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CLINICAL TRIAL STUDY

Comparison of the Effect of Different Dosages of Celecoxib on Reducing Pain after Cystocele and Rectocele Repair Surgery

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Abstract:

Background:

Administration of celecoxib reduces pain and inflammation and is associated with greater patient satisfaction.

Objective:

This study was designed to evaluate the efficacy of two different doses of oral celecoxib for reducing postoperative pain.

Methods:

This randomized clinical trial was performed on 90 patients undergoing cystocele and rectocele repair under spinal anesthesia. Patients were randomly divided into 3 groups: the first group received 200 mg/day celecoxib, the second group received 400 mg/day celecoxib and the third group was placebo. The pain was measured at 8, 16 and 24 hours after surgery using the VAS (Visual Analogue Scale) method. If the pain score was greater than 5, pethidine 1 mg/kg was prescribed. Pain score at 8, 16 and 24 hours, the need for pethidine, side effects and satisfaction score were recorded during the first 24 hours after surgery.

Results:

The pain score at postoperative 8 hours was 7.7, 3.9, and 8.1 in the 200 mg/day celecoxib, 400 mg/day celecoxib, and placebo group, respectively ($p<0.001$). Furthermore, the need for pethidine was significantly less in 400 mg/day group and with the greatest satisfaction score, $p<0.01$, respectively.

Conclusion:

Our study concludes that 400 mg/day of celecoxib can be effective against postoperative pain, following the cystocele and rectocele repair, as compared to 200 mg/day and placebo groups. Unwanted use of opioids can be avoided with economically cheaper and safer drugs.

Keywords: Celecoxib, Opioids, Pethidine, Pain, Rectocele repair, VAS.

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1. INTRODUCTION

Pain is the most significant and an inevitable postoperative surgical outcome, that can be an indicator of problems such as cardiac complications (tachycardia, hypertension), respiratory complications (atelectasis, pulmonary infections and arterial hypoxia) [1], gastrointestinal complications (decreased stomach uptake, decreased movement Paralytic intestine and ileus) and ultimately urinary retention [2]. Locating the source of the pain and its management is among the important challenges faced after surgeries [3].

Drugs such as opioids and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly exploited for the treatment of the pain [4, 5]. Whereas, opioids like morphine, that are frequently used for pain management, are associated with a great number of adverse effects such as [6]; addiction, inhibition of respiration, nausea and vomiting [7]. Nonsteroidal anti-inflammatory drugs are commonly used as pain-killer and anti-inflammatory drugs [8]. These drugs inhibit the synthesis

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of prostaglandins by inhibiting Cyclooxygenase (COXI) I and COX II enzymes [9]. Prostaglandins have many physiological characteristics including gastric mucosal proteins, tubular renal function, vascular dilatation and bronchodilation [10]. The tissue damage, due to the production of COXII and prostaglandins, instigates pain and inflammation [11].

Celecoxib is one of the most important members of the COXII enzyme inhibitor family. Recent studies around the world have examined the effects of celecoxib as a selective inhibitor (COXII) and the effects of commonly used drugs in reducing postoperative pain such as morphine, pethidine, and classic NSAIDs [12]. Compared with other common drugs, it is considered effective for postoperative pain management [13]. Most of the studies have mentioned low-dose celecoxib to be administered for the purpose however, the FDA has suggested a high dose of celecoxib (up to 400 mg), for reducing postoperative pain. Several studies have also revealed that 100 mg celecoxib can be comparable to 200 mg of the dose for the treatment of arthritis and pain management, presenting an equivalent incidence of adverse events [14]. This study was designed to evaluate the efficacy of oral celecoxib at two different doses of 200 mg and 100 mg/day for ameliorating postoperative pain following cystocele and rectocele repair surgery.

2. MATERIALS AND METHODS

In this randomized and three stratified, placebo-controlled clinical trial, all patients in the Asalian hospital, who were candidates for cystocele and rectocele repair surgery (laproscopic) in the age range of 20-50 years old, in the second trimester of the year 2015 and were in ASA (American Society of Anesthesiologist: for determination of patients' health status before the surgery) class I and II, in terms of their health and preparation for surgery and anesthesia were included. Written consent was obtained from all the patients for participation in the study.

The sample size was estimated using the formula for comparing the mean of about 90 people ($n = (Z\alpha/2+Z\beta)2 *2*\sigma2 / d2$). The subjects were free of any underlying diseases related to the kidneys, cardiovascular system, and were not hospitalized 24 hours prior to the operation.

Exclusion Criteria: Patients were administered ASA class III and IV anesthesia prior to the admission, and the exclusion criteria include use of any analgesics 24 hours before surgery, pregnancy, lactation, a history of alcohol or drug abuse, history of susceptibility to sulfonamide drugs, cardiovascular, renal, hepatic and digestive diseases and dissatisfaction to participate in the study. After receiving written consent to participate in the study, patients were randomly assigned to three groups A, B, and C, by an independent statistician using the SAS ver. 9.1 (SAS Institute Inc., Cary, NC, USA). During the grouping, the groups were matched in terms of confounding variables. All patients underwent spinal anesthesia (with 100 mg of acylocaine using needle 25, at L3-L4 or L4-L5 levels).

Based on the chosen color-codes by the patients, they were randomly divided into three groups. Given that in the Khorramabad pharmaceutical market, only 100 mg capsules of celecoxib were available and to avoid the study error:

In group A: a placebo capsule and one 100-mg celecoxib capsule were given to the patients in this group after the surgery and after 12 hours, following the first dose that was administered immediately after the surgery.

In group B: two 100 mg celecoxib capsules (200 mg) were given following a similar time interval as for the previous group.

In group C: two placebo capsules, in the same order of time (immediately after surgery and 12 hours after surgery) were given.

For all the groups, the pain was measured at 8, 16 and 24 hours after the surgery using VAS (visual analog scale: for measuring the intensity of the pain from 0-10 scale) pain assessment method. Additionally, patient demographic information was also recorded in the form.

In the case of increased intensity of the pain, 1 mg/Kg pethidine was prescribed intramuscularly, which was also recorded in data. Side effects such as nausea and vomiting, dizziness, chest pain, skin complications including urticaria and erythema during the first 24 hours were also analyzed, following the administration of analgesic. The ASSIST (Patient Satisfaction Survey: Pain Management) was used to evaluate the overall patient satisfaction score [15].

After completing the data-collection forms, the data were analyzed using SPSS software v18. Comparisons between the groups were conducted using the Cross-Wallis test, Mann-Whitney U test and one-way ANOVA. P-value <0.05 was considered to be statistically significant.

3. RESULTS

The mean age and weight of the patients in the group A were 38.23 ± 3.41 years and 60.43 ± 6.11 kg, in the group B were 37.53 ± 4.040 years and 59.31 ± 5.48 kg, and in the placebo (group C) were 37.33 ± 3.94 years and 60.5 ± 5.54 kg, respectively. Whereas, the overall mean age and weight of the patients were 37.70 ± 3.78 years and 60.02 ± 5.69 kg.

The mean of pain intensity 8 hours after surgery was 7.7 ± 2.2 with a median of 8 in group A, 3.9 ± 2.6 with a median of 3.5 in group B and in group C was 8.1 ± 2 with a median of 8 (Table **1**). Similarly, postoperative pain intensity scores at 16 and 24 hours in the three groups are presented in Table **1**.

The mean pethidine need in group C was 40.8 ± 23.2 with a median of 50, in group A was 35.8 ± 21.4 and a median of 50, and group B was 9.2 ± 18 with a median of zero (Table **2**).

Following 24 hours after the procedure, 9 and 3 cases of dyspnea were observed in groups A and B, respectively and 11 cases were observed in group C. Similarly, nausea and vomiting were reported in 5 cases in groups A and B, respectively and in 8 cases in group C. Dizziness was seen in 2 cases in group A and C, whereas, none were reported in group B. Skin problems were not observed in any of the three groups.

The overall patients' satisfaction scores, 24 hours after the surgery in groups A, B and C were, 78.33%, 36.66% and 37.96% respectively (Table **3**).

Table 1. Comparison of the mean and median pain scores at 8, 16 and 24 hours postoperatively in groups.

Statistical Index Group	Number of Samples	Mean and Standard Deviation of Pain Score	Median	P-value
8 hours postoperatively				P<0.001
Placebo group	30	8.1±2	8	
100 mg twice daily	30	7.7±2.2	8	
200 mg twice daily	30	3.9±2.6	3.5	
16 hours postoperatively				P<0.001
Placebo group	30	5.9±2.9	6	
100 mg twice daily	30	5.1±2.0	5	
200 mg twice daily	30	2.8±2.7	1.5	
24 hours postoperatively				P<0.001
Placebo group	30	4.9±2.8	5	
100 mg twice daily	30	4.2±2.6	4	
200 mg twice daily	30	1.7±1.9	1	

Table 2. Comparison of the average median deviation criterion and pethidine required by groups during the first 24 hours after surgery.

Statistical Index Group	Number of Samples	The Mean and Standard Deviation of the Need for Pethidine	Median	P<0.001
Placebo group	30	40.8±23.2	50	
100 mg twice daily	30	35.8±21.4	50	
200 mg twice daily	30	9.2±18.0	0	

Table 3. Comparison of the average satisfaction score of all patients during the first 24 hours after surgery using ANOVA.

Statistical Index Group	Number	Mean and Standard Deviation	Abundance	P<0.001
Placebo group	30	36.7	34.61	
100 mg twice daily	30	38.0	34.61	
200 mg twice daily	30	78.3	34.61	

4. DISCUSSION

In this clinical study, a comparative analysis of pain scores using the Mann-Whitney U test showed that the pain intensity in the patients receiving 400mg celecoxib in a day is significantly lower than in other groups (P<0.001). However, the placebo and 100 mg celecoxib groups were presented with comparable pain intensities and were not statistically different from each other. Similarly, we concluded that the mean pain intensity and mean need for pethidine during the first 24 hours after the operation, following 400 mg celecoxib (200 mg BID) was lower than in other groups (P <0.001) [16]. Overall satisfaction in patients was also highest in this group with minimal side effects.

Studies have shown that celecoxib at higher doses (400 mg QD) leads to more patient satisfaction, a decrease in the severity of postoperative pain during the first 24 hours after surgery, and reduces the need for pethidine [17]. However, it is also reported that the administration of 100 mg of celecoxib twice a day is safer than 200 mg in a day [18].

Alejrandro *et al*. [19], in 2003, examined the prophylactic effect of celecoxib in a double-blind, placebo-controlled study on 93 patients undergoing ENT minor surgery [20, 21]. Patients were administered a single dose of 200 mg, a single dose of 400 mg or the placebo (30-45 minutes before surgery) [22]. They concluded that celecoxib at higher doses significantly reduces the severity of the postoperative pain [23], which is in agreement with our findings. They also found that the average need for other analgesics and oral anti-diabetic drugs after discharge was significantly lower in the 400 mg group than in other groups. Despite there were some alterations in the interval of drug administration in the study (200 mg BID and 100 mg BID), outcomes of this study are similar to those of Alejrandro *et al*. [24].

A study by Nikanee *et al*., presented the effects of celecoxib and ketoprofen on 120 patients undergoing tonsillectomy. The first group received 200 mg celecoxib, the second group received 100 mg ketoprofen and the third group received a placebo, 60 minutes before the surgery and 12 hours after surgery [25]. They concluded that celecoxib is more effective and has satisfactory outcomes than opioid analgesics for managing postoperative pain. Also, the incidence of secondary hemorrhage following the surgery was lower in the celecoxib group [26].

In another study, Ruben *et al*. [27] investigated the effects of preoperative administration of celecoxib, as a part of the anti-diabetic drug, on patients undergoing anterior cruciate ligament reconstruction. Two hundred patients were administered 1000 mg of acetaminophen, 400 mg celecoxib, and 1000 mg acetaminophen with placebo, 1 to 2 hours before surgery [28]. They concluded that the administration of celecoxib before the surgery was associated with the reduction in postoperative pain (P <0.01), reduced the need for opioids (P <0.001), decreased nausea and vomiting and decreased the duration of hospitalization. Furthermore, Kashefi, Honarmand [29] reported that prophylactic use of 200 mg of celecoxib is superior to 320 mg of acetaminophen for the management of

postoperative pain in patients undergoing orthopedic surgery.

In 2003, Watcha *et al* [30]., compared the effects of rofecoxib, celecoxib and acetaminophen in preventing postoperative pain in ENT outpatients. They concluded that 50 mg of oral rofecoxib is more effective than 200 mg of celecoxib and 2000 mg of acetaminophen, also providing patient satisfaction [27]. However, our study lacks a comparative analysis with other analgesics.

Administration of celecoxib 400 mg/day reduced postoperative pain ($P < 0.001$), reduced the need for pethidine ($P < 0.001$), decreased the side effects and improved patient satisfaction. Its analgesic effects manifested quickly as compared to low dose celecoxib. Some of the limitations of the study include smaller sample size, lack of data regarding the long-term effects of the drugs and its comparison with other analgesics for postoperative pain management.

CONCLUSION

400 mg/day of celecoxib is effective for postoperative pain management following cystocele and rectocele repair, with minimal side effects, greater patient satisfaction and reduced need for opioids.

By choosing the appropriate dosage of the drug, we will be able to improve the quality of pain management in patients, prevent unprotected use of opioids and prevent loss of national funds.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Research Ethics Board of Lorestan University of Medical Sciences, approval no. IR.LUMS.REC.1383.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

CONSENT FOR PUBLICATION

Written consent was obtained from all the patients for participation in the study.

STANDARD OF REPORTING

CONSORT guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Dr. Sepideh Vahabi conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. **Dr. Siavash Beiranvand** and **Dr. Arash Karimi** designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Mahmoudreza Moradkhani and Dr.Khatereh Hassanvand coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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