The role of preoperative oral pregabalin on acute post-operative pain after orthopedic lower limb surgery

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Abstract
Introduction: Postoperative pain after orthopedic surgery has remained a challenging problem, which prolongs hospital stay and early rehabilitation. Pregabalin comes under class of gabapentinoids that have been used in postoperative pain in arthroplasty and spine surgeries but studies regarding its role as preemptive analgesia in orthopedic limb surgeries are very few.

Aim: To study the efficacy and safety of pregabalin as preemptive medication for acute postoperative pain management in patients undergoing orthopedic lower limb fracture surgeries.

Materials and Methods: A randomized double blinded prospective study was undertaken. Sixty patients were enrolled with age between 18–70 years and were divided into 2 groups. Group A - received 150mg of oral pregabalin capsule, Group B – received matched colour empty capsules. Standard spinal anaesthesia was given. Breakthrough analgesia was given with Inj. Diclofenac 1.5 mg/kg i/m. Assessment of pain was done with visual analog scale (VAS).

Results: There was marked reduction in postoperative VAS score in group A and the amount of breakthrough analgesia needed in the 24-hour postoperative period was also much lower in the Group A as compared to the Group B.

Conclusion: 150mg of oral pregabalin as preemptive medication offers satisfactory postoperative analgesia in orthopaedic lower limb fracture surgeries with very few undesirable side effects.

Keywords: Postoperative pain, Pregabalin, Gabapentinoids, Preemptive analgesia, Diclofenac, Visual analog scale.

Introduction
Proper management of postoperative pain after orthopaedic surgery is a major challenge for the surgeon as it has great impact on the functional outcome. Postoperative pain is associated with many undesirable side effects like anxiety, tachycardia, increased hospital stay, patient discomfort and prolong rehabilitation. Principles of pain management include assessment of the severity of pain, meticulous use of analgesic drugs to anticipate the response to treatment to maximize the functional status, and quality of life. There are a number of analgesic drugs available in the market but none is able to provide desired outcome and each of them come with their fair share of side effects. Currently the technique of multimodal analgesia, in which a combination of drugs acting via different mechanism of action for pain relief, and preemptive analgesia, in which drugs are administered prior to surgery to prevent postoperative pain has gained significant popularity and have found to help in the alleviation of pain after surgery.¹² This includes drugs such as local and regional anesthetic drugs, opioids, patient-controlled analgesia (PCA), NSAIDs, centrally acting drugs and gabapentinoids, clonidine, and dexmedetomidine.³

GABA analogues such as pregabalin and gabapentin are the most common gabapentinoids being used. Role of pregabalin have been studied in arthroplasty and spine surgeries but not many studies regarding its role as preemptive analgesia in orthopedic limb fracture surgeries are available.⁴⁶

Aim
The aim of the study is to compare the efficacy and safety of preoperative pregabalin in a dose of 150 mg with a placebo on acute postoperative pain in patients scheduled for orthopaedic lower limb fracture surgeries under spinal anaesthesia.

Materials and Methods
The current study was conducted in the Orthopaedics department, Govt. Medical College and Rajindra Hospital, Patiala, for duration of six months during January 2019 to June 2019. After approval from the local ethical committee, written informed consents were obtained from the patients who were planned to undergo surgeries for lower limb fractures under spinal anaesthesia. A randomized double blinded prospective study was undertaken. Sixty patients aged between 18–70 years were enrolled in the study and were randomly divided into 2 groups of 30 patients each. Exclusion criteria included known allergy to gabapentin or pregabalin, hepatic failure, renal failure, diabetes mellitus, psychiatric disorders, chronic gabapentin or pregabalin use, chronic pain and history of drug abuse.

Approximately 2 h prior to induction of anesthesia the oral medication was administered. Group A - received 150mg of oral pregabalin capsule 2 h prior to surgery, Group B – received matched colour placebo (capsules of similar appearance, but lacking the active ingredient of the drug). No other premedication was permitted. The patients were induced by standardized spinal anaesthesia technique with 12-15 mg of Bupivacaine 0.5% injected into the L4-L5 disc space by using 25-gauge needle and the surgery was performed.
The patients were assessed at 2, 4, 8, 16 and 24 hours after surgery for the severity of pain, the amount of breakthrough analgesia requirement and for any adverse effects like sedation, nausea & vomiting, headache, dizziness or visual disturbance in the immediate postoperative period.

Assessment of acute postoperative pain was done by VAS. All patients were educated to convey the amount of pain they experienced using a 10-point Visual Analogue Scale (VAS), where 0 means no pain and 10 means extreme pain. As soon as VAS exceeded 4, patients were given Inj. Diclofenac 1.5mg/kg intramuscular for breakthrough pain. The Modified Ramsay sedation scale was used to assess the sedation; patients with a sedation scale of >5 were considered as sedated.

Results
The two study groups were similar with respect to demographic details such as age, sex and duration of surgery.

Average pain scores (VAS) were significantly lower in pregabalin group than placebo group at 2, 4, 8, 16 and 24 hours after surgery. VAS score in majority of the patients in the pregabalin group was < 4. Only on nine occasions the score was >4 in Group A, whereas score > 4 on sixteen occasions in Group B.

Table 1: Mean visual analogue score

| Variable       | Pregabalin | Placebo | P- Value |
|----------------|------------|---------|----------|
| Mean VAS score | 5.5±0.8    | 7.3±1.1 | <0.001   |
| 2h after surgery | 5.5±0.8    | 7.3±1.1 | <0.001   |
| 4h after surgery | 6.4±1.2    | 8.6±0.7 | <0.001   |
| 8h after surgery | 3.6±0.6    | 7.8±0.5 | <0.0001  |
| 16h after surgery | 3.2±0.9    | 5.4±0.8 | <0.001   |
| 24h after surgery | 2.4±1.2    | 3.2±1.1 | <0.001   |

The average dose of Diclofenac required as post-operative breakthrough analgesia is also considerably lower in pregabalin group than placebo.

The sedation scores in terms of Modified Ramsay sedation score were more in the Group A as compared to group B. Sedation score > 5 on 10 occasions in Group A and on 3 occasions in Group B.

Table 2: Modified Ramsey sedation score

| Variable       | Pregabalin | Placebo | P- Value |
|----------------|------------|---------|----------|
| SEDATION score | <5         | >5      |          |
| 2h after surgery | 28         | 2       | 30       | 0        | <0.001   |
| 4h after surgery | 27         | 3       | 28       | 2        | >0.001   |
| 8h after surgery | 25         | 5       | 29       | 1        | <0.001   |
| 16h after surgery | 30         | 0       | 30       | 0        | >0.001   |
| 24h after surgery | 30         | 0       | 30       | 0        | >0.001   |

There were increased episodes of nausea at 2, 4h after the surgery in group A but there was no statistical difference in terms of vomiting and dizziness between the groups.

Discussion
Acute pain has been a predictor of overall functional outcome after any major surgery, and inadequate management has been associated with poor patient satisfaction and may lead to development of chronic pain in many patients. Orthopaedic fractures are associated with severe pain and morbidity due to extensive bone and soft tissue damage and further exacerbation by surgery, thus adequate analgesia is required in the immediate postoperative period for proper pain relief and prevention of various adverse effects associated with it. Recent advances in molecular biology has led to development of better understanding of different pain pathways and the concept of multimodal and preemptive analgesia has come into play.²

Pregabalin is a cyclic GABA analogue which exerts a specific analgesic effect in neuropathic pain. It has been found to modulate a subset of neuronal voltage sensitive Ca2+ channels which contain α2Δ-1 subunits. It is postulated that decreased entry of Ca2+ into the presynaptic neurons through these channels could reduce glutamate release, lowering neuronal excitability.⁷ Pregabalin is considered to be a first line drug for neuralgic pain due to diabetic neuropathy and postherpetic neuralgia. In addition it is also used in partial seizures, generalized anxiety disorders and chronic pain. Recently role of preemptive pregabalin for use in postoperative pain has been studied as it reduces over excitability of neurons in spinal cord and regulates the activity of excitatory neurotransmitters in brain. The usual dose used ranges from 50mg – 600 mg per day. The common side effects are mild sedation, tiredness, dizziness and unsteadiness.⁸⁹

Current study showed a reduction in the postoperative VAS score during the 2, 4, 8, 16 and 24 hours period in the pregabalin group as compared to the placebo group. Akhavanakbari, in a study of sixty patients also produced similar results; they showed 150mg dose preoperative pregabalin is a reliable method in reducing pain and pethidine consumption in orthopaedic lower limb surgery. Similar results were reported by a number of authors in joint replacement, arthroscopic and laparoscopic surgeries.¹⁰–¹⁴ YaDeau and coworkers, in a study of 30 patients undergoing total knee arthroplasty, however reported that preoperative pregabalin has no beneficial effects.⁴

The dose of Pregabalin taken in this study was 150 mg as previous studies with higher doses of pregabalin are associated with more side effects. A number of authors showed pregabalin 150mg is a better choice.¹³¹⁵ Few studies used multiple doses of pregabalin pre and postoperatively and others showed only a single preoperative dose of pregabalin 150mg is sufficient.⁴⁵

Headache, dizziness and sedation are the most commonly reported adverse effects of pregabalin (22–29%).¹⁶¹⁷ Our study also concluded the same as sedation was the most common side effect followed by nausea. Similar results were reported by Sebastian B et al¹⁵ who found that hypotension (33.33%) and dizziness (26.66%) as the most common side effects. Akhavanakbari and colleagues however found that nausea and vomiting scores.
and sedation levels at 2 h and 6 h were reduced in the pregabalin group.14

Limitation
The study had limitation though as we used single preoperative dose of 150mg Pregabalin 2 hours before surgery. However, there is no consensus about the appropriate timing, dose and duration of the drug. Moreover, we conducted this study in a single hospital; therefore, the generalizability of our findings deserves further investigation in the future.

Conclusion
In conclusion, the current study demonstrated that single preoperative doses of pregabalin 150 mg in patients undergoing orthopaedic lower limb fracture surgeries offers good postoperative analgesia and reduction in NSAIDs consumption in the 24 h postoperative period without any significant adverse effects.

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Conflict of interest
None.

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