ORIGINAL ARTICLE

Comparing the prophylactic effects of oral gabapentin, pregabalin, and celecoxib on postoperative pain management in orthopedic surgery of the lower extremity: A double-blind randomized controlled trial

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Background: Lower extremity pain after orthopedic surgery is so frequent that has led to many treatment modalities. This study aims to compare the prophylactic effects of oral gabapentin, pregabalin, and celecoxib on reducing postsurgical pain of the lower extremity orthopedic surgery. **Materials and Methods:** In a double-blind randomized controlled trial, 120 patients were randomly divided into four groups using block design randomization. 1 h before spinal anesthesia, the studied groups received 300 mg oral gabapentin; 75 mg oral pregabalin; 200 mg oral celecoxib; and starch as placebo. The severity of postoperative pain (using visual analog scale), mean arterial pressure, heart rate, opioid consumption dose, and drug side effects were recorded for six times (each 60 min up to two times and then every 6 h for the next four times). Chi-square, one-way analysis of variance (ANOVA), and ANOVA repeated measure tests were used for statistical analysis. **Results:** Significant reduction of pain severity was observed only at the first time measurement between pregabalin and placebo groups (*P*: 0.014). Patients in the pregabalin group required lower dose of opioid compared to placebo group during admission in surgical ward. There were no significant differences concerning pain reduction, opioid administration, and side effects between pregabalin, gabapentin, and celecoxib groups. **Conclusion:** Taking 75 mg oral pregabalin before lower extremity orthopedic surgery can attenuate postoperative pain, especially during the 1st h postoperation as well as less opioid consumption and much more patients' satisfaction.

Key words: Celecoxib, gabapentin, postsurgical pain, pregabalin

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INTRODUCTION

Postoperative pain differs from other types of pain because it rises during a short time after operation but can be controlled more easily than chronic pain.[1] Orthopedic surgeries cause excessive pain after a few days.[2] Optimal postoperative pain control leads to faster recovery, reduction of complications, and patient satisfaction improvement.[3]

Oral multimodal analgesia for hip and knee arthroplasty is increasingly used as a part of enhanced recovery protocols. It was designed for early postoperative pain relief and early discharge besides reducing undesirable side effects related to single-agent opioid

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administration.[4] Acute pain management after orthopedic surgery can be challenging. Postorthopedic surgery pain has different pathophysiology versus the pain associated with other surgical procedures. This is happened due to various nerve damages during different surgeries. Hence, postoperative pain control is a significant issue that requires multiple approaches to be solved.[5] Poor postoperative pain control can lead to complications such as delayed hospital discharge, long-term use of opioids, pulmonary edema and atelectasis, hypoxemia and cardiovascular diseases. Pain can also restrict patients' movement and result in more risk of thromboembolism and less gastrointestinal (GI) and genitourinary tract motility.[6,7] Poor pain control in orthopedic surgeries prevents the patient to participate in rehabilitation schedules that contributes to prolonged recovery time, reduction of limb force, joint stiffness, joint pain, and more local pain.[8] Chronic pain can destroy the quality of patients' life.[9] Postsurgical pain management can bring mortality, admission time in hospital, and treatment costs down.[10] Although opioids are commonly used for lessening postsurgical pain , their use is accompanied by some limitations.[2] Previous findings have shown that multimodal analgesia (combination of different methods of pain control) both intra- and post-operative ones are more effective.[11] Gabapentin and pregabalin have several pharmacological mechanisms including contrasting with L-amino acid transporters and prevention of Ca^{2+} transmission through high-voltage gated channels, which cause less release of neurotransmitters and synaptic excitability.[12,13] Reduction of Ca^{2+} influx guides to fewer release of stimulating amino-acids and substance-p and results in neuronal suppression.[14] Gabapentin, the analog of gamma-aminobutyric acid, is an antiepileptic drug which is used for pain control nowadays.[6]

Previous studies showed that gabapentin controls limb's phantom pain effectively.[15] Pregabalin attaches to its neuronal calcium channels and affects the neurotransmitter release. It is beneficial for controlling fibromyalgia, neural cord pain, and postsurgical pain and has a suitable pharmacokinetic profile with no dose-dependent absorption.[16]

Studies on patients undergoing orthopedic surgery showed that pregabalin decreases pain score in these patients compared to placebo.[5] Gabapentin and pregabalin were effective in neuropathic pain control like postsurgical pain.[17]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly considered for postsurgical pain without having opioid-related side effects.[18] NSAIDs are potential analgesics without making sedation that is commonly seen with opioids' consumption. NSAIDs have shown a reduction in morphine use by 27% during the first 24 h after operation.[19]

Celecoxib inhibits cyclooxygenase, especially COX-2 and reduces the prostaglandins production. This drug has renal and cardiovascular complications. It is used for osteoarthritis and gout treatments and has analgesic effects after operation. Research showed that oral celecoxib reduced postsurgical pain as effective as 600 mg aspirin or 1000 mg paracetamol.[20]

Due to lack of studies comparing different abovementioned modalities with respect to postorthopedic surgery pain of lower extremity, we compared the prophylactic effects of oral gabapentin, pregabalin, and celecoxib on postoperative pain reduction with placebo in these kinds of surgeries.

SUBJECTS AND METHODS

This study was approved by the Isfahan University of Medical Sciences' Institutional Review Board, registered in the WHO clinical trial registration site (IRCT20180722040557N1) and received written informed consent from all individuals involved in the trial.

A double-blind randomized controlled trial was performed to compare the prophylactic effects of oral gabapentin, pregabalin, celecoxib, and placebo on controlling postorthopedic surgery pain of the lower extremity under spinal anesthesia in Al Zahra and Kashani Hospitals, Isfahan, Iran, from August 15, 2018, to October 9, 2018.

Inclusion criteria were candidates for elective lower limb orthopedic surgery, lack of contraindications for spinal anesthesia, increased intracranial pressure, coagulation disorders and restriction for sitting position, patient's consent to spinal anesthesia, age range of 16–78 years, absence of uncontrolled systemic diseases including hypertension, ischemic heart disease, heart failure, etc., and the American Society of Anesthesiologists (ASA) physical status classes I and II.

Exclusion criteria include patient's refusal to participation, failure of spinal anesthesia (more than twice), requirement to the different anesthetic method, and prolonged surgical time.

After receiving the ethic committee approval, 120 candidates for lower limb orthopedic surgery, who met the above inclusion criteria, were selected and received written consent. After that, they were assigned to four groups using block design randomization: numbers from 1 to 30 were allocated to the first group, numbers from 31 to 60 were put in the second group, numbers from 61 to 90 were allocated to the third group, and finally, numbers from 91 to 120 were

assigned to the fourth group. Patients were blind to their medications intentionally to design a double-blind study. A person, who did not have any role in data collecting, put drugs into the same capsules with different codes. Starch was used as placebo. An anesthesiologist, who gave the drugs, was also blind to the capsules' content.

Two trained personnel collected all data separately to increase the accuracy of data collection. The data of 20 cases were excluded from the analysis due to the mismatch of pain severity reported to data collectors. Hence, the final analysis was done with a data pool of 100 cases [Figure 1].

One hour before spinal anesthesia induction, one of the following three medications was given to separate groups: 300 mg gabapentin (Abidi company, Iran) for the first group, 75 mg pregabalin (ACTOVERCO company, Iran) for the second group, and 200 mg celecoxib (Daroupakhsh company, Iran) for the third group. 2 g starch was used as placebo for the fourth group.

All of the patients in the operating room underwent a standard heart rate (HR), SPO2 saturation, and blood pressure monitoring. Before spinal anesthesia, all of the patients received 10–15 cc/kg isotonic saline and then spinal anesthesia was performed by a 23–25-gauge needle on L3–L4 and L4–L5 levels using the midline approach. Bevel of needle was inserted vertically in dura mater to minimize the transverse incision of dura. Once the needle touched the subarachnoid space, it was turned for 90° counterclockwise. Barbotage technique was used to confirm the needle's position in the subarachnoid space. We tried

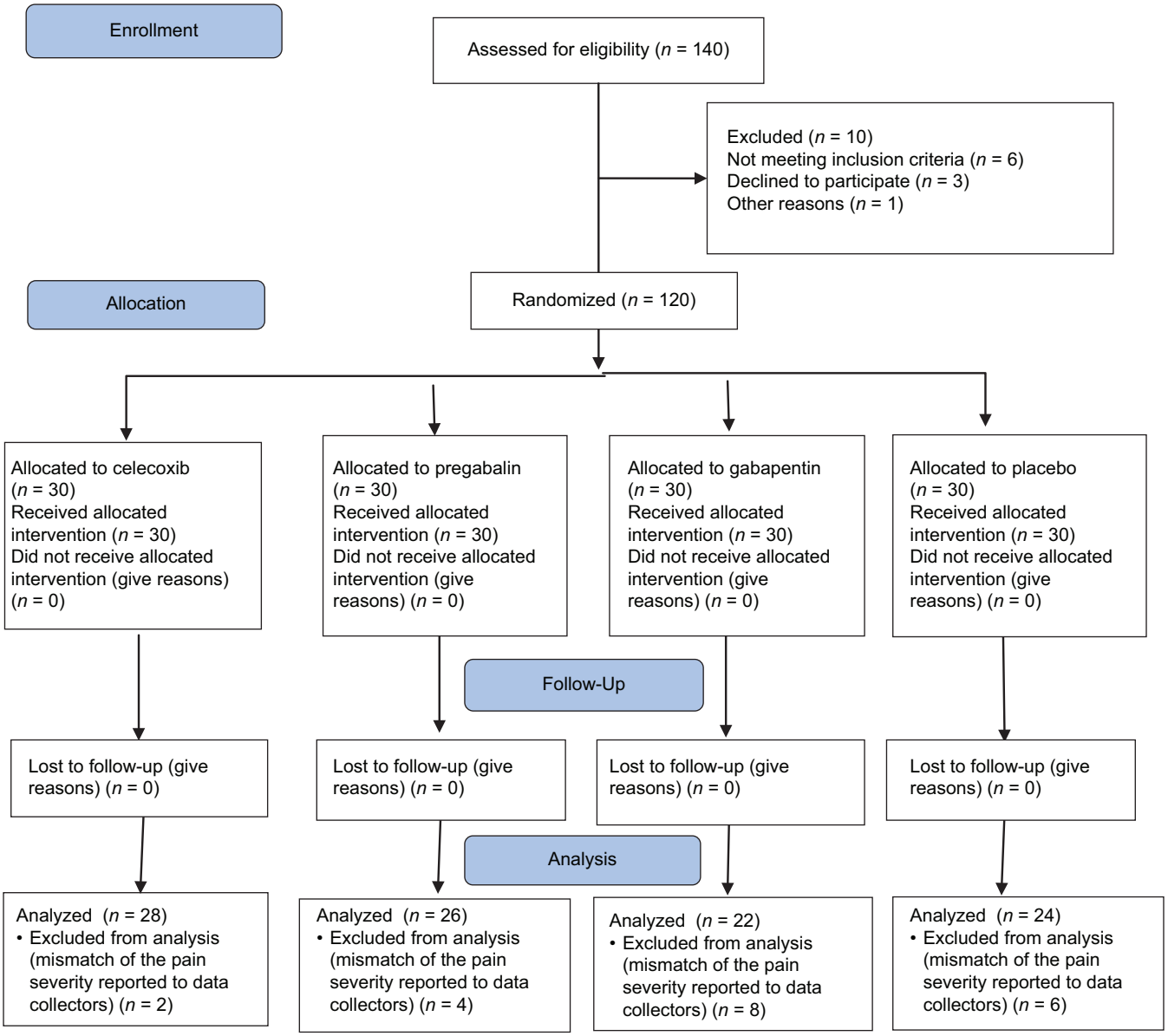

Figure 1: CONSORT 2010 flow diagram

spinal anesthesia no more than twice for each patient so after two failings, the patient was excluded from our study. Bupivacaine 0.5% or marcaine (2.5–3 cc) was injected within 10 min for local anesthesia. After that, the patient's bed was set to prevent high spinal cord position and reduce the risk of saddle anesthesia. The pinprick test was applied to check the sensory block level and assure analgesia at the T10 level, which was suitable area for surgical incision. Patients underwent noninvasive blood pressure, electrocardiogram, and pulse oximetry monitoring in a standard way. Whenever the patient's blood pressure dropped >30% from the basic level, intravenous (IV) ephedrine 5 mg was injected. For controlling bradycardia (HR < 50/min), IV atropine 0.5 mg and for nausea/vomiting reduction, IV ondansetron 4 mg were considered. Mean arterial pressure (MAP) and HR were recorded before anesthesia. Then, pain score using visual analog scale, MAP, HR, patient's opioid consuming dose (based on patient's requirement), and probable drug-induced side effects including chill, headache, nausea, vomiting, dizziness, and fever were documented six times. Two measurements were done in the recovery room (every 60 min for 2 h), and four measurements were done in the surgical ward (every 6 h up to 24 h).

The age, weight, gender, preanesthesia MAP and HR, anesthesia time, and ASA physical status were documented for each patient.

Statistical analysis

Collected data were analyzed using Chi-square test (for qualitative data), one-way analysis of variance (ANOVA), ANOVA-repeated measure, and *post hoc* tests using SPSS version 20 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered as significant for confidence interval of 95%.

RESULTS

This study evaluated 120 patients fallen into four equal groups. Six patients in the placebo group, eight patients in the gabapentin group, four patients in the pregabalin group, and two patients in the celecoxib group were excluded due to data mismatching of collectors. Finally, the analysis was conducted with 100 patients.

There were no significant differences between groups regarding age, weight, gender, ASA class, preanesthesia MAP and HR, and mean anesthesia time [Table 1].

Significant differences concerning pain score were only observed at the first time measurement between pregabalin and placebo groups using *post hoc* tests ($P = 0.014$).

Significant differences between placebo group and others were not found at other times.

In addition, gabapentin, pregabalin, and celecoxib drugs did not make significant differences at all times regarding pain severity. Pregabalin group had significantly less opioid consumption during hospitalization in surgical ward than placebo one [Table 2].

Post hoc tests revealed that MAP for pregabalin group was significantly less than MAP for placebo one at time 1 ($P = 0.04$) and time 6 ($P = 0.02$). Moreover, MAP for celecoxib group was significantly less than control group at time 2 ($P = 0.03$).

There were not any significant differences between groups regarding HR by pair at all times [Table 3].

Placebo, gabapentin, pregabalin, and celecoxib groups had 19, 16, 15, and 15 cases who sustained probable side effects, respectively (79.1%, 72.7%, 57.7%, and 53.5%, respectively).

The most frequent side effects in placebo, gabapentin, pregabalin, and celecoxib groups defined as chill (29%),

Table 1: Demographic characteristics of participants

Variables	Mean±SD				*P*
	Placebo	Gabapentin	Pregabalin	Celecoxib	
Age/year	45.29±17.42	39.91±16.95	34.35±12.60	44.46±17.23	0.75
Weight/kg	74.96±8.03	73.73±5.25	74.73±13.06	72.52±6.32	0.06
Gender, *n* (%)					
Male	19 (79.1)	17 (77.2)	19 (73)	25 (89.3)	0.49
Female	5 (20.9)	5 (22.8)	7 (26)	3 (10.7)	
ASAs physical status, *n* (%)					
I	19 (79.2)	18 (81.8)	17 (65.4)	20 (71.4)	0.55
II	5 (20.8)	4 (18.2)	9 (34.6)	8 (28.6)	
Mean anesthesia time/hour	3.52±0.56	3.55±0.51	3.57±0.51	3.71±0.41	0.51
Heart rate/minute (before anesthesia)	85.25±14.40	79.18±18.17	91.19±13.13	82.89±18.10	0.073
Mean arterial blood/mmHg pressure (before anesthesia)	209.56±27.3	196.21±26.6	209.93±28.9	205.78±28.9	0.31

ASAs=American Society of Anesthesiologists; SD=Standard deviation

Table 2: Pain score and pethidine consumption dose shown for each group at different times

Variables	Time	Group	Mean±SD	Within group - *P*	Between-group - *P*
Pain score (using VAS)	First time measurement	Placebo	4.83±1.78	0.02	0.017*
		Gabapentin	3.83±2.90		
		Pregabalin	2.65±2.65		
		Celecoxib	3.25±2.38		
	Second time measurement	Placebo	0.58±1.57	0.09	0.219
		Gabapentin	0.001±0.001		
		Pregabalin	0.001±0.001		
		Celecoxib	0.29±1.5		
	Third time measurement	Placebo	0.88±1.4	0.36	0.260
		Gabapentin	1.86±3.6		
		Pregabalin	0.62±1.7		
		Celecoxib	1.61±2.83		
	Fourth time measurement	Placebo	6.08±3.09	0.40	0.359
		Gabapentin	7.09±2.7		
		Pregabalin	6.42±3.8		
		Celecoxib	5.46±3.18		
	Fifth time measurement	Placebo	8.13±2.93	0.83	0.578
		Gabapentin	8.27±2.65		
		Pregabalin	7.08±3.85		
		Celecoxib	7.75±3.34		
	Sixth time measurement	Placebo	3.88±2.27	0.98	0.940
		Gabapentin	3.91±2.79		
		Pregabalin	4.00±3.32		
		Celecoxib	4.36±3.72		
Pethidine consumption (mg)	Recovery time	Placebo	32.50±15.00	0.5	
		Gabapentin	35.00±21.21		
		Pregabalin	20.00±0.00		
		Celecoxib	31.46±36.7		
	Admission time in surgical ward	Placebo	53.95±26.69	0.03*	
		Gabapentin	43.75±19.66		
		Pregabalin	22.12±28.57		
		Celecoxib	48.91±34.93		

**Post hoc* tests revealed that the significant differences were related to pregabalin and placebo groups. VAS=Visual Analog Scale; SD=Standard deviation

headache (31%), chill (19%), and vomiting (21%), respectively. Having mentioned that, though, there was no significant difference between these groups ($P = 0.28$).

Evaluations found that the highest mean for consuming dose of ephedrine was 13.33 ± 5.77 mg and related to placebo group. However, only one patient in the celecoxib group and one patient in pregabalin had needed ephedrine. Hence, no significant differences for ephedrine consumption were observed between groups ($P = 0.66$). Atropine was required only for two patients (in pregabalin and celecoxib groups) with no significant differences between groups ($P = 0.5$).

Pregabalin group had announced significantly higher levels of satisfaction compared to others [Table 4].

DISCUSSION

Postoperative pain is a widespread and challenging complication in patients undergoing surgical procedures, especially orthopedic surgeries which can lead to long-term opioid use and diseases. Due to the wrenching and destructive effects of postoperative pain, many researchers have struggled through variety of methods to control it but there is no consensus on a standard method for postsurgical pain control.

We found that pregabalin group experienced significantly less pain severity at the recovery time compared to the control group, but other drugs (gabapentin and celecoxib) did not significantly reduce the pain during recovery time. Significant reduction in pain score was not found between four groups during patients' follow-up at surgical ward. Pregabalin group significantly needed least pethidine dose during admission in surgical ward while the placebo group required the most amount of it. Hence, pregabalin is highly recommended before orthopedic surgery of lower extremity.

Previous findings claimed that postoperative consumption of parecoxib sodium had opioid-sparing and pain reduction

Table 3: Hemodynamic variables in all groups at different times

Variables	Time	Group	Mean±SD	Between-group - *P*
MAP/mmHg	First time measurement	Placebo	95.38±13.21	0.033*
		Gabapentin	89.71±9.57	
		Pregabalin	86.65±9.62	
		Celecoxib	87.46±12.07	
	Second time measurement	Placebo	91.77±12.95	0.043*
		Gabapentin	88.95±9.80	
		Pregabalin	87.26±7.82	
		Celecoxib	83.73±9.66	
	Third time measurement	Placebo	89.76±8.33	0.053
		Gabapentin	89.69±7.19	
		Pregabalin	86.46±7.30	
		Celecoxib	91.89±5.58	
	Fourth time measurement	Placebo	92.41±9.37	0.387
		Gabapentin	89.31±5.36	
		Pregabalin	89.85±5.92	
		Celecoxib	91.89±5.58	
	Fifth time measurement	Placebo	89.11±7.93	0.941
		Gabapentin	88.63±5.21	
		Pregabalin	89.12±5.27	
		Celecoxib	89.69±5.01	
	Sixth time measurement	Placebo	89.20±8.83	0.024*
		Gabapentin	84.62±6.5	
		Pregabalin	83.02±7.47	
		Celecoxib	87.28±7.20	
HR/minute	First time measurement	Placebo	74.67±16.25	0.050
		Gabapentin	66.64±12.39	
		Pregabalin	75.96±12.12	
		Celecoxib	68.64±13.41	
	Second time measurement	Placebo	76.25±14.48	0.085
		Gabapentin	69.23±13.51	
		Pregabalin	75.35±11.64	
		Celecoxib	68.71±13.02	
	Third time measurement	Placebo	82.46±4.62	0.253
		Gabapentin	80.59±4.98	
		Pregabalin	79.46±6.47	
		Celecoxib	81.32±5.05	
	Fourth time measurement	Placebo	81.83±3.27	0.568
		Gabapentin	81.50±3.58	
		Pregabalin	80.15±5.80	
		Celecoxib	80.79±4.80	
	Fifth time measurement	Placebo	81.33±3.72	0.916
		Gabapentin	80.77±3.69	
		Pregabalin	80.65±4.43	
		Celecoxib	80.57±4.55	
	Sixth time measurement	Placebo	81.04±2.38	0.137
		Gabapentin	79.91±3.72	
		Pregabalin	79.23±3.81	
		Celecoxib	78.86±3.82	

**Post hoc* tests found that significant differences at time 1 and time 6 were dedicated to pregabalin and placebo groups, while there were significant differences at time 2 between placebo and celecoxib ones. MAP=Mean arterial pressure; HR=Heart rate; SD=Standard deviation

effects after total knee arthroplasty surgery.[18] Another study on patients undergoing spinal surgery revealed that the preoperative administration of pregabalin significantly reduced pain scores and enhanced functional outcome compared to placebo.[5] A systematic review, that evaluated oral celecoxib effects, realized that it had a significant effect on postsurgical pain reduction without any significant side effects.[21] Another study in the same patients showed that

Table 4: Frequency distribution of patients' satisfaction levels

Groups	Satisfaction level	Placebo	Gabapentin	Pregabalin	Celecoxib	*P*
Satisfaction levels rate (%)	Absolutely satisfied	0	9.1	30.8	15.4	0.001
	Satisfied	12.5	18.2	38.5	23.1	
	Unsatisfied	41.6	13.6	7.7	11.5	
	Absolutely unsatisfied	29.2	31.8	19.2	15.4	
	No comment	16.7	27.3	3.8	34.6	

COX-2 selective inhibitors decreased postoral surgery pain as same as traditional NSAIDs besides clinical advantages in relation to GI safety.[22]

Analgesic studies has shown that oral celecoxib with equivalent dose to 600 mg aspirin or 1000 mg paracetamol can be effective in postoperative pain reduction.[20] A study on patients undergoing spinal surgery showed that use of 400 mg oral celecoxib could significantly reduce postoperative pain.[23]

Li *et al*. claimed supporting evidences for perioperative administration of oral pregabalin because of its postoperative pain relief effects in a safe way.[24]

Pourfakhr *et al*. declared that consuming 75 mg oral pregabalin before anesthesia induction can effectively control pain after septorhinoplasty procedure with rare complications.[25]

Amjad study on patients who underwent open cholecystectomy revealed that preoperative administration of 150 mg oral pregabalin had no more pain relief effects in comparison with 200 mg oral celecoxib while prevalence of side effects was more for pregabalin group.[26]

A meta-analysis study assessed effects of pregabalin on attenuating postoperative pain following thoracotomy and it found that pregabalin can prevent postoperative pain and cause less neuropathic pain and opioid consumption.[27]

Anand study evaluated analgesic effects of pregabalin after laparoscopic cholecystectomy and claimed that preoperative administration of 150 mg pregabalin orally can control postoperative pain noticeably and reduce opioid requirements as well as reduce nausea and vomiting besides higher satisfaction level of patients.[28]

This study was performed with some limitations for instance groups' matching based on the type of surgery.

CONCLUSION

Taking 75 mg oral pregabalin before lower extremity orthopedic surgery can attenuate postoperative pain, especially during the 1st h postoperation as well as less opioid consumption, less MAP, no more side effects, and much more patients' satisfaction.

It is recommended to be administered before these surgical procedures. Concerning the restrictions of the current study and impact of multimodal analgesia regimen on frequency of short-term and long-term opioid use, more studies are required to be done.

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Conflicts of interest

There are no conflicts of interest.

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