

	Meloxicam (n=35)	Celecoxib (n=35)	p-value
Heart rate (beats/min)	79.4±4.2	76.3±6.4	0.01
Systolic blood pressure (mmHg)	115.7±5.6	116.1±5.6	0.75
Diastolic blood pressure (mmHg)	78.9±3.2	77.7±6.1	0.33
SPO2 (%)	97.1±1.5	97.8±1.1	0.035
Mean Extubation Time (minutes)	7.83.4±	7.53.8±	0.16

SD: Standard Deviation.

Table 3
Frequency of postoperative confusion, vomiting and additional analgesic administration during the first 24 hours following surgery

	Confusion n(%)			Vomiting n(%)			Additional Analgesic Administration n(%)		
	meloxicam	celecoxib	p-value	meloxicam	celecoxib	p-value	meloxicam	celecoxib	p-value
On admission to recovery	0(0)	0(0)	1	2(5.7)	0(0)	0.61	0(0)	0(0)	1
1h after surgery	7(20)	5(14.3)	0.53	2(5.7)	0(0)	0.61	0(0)	5(14.3)	0.054
2h after surgery	6(17.1)	0(0)	0.025	1(2.9)	0(0)	0.99	0(0)	7(20)	0.011
6h after surgery	0(0)	0(0)	1	1(2.9)	2(5.7)	0.99	16(45.7)	10(28.6)	0.14
12h after surgery	0(0)	0(0)	1	1(2.9)	3(8.6)	0.61	24(68.6)	16(45.7)	0.053
24h after surgery	0(0)	0(0)	1	1(2.9)	3(8.6)	0.61	10(28.6)	6(17.1)	0.025

(Table 3). However the frequency of additional analgesic administration was higher in patients receiving meloxicam during 24 hours postoperatively (Table 3).

Mean severity of pain was approximately similar in both groups on admission to recovery room. (Table 4). The severity of pain was higher in participants receiving celecoxib at the 1st and 2nd hour following the operation; however, the severity of pain was higher in patients receiving meloxicam at the 6th hour post-operatively. There was no significant difference in the severity of pain, between the two groups, at the 12th and 24thhours following surgery (Table 4).

Discussion

In the present study, we found that both groups had similar levels of blood pressure, although patients receiving meloxicam had significantly higher heart rates. Blood O2 saturation was significantly higher in patients receiving celecoxib. However, both differences do not seem to be of clinical significance. Adverse hemodynamic effect including hypotension and bradycardia were not detected in either group. Therefore, both medications seem to be safe in this regard. Patients receiving celecoxib had better consciousness states. Celecoxib administration was associated with decreased post-operative nausea and vomiting, during the first two hours after the operation, in comparison to meloxicam. Hawkey et al in their study concluded that meloxicam was significantly better tolerated in terms of dyspepsia, nausea and vomiting, abdominal pain and diarrhea comparing with diclofenac in investigating tolerability of the two drugs in a setting of over a 28-day period oral administration[16]. However we could not find any study comparing the gastrointestinal tolerability of meloxicam and celecoxib in perioperative period.

Meloxicam was associated with decreased severity of pain in the first two postoperative hours. This may be due to the fact that celecoxib reaches peak plasma concentrations after approximately 2-3 hours but meloxicam reaches maximum plasma concentration (Cmax) at 2.5-7 hours after a 15mg dose[17, 18] and our patients had their administration two hours before surgery. The total mean severity score of pain in both groups was not significantly different during the whole 24 hours post-operatively. Although the mean VAS scores had been nearly the same at 24th hour, the additional analgesic administration has been more in meloxicam group statistically. This might be based on the violence of nurses from following the current survey protocol in administering analgesic in the ward.

Al-Sukhun et al indicated that preemptive administration of low dose celecoxib was associated with significant postoperative analgesia in minor oral surgery[19]. They administered a standard oral dose of 200 mg celecoxib, preemptively 1 h before surgery and this may explain the efficacy of celecoxib in recovery

Table 4
Comparison of pain severity between meloxicam and celecoxib receiving groups during the first 24 hours following surgery as mean±SD

	VAS score		
	Meloxicam (n=35)	Celecoxib (n=35)	p-value
On admission to recovery	1.03±1.3	1.03±1.2	1
1h after surgery	2.1±1.2	3.1±1.7	0.007
2h after surgery	2.3±1.2	3.2±1.7	0.008
6h after surgery	4.5±2.0	3.4±1.7	0.022
12h after surgery	4.9±2.0	4.0±2.2	0.07
24h after surgery	3±1.5	2.6±1.6	0.29

period according to peak plasma concentrations and surgery duration. Boonriong et al concluded in their study that celecoxib showed no significantly difference from placebo at any time points in reducing post-operative pain[20]. Aoki et al concluded that in the setting of surgery with local anesthesia, premedication with meloxicam was effective in reducing postoperative pain in oral outpatient surgery[21].

Our study was limited in some aspects. In the current study, small sample size and restriction of population to candidates of lower extremity surgery can interfere with generalizability. Also, capability of participants to understand and follow the instruction of VAS may confound the observation.

It is concluded that celecoxib and meloxicam have similar effects on postoperative pain in lower extremity surgery. However, because of more rapid Cmax of celecoxib, it should be administered more closely to the surgery. Both medications are well-tolerated and can be selected based on clinical indications and surgery duration. Further studies comparing the gastrointestinal tolerability of meloxicam and celecoxib in perioperative period is recommended.

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