ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 07 | July - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EVALUATION OF EFFECTIVENESS OF SINGLE ORAL DOSE PREGABALIN ON DURATION OF ANALGESIA IN PATIENTS UNDERGOING LOWER LIMB ORTHOPAEDIC SURGERIES UNDER SPINAL ANAESTHESIA – A CROSS-SECTIONAL RANDOMIZED COMPARATIVE STUDY

Anaesthesiology

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ABSTRACT

This study was conducted with the main purpose to evaluate whether preoperative single dose of oral Pregabalin has any effect in postoperative analgesic requirement in patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia, and it's associated adverse effects. This is a cross-sectional randomized comparative study conducted on 80 patients, divided into two groups viz. Group-A and Group-B of 40 each. Patients belonging to Group-A received placebo capsule orally 1 hour before surgery and patients in Group-B received capsule Pregabalin 150mg orally 1 hour before the surgery. Results revealed that, there was a statistically significant ($p < 0.05$) reduction in VAS score following the administration of 150 mg oral dose of Pregabalin at 2 hr, 4 hr, 6 hr, and 12 hr post-surgery. Time for the first request for postoperative rescue analgesia was significantly ($p < 0.001$) prolonged in Pregabalin group. Furthermore, there were no postoperative complications observed following administration of Pregabalin at the dose of 150 mg for patients undergoing lower limb orthopaedic surgeries under spinal anesthesia. In conclusion, the administration of a single dose of oral Pregabalin 150 mg one hour prior to surgery in patients undergoing lower limb orthopaedic surgeries under spinal anesthesia was efficacious in delaying the first request for postoperative analgesics and decreasing postoperative pain without any adverse effects.

KEYWORDS

Pregabalin, Orthopaedic surgeries, Pain, Rescue analgesia

INTRODUCTION

Orthopaedic surgeries are frequently associated with moderate-to-severe postoperative pain, that can decrease mobility in the immediate postoperative period, interfere with postoperative rehabilitation, and delay hospital discharge. Pain may also become chronic.[1] Postoperative pain has significant impact on the surgery outcome due to many adverse effects like tachycardia, hypertension, ischemia, reduced alveolar ventilation, poor wound healing and patient discomfort.[2]

Spinal anaesthesia is the most popular anaesthesia technique worldwide in orthopaedic lower limb surgeries.[3] However, its relatively short duration of action may limit the excellent postoperative analgesic effect.[4] Thus, many adjuvants had been used to improve postoperative analgesia and decrease consumption of postoperative analgesics.[3] Gamma amino-butyric acid (GABA) analogues like Pregabalin and its developmental precursor Gabapentin are being used as preemptive analgesics.[5] Pregabalin plays its role in treatment of acute post-operative pain by decreasing the excitability of dorsal horn neurons caused by tissue damage.[6] The anti-nociceptive effect of preemptive analgesia develops by preventing the development of triggering hyperplastic changes at the surgical site in response to a noxious stimulus. It also has a central neural desensitization effect that may prevent the amplification of future impulses at the surgical site.[7]

Moreover, various research investigators demonstrated the effectiveness of Pregabalin in the improvement of postoperative analgesic effect and decreased postoperative opioid consumption.[8,9] Akhavanakbari et al., reported that preemptive Pregabalin in an oral dose of 150 mg offers good postoperative analgesia in lower limb orthopaedic surgeries under spinal anesthesia.[9]

With this background, the present cross-sectional randomized comparative study was designed with the main objective to determine whether preoperative single oral administration of Pregabalin has any effect in postoperative analgesic requirement in patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia, and to study its adverse effects if any.

METHODOLOGY

Study design and patients

This is a cross-sectional randomized comparative study conducted on total of 80 patients at the Orthopaedic Department, in J.J.M. Medical College, Davangere, Karnataka, India. The study was approved by institutional ethical committee and informed consent was obtained from all the patients.

Inclusion criteria

1. Patients with age group of 20-40 years of either gender.
2. Patients posted for elective lower limb orthopaedic surgeries under spinal anesthesia (SA).
3. Patients with ASA I and ASA II.

Randomization

A total of 80 selected patients were randomly divided into two groups *viz.* Group-A and Group-B of 40 each. Patients in Group-A received capsule placebo orally 1 hour prior to surgery and patients in Group-B received capsule Pregabalin 150mg orally 1 hour prior to surgery.

Experimental procedure

Anaesthesia technique:

Under complete aseptic precautions and in lateral position, the line connecting the two iliac crests (Tuffier's line) was identified to detect the level of L3-L4 or L4-L5 inter-vertebral space. 3 mL of lignocaine 2% were infiltrated at midline at the level space for local anaesthesia. Spinal anaesthesia was performed via midline approach using a 23-gauge sharp tip spinal needle, injecting 2.5 mL of hyperbaric Bupivacaine (0.5%). The patients were then turned to supine position, with 15-degree head elevation. They were left in this position for 20 mins, during which hemodynamic parameters were closely monitored and sensory and motor block criteria assessed. Hemodynamic parameters were monitored every 3 mins during the first 30 mins after spinal anesthesia. Patients who showed a decrease in mean arterial pressure to less than 65 mmHg received intravenous ephedrine 5 mg. Those who showed a decrease in heart rate to less than 50 beats/min received atropine 0.5 mg intravenously.

Assessment parameters

The visual analogue score (VAS) was used to evaluate postoperative analgesia immediately after surgery, every 2 hr. for the first 6 hr. and then every 6 hr. up to 24 hr. Whenever VAS exceeded 4, 75 mg Diclofenac sodium was administered as intravenous infusion as rescue analgesia. Time since spinal anaesthesia to first requirement of rescue analgesia, total analgesic requirement in first 24 hours, VAS scores, side effects of the drug were recorded in first 24 hours postoperatively.

Statistical analysis

Data were entered in Microsoft Excel 2019 and statistical analysis was done using IBM Statistical Software for Social Sciences (SPSS) version 25. Categorical variables were represented in the form of percentages, frequencies and association between variables were assessed with Chi-square test. Continuous variables were presented as descriptive statistics (Mean and Standard deviation) and inter group comparison of variables has been done with unpaired t-test. P-value of <0.05 was considered statistically significant.

RESULTS

The mean age of patients was found to be 31.60 ± 6.30 and 30.90 ± 7.10 in Group-A and Group-B respectively with male predominance in both the groups (Group-A: 85%; Group-B 88%) as compared to female patients (Group-A: 15%; Group-B 13%). However, there were no statistically significant difference observed between the groups with respect to age (P = 0.629) and gender(P = 0.713) based on the Chi-square test. All the patients enrolled in the study belonged to ASA physical status I (Table 1).

Table 1: Demographic characteristics of study subjects

Variables	Group-A (Placebo)	Group-B (Pregabalin)
Age (years)		
20-29	40.00	47.50
30-39	40.00	30.00
40	20.00	22.50
Mean ± S.D.	31.60 ± 6.30	30.90 ± 7.10
P = 0.629		
Gender		
Male	85.00	88.00
Female	15.00	13.00
P = 0.713		
ASA Grade		
ASA I	100	100

A statistically significant ($p < 0.05$) reduction in VAS score was observed between groups *viz.* Group-A and Group-B at 2 hr., 4 hr., 6 hr., and 12 hr. postoperative time intervals . However, VAS score was not statistically significant between the two groups at 18 hr. (P = 0.350) and 24 hr. (P = 0.670) postoperative time intervals (Table 2).

Table 2: Distribution of patients based on VAS score

Time Interval	Visual Analog Score (VAS)		p-value
	Group-A (Placebo)	Group-B (Pregabalin)	
2 hr.	3.30 ± 1.22	0.03 ± 0.16	0.001
4 hr.	4.23 ± 0.70	2.48 ± 0.82	0.001
6 hr.	5.75 ± 1.32	4.88 ± 0.69	0.001
12 hr.	4.48 ± 0.88	3.85 ± 0.74	0.001
18 hr.	4.45 ± 1.04	4.68 ± 1.12	0.350
24 hr.	3.38 ± 0.93	3.48 ± 1.18	0.670

The results of distribution of patients based on time of requirement of rescue analgesia was represented in Table 3. Results delineated that in Group-A, all 40 patients had asked for first rescue analgesia between 2-4 hr, whereas, 21 (52.5%) and 19 (47.5%) patients from Group-B had asked for first rescue analgesia between 5-7 hr. and 8-10 hr. respectively. In Group-A, 32 (80%) and 8 (20%) patients had requested for second dose of rescue analgesia at 8-10 hr. and 10-15 hr. postoperative time intervals respectively; While in Group-B, only 1 (2.5%) each has requested for second dose of rescue analgesia at 8-10 hr. and 10-15 hr. postoperative time intervals. Third request for rescue analgesia was received from 35 (88%) patients in Group-A at 15-24 hr. These findings inferred that the time for the first and second postoperative rescue analgesia was significantly ($p < 0.001$) prolonged in Group-B as compared to Group-A.

Table 3: Distribution of patients based on requirement of rescue analgesia

Request of Rescue Analgesia	Time (hr.)	Group-A (Placebo)	Group-B (Pregabalin)	P-Value
Time for the first request of rescue analgesia (hr.)	2-4	40 (100%)	0	0.001
	5-7	0	21(52.5%)	
	8-10	0	19(47.5%)	
Time for the second request of rescue analgesia (hr.)	2-4	0	0	0.001
	5-7	0	0	
	8-10	32(80%)	1(2.5%)	
	10-15	8(20%)	1(2.5%)	
	15-20	0	21(52.5%)	
Time for the third request of rescue analgesia (hr.)	2-4	0	0	0.001
	5-7	0	0	
	8-10	0	0	
	10-12	0	0	
	13-15	0	0	
	15-24	35(88%)	0	

It was found that total dose rescue analgesia requirement i.e., postoperative Diclofenac consumption was significantly ($p < 0.001$) lower in Group-B when compared to Group-A patients (Figure 1).

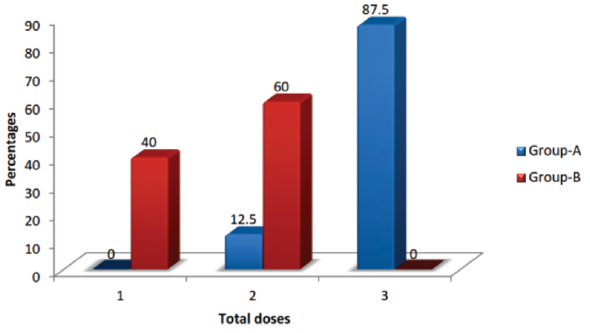

Figure 1: Distribution of patients based on total doses of rescue analgesia

There were no postoperative complications observed between Group-A and Group-B (Table 4).

Table 4: Distribution of patients based on incidences of adverse effects

Adverse Effects	Group-A (Placebo)		Group-B (Pregabalin)	
	Count	%	Count	%
Yes	0	0	0	0
No	40	100	40	100
Total	40	100	40	100

DISCUSSION

Orthopaedic surgeries are considered as one of the most painful procedures in the postoperative period.[10] Pregabalin which is a GABA analogue when administered orally in preoperative period has been reported to prolong the blockade of spinal anaesthesia and reduce acute postoperative pain. Therefore, in the present study we mainly aimed to evaluate whether preoperative oral administration of Pregabalin has any effect in postoperative analgesic requirement in patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia, and it's associated adverse effects.

Our study findings revealed that there was a statistically significant ($p < 0.05$) reduction in VAS score following administration of 150 mg oral dose of Pregabalin at 2 hr., 4 hr., 6 hr., and 12 hr. postoperative time intervals when compared with the placebo group. Time for the first and second request for postoperative rescue analgesia was significantly ($p < 0.001$) prolonged for Pregabalin group. Furthermore, total dose of rescue analgesia requirement i.e., postoperative Diclofenac consumption was significantly ($p < 0.001$) lower in oral Pregabalin (150 mg) group when compared to placebo group. Furthermore, there were no postoperative complications observed following administration of Pregabalin 150mg among patients. These findings were comparable with effects of Pregabalin reported by various other research investigators reported in the literature for control of postoperative pain in patients undergoing orthopaedic surgeries. Sebastian et al., demonstrated oral Pregabalin as effective preemptive analgesic in lower limb orthopaedic surgeries under spinal anaesthesia.[11] Studies reported by Akhavanakbari et al., Eman et al., and Trivedi et al., revealed that a single preoperative oral dose of Pregabalin 150mg is an effective method for reducing postoperative pain, opioid and NSAIDs consumption in patients undergoing orthopaedic and abdominal hysterectomy surgeries.[9,12,13]

Furthermore, Buvanendran et al., demonstrated that oral 300mg Pregabalin administration preoperatively to patients undergoing total knee replacement surgery under continuous spinal anesthesia was high enough to reduce the hypersensitivity of the central nervous system after 6 hr.[14] Bafna et al., reported that oral Pregabalin administration at 150 mg dose showed a significantly longer duration of effective analgesia than gabapentin in patients undergoing gynecological surgeries under spinal anesthesia.[15] Cegin et al., reported significant prolongation of sensory and motor blockade with the use of Pregabalin at different dose levels *viz.* 75, 150 or 300 mg.[16]

Pregabalin is a lipophilic GABA analogue approved by FDA for clinical use. It is superior to other routinely used analgesics as it reduces the anxiousness of the patient and is effective against neuropathic component of pain which is available at a reasonable cost. Pregabalin binds to the α2-δ subunit of voltage-gated calcium channels and modulate the release of several excitatory neurotransmitters such as glutamate, norepinephrine substance. Hence pregabalin reduces the hyperexcitability of the dorsal horn neurons of spinal cord that is induced by tissue damage and thereby decreases perception of acute postoperative pain. In addition, use of Pregabalin as preemptive analgesia helps in the control of postoperative pain by its anti-allodynic and antihyperalgesic activity.

CONCLUSION

In conclusion, administration of single oral dose of 150 mg Pregabalin one hour before surgery in patients undergoing lower limb orthopaedic surgeries under spinal anesthesia was efficacious in delaying the first request for postoperative analgesics and decreasing postoperative pain without any adverse effects. Pregabalin being an oral drug would be easy for the patients to take and is an effective preemptive analgesic in the management of perioperative pain.

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