Determination of Preemptive Analgesic Efficacy of Celecoxib in Patients Undergoing Major Lower Limb Orthopaedic Surgery

Ali Akhtar*
Sumair Nasim Qureshi**
Ali Shami***

**Associate Professor*
***Senior Registrar*
****Assistant Professor*

Department of Orthopaedic Surgery at Pakistan Institute of Medical Sciences Islamabad

Objective: To evaluate effect of oral Celecoxib 100 mg in terms of mean VAS as preemptive analgesic agent in orthopaedic patients undergoing major lower limb surgery by comparing with placebo.

Study Design: Randomized controlled trial.

Place and Duration: The study was conducted between April 2008 to October 2008 in the Department of Orthopaedic Surgery at Pakistan Institute of Medical Sciences Islamabad.

Materials and Methods: In this study, 80 patients undergoing major lower limb surgeries were divided in two equal groups; 40 patients in group A received Celecoxib 100 mg 40 minutes before surgery and while 40 patients in group B received placebo 30 minutes before surgery. Comparison of two groups was done for mean visual analogue score (VAS) on first postoperative day at 6 am. T-test was applied for statistical difference (p-value <0.05 was taken as significant).

Results: The mean VAS group A was 4.24 ± 1.097 and in group B was 8.13 ± 1.017. p-value was 0.000 (statistically significant)

Conclusion: The Celecoxib, as preemptive can significantly reduce the postoperative pain score as compared to placebo analgesic in major lower limb orthopaedic surgeries.

Key Words: Celecoxib; preemptive analgesic; visual analogue score.

Address for Correspondence
Dr. Ali Shami
Assistant Professor
Department of Orthopaedic Surgery at Pakistan Institute of Medical Sciences Islamabad
Email: dralishami@gmail.com

Introduction

Pain management in surgical patients has been a major concern over the last few decades and especially in recent years. Even with advancements in understanding of pathophysiology and pharmacotherapeutics of surgical pain, it still remains under treated and poorly controlled.[1]

Inadequately treated pain can lead to myocardial ischemia, infarction, pulmonary infections, paralytic ileus, urinary retention, thrombo-embolism, impaired immune functions and anxiety. Subsequently, this may result in patient dissatisfaction, impaired patient rehabilitation and prolonged hospitalizations.[2]

Orthopaedic procedures can cause severe intra-operative and post-operative pain that can be a challenging task to adequately control postoperative pain particularly following hip and knee arthoplasty.[3,4]

It is important to achieve optimal post-operative pain control because inadequate treatment of pain can have many negative consequences, including decreased immune response and adverse psychological effects, such as anxiety, depression, hopelessness, anger, hospitality, poor interpersonal relations and suffering.[5]

Intravenous (IV) opioids have not been as effective for post-operative pain control in orthopaedic surgery as in major abdominal surgery.[6] Post-operative pain control after knee surgery is one of the most important pre-requisites for early rehabilitation.[7] Post-operative pain after knee arthoplasty has been controlled by oral or intramuscular opioids, patient-controlled IV opioids, patien-controlled epidural analgesia (PCEA) or single-dose/continuous-dose femoral nerve blocks (CFNB).[8] Improving early postoperative analgesic can enhance patient rehabilitation and also influence the long-term evolution of pain syndromes.[9]

The concept of preemptive analgesia, which is an analgesic treatment initiated before, as opposed to after the surgical procedure, was introduced to protect the central nervous system from deleterious effects of noxious stimuli, and the patient from the resulting allodynia, and increased pain.[10]

Recently, several types of drugs have been reported in many clinical trials, especially non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs. These drugs provide analgesic effect by inhibiton of prostaglandins synthesis at the site of tissue injury and in the central nervous system. When given in perioperative period, they have shown significant opioid-sparing effect, reduction in opioid analgesic consumption, postoperative pain reduction, and patient satisfaction compared with placebo.[11]

Celecoxib is a selective cyclooxygenase (COX)-2 inhibitor and an effective analgesic for acute postoperative pain although pre-operative non selective NSAID use increases the risks of bleeding, Celecoxib has no effects on serum thromboxane or platelet functions. Celecoxib also has similar analgesic effects in comparison with conventional nonselective NSAID.[12,13]

Celecoxib is a highly selective COX-2 inhibitor and primarily inhibits this isoform of cyclooxygenase, whereas nonselective NSAIDs like aspirin, naproxen and ibuprofen inhibit both COX-1 and COX-2. Celecoxib is approximately 10-20 times more selective for COX-2 inhibition over COX-1. This selectivity allows Celecoxib and other COX-2 inhibitors to reduce inflammation (and pain) while minimizing gastrointestinal adverse drug reactions (e.g. stomach ulcers) that are common with non-selective NSAIDs.[14] COX-2 inhibitors commonly used include Celecoxib, Valdecoxib, Etoricoxib and Lumiracoxib.[15]

Recent research shows that the use of COX-2 inhibitors as a preemptive analgesic improves post operative pain and decrease the overall use of opioids following surgery. In this review, clinical studies supported the efficacy of using COX-2 inhibitors as a preemptive analgesics for multiple procedures including thoracotomies, arthroscopic knee surgeries and laparoscopic cholecystectomies.[16,17]

By controlling pain through pre emptive measures we will be able to decrease post operative pain that will be measured by visual analogue scale (0 to 10) and will be able to help our patients for better pain control and also for early mobilization. We aimed to determine the effect of oral Celecoxib 100 mg in controlling pain of patients undergoing major lower limb surgery, which will also help in streamlining the first line appropriate treatment modality.

Materials and Methods

This randomized controlled trial was conducted between April 2008 to October 2008 in the Department of Orthopaedic Surgery at Pakistan Institute of Medical Sciences Islamabad. In this study, 80 patients undergoing major lower limb orthopaedic surgeries were divided in two equal groups. 40 patients in group A received Celecoxib 100 mg and 40 patients in group B received Placebo 30 minutes before surgery. All the patients were between the age of 18-70 years with no history of ulceration of G.I.T, allergy to NSAIDs, bleeding disorders, renal insufficiency, bronchial asthma and none of them was polytrauma patient. All the patients were also kept on fixed doses of Diclofenac sodium 2 hourly post operatively. Pain on movement of the limb was assessed at 6 am in the next morning by using Visual Analogue Scale (VAS). Data collection was done by using pre

designed proforma. All the analysis was done using SPSS version 10. Mean and standard deviations were calculated for continuous variables like age and pain score. Whereas, frequencies and percentages were calculated for categorical variables like sex, operated side and type of surgery.

Independent samples t - test to compare mean pain score in two groups. P-value ≤ were considered significant.

Results

There were total 80 patients included in this study and were divided into 2 groups with 40 in each group.

In group A, there were 23 (57.5%) male patients and 17 (42.5%) female patients. The female to male ratio in this group was 1:1.35. In group B, there were 25 (62.5%) male patients and 15 (37.5%) female patients. The female to male ratio in this group was 1:1.67.

In group A, the mean age of the patients was 43.45 ± 1.097 years. While in group B, the mean age of the patients was 45.78 ± 1.017 years.

In group A, right side was operated among 16 (40%) patients and left side was operated among 24 (60%) patients. In group B, there were 13 (32.5%) patients who had surgery on right side and 27(67.5%) patients who had surgery on left side.

Total hip replacement was done among 5 (12.5%) patients in group A and 3 (7.5%) patients in group B. One (2.5%) patient in group A had interlocking intramedullary nail of tibia, while none of the patient had this procedure in group B. Distal femur locking plate and reconstruction nail of femur was done in one (2.5%), 4 (10%), 2 (5%) patients in group B, while none of the patients had these surgeries in group A. Open reduction and internal fixation of tibia with DCP plate was done in 2 (5%) patients in group A and 3 (7.5%) patients in group B. Intramedullary interlocking nail of femur was done is 15 (37.5%) patients in group A and 10 (25%) patients in group B. Austin Moore hemiarthoplasty was done in 1(2.5%) patients of group A and 4 (10%) patients of group B. Dynamic hip screw with side plate(DHS) was done in 11(27.5 %) in group A and 10 (25%) patients of group B. Retrograde intramedullary nailing of femur, total hip replacement (metal on metal) was done in 2 (5%) and 1(2.5%) patients in group A, while none of the patient in group B had these procedures done. Two (5%) patients in group B had open reduction internal fixation of acetabulum while in group B none of the patients had this surgery. There were 2 (5%) patients in group A and 1(2.5%) patients in group B who had total knee replacement (Table I).

Table I. Frequency and Percentages of Type of Surgery in Both the Groups (n=80)

Type of Surgery	**Group A** n (%)	**Group B** n (%)
Total Hip Replacement	5 (12.5)	3 (7.5)
Tibial Interlocking Nail	1 (2.5)	0
Arthroscopy	0	1 (2.5)
Distal Femoral Locking Plate	0	4 (10)
Reconstruction Nail (Femur)	0	2 (5)
Open Reduction Internal Fixation Tibia (Plate)	2 (5)	3 (7.5)
Antegrade Femoral Interlocking Nail	15 (37.5)	10 (25)
Austin Moore Hemiarthroplasty	1 (2.5)	4 (10)
Dynamic Hip Screw with Side Plate	11 (27.5)	10 (25)
Retrograde Femoral Interlocking Nail	2 (5)	0
Total Hip Replacement (Metal on Metal)	1 (2.5)	0
Reconstruction of Acetabular Fracture	0	2 (5)
Total Knee Replacement	2 (5)	1 (2.5)
Total = n	**40 (100)**	**40 (100)**

The mean VAS in group A was 4.23 ± 1.097 and in group B was 8.13 ± 1.017. The two groups were also compared for any statistical difference. Student t-test was applied and p-value was 0.000 (<0.05) which showed that there was a significant difference between the two groups (Table II).

Table II: Comparison of Mean Pain Score of Patients in Both the Groups (n = 80)

		n	Mean	SD	p-value*
Mean Pain Score	Group A	40	4.23	1.097	0.000
	Group B	40	8.13	1.017	

Discussion

This study compared the outcome of Celecoxib as preemptive analgesia in management of postoperative pain in major lower limb orthopaedic surgeries by measuring the postoperative mean VAS score.

Celecoxib has been considered as a preemptive analgesia in many studies for the postoperative pain in different surgeries like laparoscopic cholecystectomy, thoracotomy and few orthopaedic procedures like arthroscopy or arthroplasty, etc.[16,17] Few trials are available on the efficacy of Celecoxib which had been evaluated in isolated surgical procedures like Huang, et al.[18] studied efficacy of Celecoxib in total knee arthroplasty. In his study, 80 patients underwent total knee arthoplasty. 40 patients received a single 400 mg dose of Celecoxib 1 hour before surgery while 40 patients in other group received Placebo.

Shen B.[19] studied its efficacy in total knee replacement and Reubin SS, et al.[20], used Celecoxib in anterior cruciate ligament injury repair. Like our study, visual analogue scale (VAS) was one of the outcome parameter. They found that resting VAS pain score improved significantly in the Celecoxib group compared with controls at 48 hours (2.13 ± 1.68 vs 3.43 ± 1.50, p=0.03) and 72 hours (1.78 ± 1.66 vs 3.17 ± 2.01, p=0.02) after surgery. However, this difference was not significant statistically. In our study, the mean VAS was significantly less than the control group (4.23 ± 1.097 with Celecoxib and in 8.13 ± 1.017 with placebo, $p < 0.05$). But we can see that average VAS was lower in their study than ours. This might be due to the reason that they have used higher dose of Celecoxib i.e 400 mg while we used a dose of 100 mg. Furthermore, they continued Celecoxib postoperatively while we used a fixed dose of Diclofenac Sodium postoperatively.

Waikakil W, et al.[11] performed a randomized double blinded placebo controlled trial in which 99 patients underwent major orthopaedic surgery. They used Celecoxib in a dose of 400 mg which is higher than that of ours. However, the reduction of pain score observed in our study was significant.

In another study by Ruben SS, et al. [20] two hundred consecutive patients were randomized to receive acetaminophen 1000 mg and either Celecoxib 400 mg or placebo 1 hour before anterior cruciate surgery. This study favours the observations in our study that preemptive Celecoxib may reduce the pain scores.

We used VAS as an outcome parameter in our study in a wide range of major orthopaedic procedures while other studies were done in only limited surgical procedures. VAS is universally accepted and has been used by almost every author included in this discussion. VAS can be easily reproduced and applied easily among our population. We use Celecoxib in dose 100mg while other used 400mg. However, our results were statistically significant and highlight that even a lower dose of Celecoxib can work as preemptive analgesia. In our study, placebo usage may present ethical concerns in postoperative care of major orthopaedic surgery we therefore adopted a postoperative analgesia in every patients based on Diclofenac sodium.

Conclusion

This study concluded that Celecoxib when used as preemptive analgesia in major lower limb orthopaedic surgeries can significantly reduce the postoperative pain score as compared to placebo. So, it is recommended that Celecoxib should be given before the major orthopaedic surgical procedure as an preemptive analgesia.

References

1. Chanrakantan A, Glass PSA. Multimodal therapies for postoperative nausea and vomiting and pain. Br j Anaesth. 2011; 107:27-40.
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experiences: results from a national survery suggest

postoperative pain continues to be undermanaged. Anesth Analg. 2003;97:534-40.
3. Gandhi K, Viscusi E. Multimodal pain management techniques in hip and knee arthroplasty. The journal of New York school if regional anaesthesia. 2009;13:1-8.
4. Vaduveku N, Mitra S, Narayan D. Recent advances in postoperative pain management. Yale journal of biology and medicine. 2010;83:11-25.
5. Beaulieu AD, Peloso PM, Haraoui B, Bensen W, Thomson G, Wade J. Once daily, controlled release Tramadol and sustained release Diclofenac relieve chronic pain due to osteoarthritis. Eastern Mediterranean Health journal. 2008;14:82-9.
6. Khalid M, Ali M, Habib L, Rehman A. Pre emptive analgesic efficacy of diclofenac sodium in orthopaedic surgery. Pak orthopedic Association. 2009;21:50-4.
7. Nasir M, Ahmed M, Latif K. Pre emptive pain; control comparison of ketorolac and diclofenac sodium. Professional Med J. 2007;14:591-7.
8. Karaslaan D. Sivaci R, Akbukut G preemptive analgesia in laparoscopic cholecystectomy, A randomized controlled study. Pain practice 2006;6:237-41.
9. Remerand F, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L. The early and delayed analgesic effects of ketamine after total hip arthoplasty. Anaesth Analg 2009;109:1963-71.
10. Spencer L, Christopher W. The effect of analgesic technique on postoperative patient reported outcomes including analgesia.: A Systematic review. Anesth Analg 2007;105:789-808.
11. Waikakul W, Chalachewa T, Tantisrin N, Suranutkarin P, Saengpetch N. Combination of Gabapentin and Celecoxib for analgesia after major orthopedic surgery: a randomized. Controlled trial. Asian Biomedicine 2011;5:101-10.
12. Bratwall M, Turan I, Jakobsson J. Pain management after elective hallux valgus surgery: a prospective randomized double-blind study comparing Etoricoxib and Tramadol. ANesth Analg 2010;111;544-9.
13. Clemett D, Goa KL. Celecoxib a review of its use in osteoarthritis. Rheumatoid arthritis and acute pain. Drugs 2000;59:957-80.
14. Conaghan PG. A Turbulent decade for NSAIDs: update on current concepts of classifications, epidemiology, comparative efficacy and toxicity. Rheumatol Int 2012;32:1491-502.
15. Kaye AD, Baluch A, Kaye AJ, Ralf G, Lubarsky D. Pharmacology of cycooxygenasee-2 inhibitors and preemptive analgesia in acute pain management Current opinion in Anesthesiology 2008;21:439-45.
16. Sandhu T, Paiboonworacht S, Ko-iam W. Effects of preemptive analgesic in laparoscopic cholecystectomy: A double-blind randomized controlled trial. Surgical Endoscopy 2011;25:23-7.
17. Celik JB, gormus N, Gormus ZI, Okesli S, solak H. Preoperative analgesia management with Rofecoxib in thoracotomy patients. Journal of Cardiothoracic and Vascular Anesthesia 2005;19:67-70.
18. Huang YM, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative administration of Celecoxib in pain management after total knee arthoplasty – a randomized, controlled study, BMC Musculoskeletal Disorders 2008;9:77.
19. Shen B, Tang X, Yang J, Li , Zhou ZK, Kang PD, Pei FX. Effects of perioperative administration of Celecoxib on pain management and recovery of function after total knee replacement. Zhonghua Wai Ke Za Zhi 2009;47:116-19.
20. Reuben SS, Ekman EF, Charron D. Evaluating the analgesic Efficacy of administering Celecoxib as a component of multimodal analgesia for outpatient anterior cruciate ligament reconstruction surgery anesth analg 2007;105:222-7.