

Effect of Celecoxib and Pregabalin Therapy on Pain and Physical Function of Patients Undergoing Total Hip Arthroplasty

Alireza Manafi Rasi, Mohammad Reza Ebrahimiinia, Mohammad Emami Tehrani Moghadam, Gholam Hussein Kazemian, Salim Khani

Department of Orthopaedic Surgery, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: Despite the successes in Total Hip Arthroplasty (THA) surgery, some of these patients experience severe pain and decline in performance after surgery. The purpose of this study was to evaluate the effects of Celecoxib and Pregabalin on postoperative pain and physical dysfunction of these patients.

Methods: A randomized, double-blind trial was conducted on patients older than 15 years who underwent THA surgery. Patients were randomly assigned to two equal groups of receiving Celecoxib and Pregabalin (CP), and Celecoxib and placebo (C) groups. Group CP patients received a 100 mg Celecoxib capsules and Pregabalin 75 mg capsules twice a day, and group C received 100mg Celecoxib capsules along with placebo twice a day. The level of pain was evaluated using visual analog scale on operation day, third day and two weeks after surgery. The patient's function was assessed through Oxford Hip Score questionnaire. Data were analyzed using SPSS V.20. $P < 0.05$ was considered statistically significant.

Results: A total of 116 patients participated in the study, 58 patient in the group treated with Celecoxib and Pregabalin (CP) and 58 patients treated with Celecoxib (C). The mean and standard error of VAS scores on the CP group was lower than group C in the 14th day post-surgery. The mean morphine usage was significantly lower in the CP group than C group in the 3rd day post-surgery ($P < 0.02$). 86% of patients in CP group ($n = 50$) and 12% of C Groups ($n = 7$) suffered from nausea.

Conclusion: Results of this study showed that the use of Celecoxib and Pregabalin is effective in reducing pain and morphine consumption without bleeding risks in patients undergoing THA. Further studies are needed to generalize these findings.

KEYWORDS: Celecoxib, Pregabalin, total hip arthroplasty (THA), oxford hip score (OHS)

INTRODUCTION

Hip fracture is one the most important health concerns and main cause of mortality, particularly among young adults and adolescents [1]. Severity and disability imposed by this condition is higher than other illnesses. In recent years, we have witnessed accidents as the main cause of death in our country. Hip fracture is rising in the elderly. The incidence of hip fracture has increased in the recent years. The mortality rate of hip fractures is about 15-20% and it is 0.9% higher in comparison with other orthopedics conditions [1-3].

Total hip arthroplasty drew much attention from researchers and physicians in recent years, leading more day to day requests for surgery. The total hip arthroplasty is performed widely in all around the world. It is estimated that there are about 170 thousands case of surgery in United States and 300 thousand cases in the world every year. There are many indications for THA, but the most common indication is osteoarthritis and resembles 70% of all cases. Other indications include trauma, Paget's disease, osteonecrosis of femur head, lupus, ankylosing spondylitis, rheumatoid arthritis [3, 4].

Accidents and trauma are the most common causes of disease in Iran and most of these patients suffer from hip bone fractures, which are a painful skeletal condition, and also, THA is a one of the most orthopedics surgery that performed on this kind of patients. Hence, the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in pain control [1]. Mechanism of action of NSAID is inhibition of Cyclooxygenase enzymes activation and blocking prostaglandins production. The mediator of inflammation response is COX-2, primarily released late, because its release by macrophages, monocytes, synovial leukotrienes and fibroblasts last about one to three hours. Most of typical NSAIDs such as Naproxen, Aspirin, Ibuprofen, and Ketoprofen inhibit both COX-1 and COX-2 enzymes. So, the health and safety of gastrointestinal mucosa, as well as interfere with platelet aggregation are both

* **Corresponding Author:** Dr. Mohammad Reza Ebrahimiinia, Resident of Orthopaedic Surgery, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: m.ebrahimi110@yahoo.com

hard to maintain. Celecoxib is one of NSAID that inhibit COX-2, was confirmed in 1998 by American pharmaceutical association. This drug has been used for analgesic, anti-inflammatory, and fever properties, and used in treatment of rheumatoid arthritis, osteoarthritis, and dysmenorrhea. Celecoxib does not inhibit COX-2 enzymes at therapeutic doses, thus, it hasn't any interference with platelet functions and health of gastrointestinal mucosa [2]. However, due to mild gastrointestinal complications, caution in use of COX-2 inhibitors drugs, particularly in patients with a history of gastric problems is necessary [1]. Celecoxib due to some desirable properties such as long plasma half-life of 11 hours compared with conventional NSAIDs with a half-life of about 4-6 hours, maximum daily dose of two doses, mild and minimum side effects; is very suitable in pain control [3].

Pregabalin is structural analogy of Gama-butyric acid (GABA) that have analgesic, anxiolytic effects and nowadays using Pregabalin in treatment of neuropathic pain has been confirmed (proved)[4].

As pain is the most common indication for THA surgery in advanced hip diseases, so the main task of treatment team is pain control in these patients. Given the scarcity of studies in this area, this study conducted for evaluation of Celecoxib and Pregabalin effects on pain and function of patients undergoing THA surgery at Imam Hossain Hospital.

Method

This is a double blind randomized clinical trial study on patient undergoing THA that conducted in Imam Hossain hospital in 2013. Patients who were diagnosed by an orthopedist as case of THA surgery and age more than 15 years; entered study after completing a written consent form. Patients with loss of consciousness, unstable vital signs, medication allergy to Celecoxib and Pregabalin, have alcohol and drug history, pain medication use history, history of using Pregabalin- Gabapentin- nonsteroidal anti-inflammatory drugs-COX-2 inhibitors, have mental disorders, renal failure; were excluded from study. Patients who met the study criteria were assigned to two groups of receiving Celecoxib and Pregabalin, and receiver of Celecoxib and placebo, respectively.

The first group received Celecoxib capsules 100 mg daily (2 times) with Pregabalin capsules 75 mg daily (2 times a day). The second group received Celecoxib 100mg daily (2 times) with placebo (2 times). Pain scores was evaluated by visual analog score on the day of surgery, third day after surgery and two weeks after operation by another resident who was unaware of the patients grouping. Also, the patients function was measured by Oxford hip scores questionnaire at second and fourth week post-surgery [9]. Morphine consumption amounts were evaluated in the three days after surgery in both groups. The collected data were analyzed by SPSS v.20 software. $p < 0.05$ considered statistically significant.

RESULTS

A total of 116 patients participated in the study; 58 patients in Celecoxib and Pregabalin group (CP) and 58 patients in the Celecoxib and placebo group (C). Table 1 shows the participant's demographic data. Mean \pm SD deviation of patient's age was 62 ± 13 years. 7 patients (12%) of CP group and 2 patients (3.4%) in group C had history of hypertension. There were 4 patients (6.8%) in group CP and 3 patients (5.1%) in group C that have history of diabetes mellitus. Moreover, the reported history of nervous system disorders was 3 patient (5.1%) in group CP and 2 patients (3.4%) in group C.

The main indications of THA surgery in study participants were as follows: 36 patients (40%) because of trauma and 15 patients (17%) due to arthrosis and osteonecrosis in group C received surgery. In CP group 40 patients (46%) due to trauma and 9 patients (10%) because of arthrosis and osteonecrosis underwent surgery.

Table 1. the participants demographic data

Variable	Marital status	Total	CP	C	P
age		62 \pm 13	63 \pm 5	61 \pm 6	0.35
Marital status	Single	52 (45.1%)	20 (35.2%)	32 (54.9%)	0.1
	married	64 (54.9%)	38 (64.8%)	26 (45.1%)	
History of disease	HTN	9 (15.5%)	7 (12%)	2 (3.4%)	0.583
	Diabetes	7 (12%)	4 (6.8%)	3 (5.1%)	
	CNS	5 (8.6%)	3 (5.1%)	2 (3.4%)	
Cause of THA	Trauma	76 (65%)	40 (46%)	9 (10%)	0.41
	Arthrosis	24 (27%)	36 (40%)	15 (17%)	
complication	vomiting	12 (10.3%)	5 (8.6%)	7 (12%)	0.419

The Mean \pm SD of VAS-scores of both groups was 10 on the day of surgery. On the third day after surgery, the scores were 6.4 ± 0.7 in group C and 6.1 ± 0.3 in group CP. In the fourteenth day after the operation, these values were 3.2 ± 0.7 and 2.1 ± 0.4 in the groups C and CP, respectively (Table 2).

The Mean±SD of Oxford hip score on the fourteenth day after surgery were 23.3 ± 4.5 and one month after surgery were 27.1 ± 0.5 . These values in group CP patients on the above mentioned time was 24.1 ± 3.7 and 27.8 ± 0.4 respectively (Table 2).

The group C patient's morphine usage were 19.8 ± 8.5 on surgery day, 18.5 ± 7.4 on the second day after surgery, and 7.4 ± 3.1 on the third day after surgery. The values in CP patients were 16.5 ± 7.4 , 16.1 ± 6.3 and 5.3 ± 2.7 , respectively (Table 2).

Table 2. VAS score, Oxford hip score, and morphine usage of participants				
Test	Group	Baseline	Time 1	Time 2
VAS Score	C	10	Day 3 6.4 ± 0.7	Day 14 3.2 ± 0.7
	CP	10	6.1 ± 0.3	2.1 ± 0.4
Oxford Hip Score	C	-	Day 14 23.3 ± 4.5	Day 30 27.1 ± 0.5
	CP	-	24.1 ± 3.7	27.8 ± 0.4
Morphine usage	C	19.8 8.5	Day 1 18.5 ± 4.7	Day 2 7.4 ± 3.1
	CP	16.5 7.4	16.1 ± 6.3	5.3 ± 2.7

To test the effects of drugs between groups, repeated measures analysis of variance was performed. Results show that mean pain scores on the fourteen days after surgery in comparison with third day after surgery, reduced significantly in both groups ($p < 0.01$). Also, there wasn't any significant differences in mean pain scores of both groups in the fourteen days after surgery ($p < 0.01$). So that, mean and standard deviation of pain scores in the CP group were lower than C group ($p < 0.01$). No significant difference in pain score between the two groups was found on the third day and the beginning of the study (Figure 1).

There was significant increase in the mean oxford hip scores of thirtieth days than fourteen days after surgery ($p < 0.001$). There was not any significant difference between the mean scores of the two groups on fourteen and thirty days after surgery ($p < 0.01$) (Figure 2).

A significant reduction in morphine usage of both groups has been seeing at the 3rd day of surgery in comparison with the day of operation. The results of multivariate analysis of variance showed that the average morphine use of CP group was significantly lower than group C three days after surgery ($p < 0.02$) (Figure 3).

Figure 1. Diagram of change in pain scores

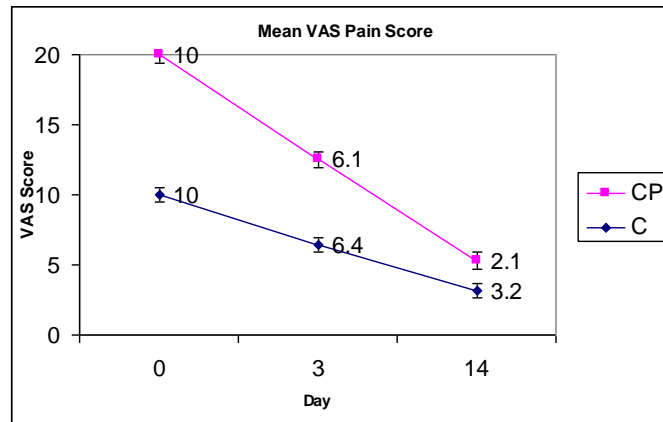


Figure 2. Diagram of change in Oxford hip scores

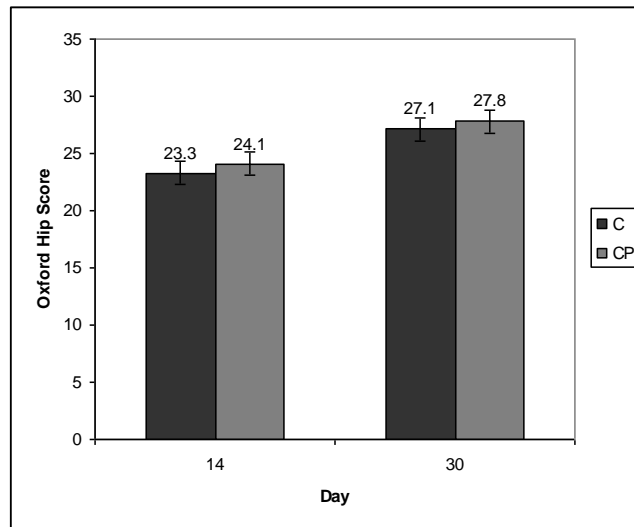
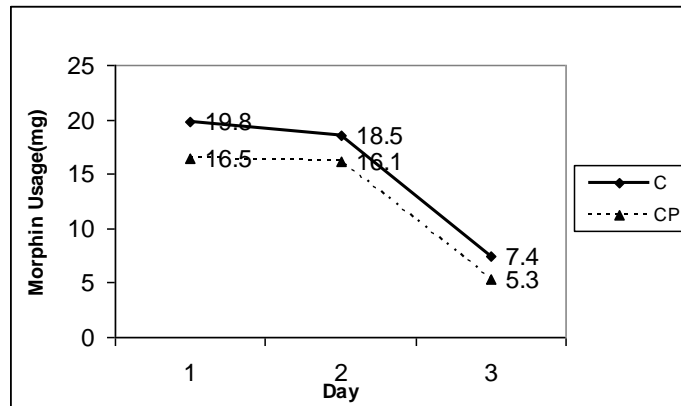


Figure 3. Diagram of morphine usage changes



Nausea were occurred in 5 patients in CP (8.6%) and 7 patients in C (12%) group. There was not any significant difference between two groups regarding to procedure's complication. There wasn't any significant correlation between pain scores, oxford hip scores, and morphine usage at different times of the study and underlying disease, age, and gender of patients.

Discussion

The findings of this study showed that the use of Celecoxib with Pregabalin and/or Celecoxib alone, both methods are effective for reducing pain of patients after THA surgery; although the patients in group CP have less pain than patients in group C on the fourteenth day; and this reduction was found significant too. In addition, CP group used smaller amount of morphine than C groups in the post-operative periods.

Coxibs are known category of analgesic for post-surgery pain control. Prescription of this drugs before surgery cause pain reduction and increase patient's satisfaction, also reduce postoperative analgesic consumption. Rueben and colleagues tested the dose of 200 mg of Celecoxib and 50 mg of rofecoxib before surgery [10]. Their research showed that Celecoxib and rofecoxib reduce morphine use in patients.

According to latest statistics published in United States, hip fracture is the most common cause of hospital admissions and bed occupancy, about 340,000 beds in year. Total hip replacement is done due to variety of reasons and osteoarthritis is the most common cause which includes 70% of all cases. Other causes includes trauma, Paget's disease, osteonecrosis of head of femur, lupus, ankylosing spondylitis, and rheumatoid arthritis [3, 4].

Total hip arthroplasty is final treatment of advanced osteoarthritis of hip joints and also, it is the treatment of choice for femoral neck fractures in elderly patients who are functionally active and have good bone quality [5]. Choosing the right treatment in older patients is very important because patients will have more efficient life and fewer complication; revision surgery need is reduces, particularly in elderly who surgery is associated with

numerous risks. Mariconda and colleagues were studied 250 patients who underwent total hip arthroplasty for a period of 16 years, and at the end they assert that quality of life and hip joint function is significantly improved [6]. Pietrzak and co-workers studied 29 patients with osteoarthritis in a clinical trial and evaluate their condition for a period of 16 years. Although the factors involved in hip fracture in the elderly are numerous, but osteoporosis has been suggested as the major cause of hip fracture in elderly. In the present study 35% of patients had arthrosis and osteonecrosis problems, and the mean age was 62 years, which determine the importance of this issue [5]. NSAIDs are known drugs that reduce narcotics consumptions about 30-50% [11], although their side effects are still unknown. In the present study, morphine usage of CP group was significantly lower than group C ($p < 0.01$). Although some previous studies have shown that using non-selective NSAIDs in preoperative period increase the risk of bleeding [12].

Non-selective NSAIDs inversely inhibit COX and interfere with platelets function, while selective NSAIDs have less antiplatelet effects than non-selective counterparts. In the present study, daily doses of Celecoxib didn't cause any side effects in both groups in terms of bleeding. Cox-2 selective inhibitors may improve gastrointestinal tolerability and lower risk of cardiovascular disease [13]. Studies have shown that Cox-2 selective inhibitors increase risk of cardiovascular disease, myocardial infarction, and heart stroke [14]. Another previous study showed that the use of Celecoxib increase the risk of cardiovascular disease compared with placebo [15].

There are many research about effects of Pregabalin use on morphine usage and pain control in orthopedic surgeries; but many of them reported nausea and vomiting [16, 17], drowsiness, lethargy, extremities edema, and head ache [12] due to Pregabalin consumption; because the recommended dosage for Pregabalin is 600 mg daily, while in the present study nausea were appeared in 7 patients of group CP which use a daily dose of 150 mg Pregabalin.

Pregabalin in combination with Celecoxib have significant effect on reducing morphine use of CP group compared with group C. while, in a previous stud, daily administration of 600 mg Pregabalin have the effect of reducing total morphine use, but prescription of typical dose of 300 mg a day didn't cause any reduction in narcotic use.

Pregabalin is a structural analog of Gama-aminobutyric acid and have analgesic, anticonvulsant, and anxiolytic effects. Nowadays, its usage for treatment of neuropathic pains has been demonstrated. The mechanism of it action is binding to pre-synaptic alpha2 GABA subtypes and voltage-dependent calcium channels, which are very wide spread in brain and spinal cord. Stimulation of pre-synaptic alpha-2-GABA groups inhibits the release of excitatory neurotransmitters including glutamate, norepinephrine and calcitonin related-gene; with this action, neurons in the central nervous systems with excessive stimulation are returns to normal [3, 4].

Using Celecoxib after total hip and total knee surgeries decrease the patient's pain. Moreover, morphine prescription significantly reduced patient's pain in the first three days after surgery in the treatment group. The findings of current study showed that the use of Celecoxib reduces postoperative pain and morphine use. However, it uses with Pregabalin work better in reducing patients pain in the third day after surgery.

In Huang's study, taking Celecoxib before THA surgery reduces pain in two and three days after surgery and reduced morphine usage; also, there wasn't any case of bleeding. Results of Huang study regarding to effect of Celecoxib on reducing pain scores and morphine use is consistent with the findings of the present study.

One of the limitation of this study is lack of placebo group. The reason for absence of placebo group in this study was ethical issues; because patients should be able to get analgesic and pain killers after painful THA surgery. Another limitation is the small sample size, prospective studies need larger sample size and even better would be conduct a multi-center study. In considering the questions remain regarding the effects of different doses and similarly, the pattern of Pregabalin impacts on pain of different group of patients with different gender that present in different surgeries, it seems that conducting different research in this area is needed.

Conclusion

The findings of this study show that the use of Celecoxib with Pregabalin rather than using Celecoxib alone, have better efficacy, so that patient's pain scores in fourteen days after surgery are lower. Additionally, morphine use in Celecoxib with Pregabalin compared to Celecoxib group, decreased significantly.

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