Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Evaluation of Different Doses of Pregabalin for Post-operative Analgesia in Ankle and Foot Surgeries

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Abstract

Background: Administration of pre-emptive analgesia with pregabalin is more potent than gabapentin. The aim of this study is to evaluate the effect of different doses of pregabalin on post-operative analgesia after ankle and foot surgeries when used before the onset of pain.

Materials and Methods: Total 90 patients of the American Society of Anesthesiology Grade I or II, posted for ankle and foot surgeries under spinal anesthesia, were randomized to three groups using computer generated random number list. Patient of Group A received oral pregabalin 150 mg, Group B received oral pregabalin 75 mg, and Group C received oral diazepam 10 mg. Tablet paracetamol 1 g given to all three groups after 2 h of surgery. Injection tramadol was used for rescue analgesia as requested by patients when VAS was more than 3. Outcomes measured include the total consumption of tramadol, VAS score, sedation, and other side effects recorded at 2, 4, 6, 12, and 24 h.

Results: The total consumption of tramadol was 133.56 ± 49.27 mg in Group A, 206.33 ± 77.19 mg in Group B, and (210.73 ± 63.35 mg) in Group C. VAS score was lowest up to 24 h in Group A, then Group B, and Group C. There was no significant difference in other variables between the groups. Sedation score was more in Group A, then Group B, and Group C.

Conclusion: Oral pregabalin in a dose of 150 mg offer prolonged analgesia and reduced the consumption of rescue analgesics when used preoperatively, as compared to oral pregabalin 75 mg with fewer side effects also.

Keywords: Pregabalin, Diazepam, Post-operative analgesia

INTRODUCTION

Pain control in the post-operative period can have a notable effect on the overall outcome of the patient and surgical procedure. Orthopedic surgeries are among the most painful surgical procedure and the patient is at high risk of inadequate post-operative pain control.[1,2] Many types of medicines are available to help control pain, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics, etc., but are not free from their side effects, that is, respiratory depression, gastrointestinal bleeding and hemorrhage, toxicity etc.[3]

Access this article online

www.ijss-sn.com

Month of Submission : 09-2020
Month of Peer Review : 09-2020
Month of Acceptance : 10-2020
Month of Publishing : 11-2020

Gabapentin and pregabalin have antiallodynic and antihyperalgesic properties.[4] Mechanism of pregabalin is same as to gabapentin, it binds to the α2-δ subunit of presynaptic, voltage-dependent calcium channels that are widely distributed throughout the central and peripheral nervous system.[5,6] Thereby reduces the release of several neurotransmitters such as glutamate, norepinephrine, serotonin, dopamine, and substance P. Pregabalin is structurally and functionally related to inhibitory neurotransmitter GABA also.

Thus, the objectives of our study, to evaluate the efficacy 150 mg and 75 mg of pre-operative pregabalin on post-operative analgesia, requirement of additional analgesic in

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the post-operative period, and the incidence of side effect, that is, dizziness, headache, nausea, vomiting, etc.

MATERIALS AND METHODS

This prospective, randomized, and double-blind study was conducted in the Department of Anesthesiology, N.S.C.B. Medical College, Jabalpur (M.P). After local institutional ethics committee approval, and informed consent of the patient, 90 patients (30 each) between 20 and 40 years of age, ASA Class I and II, undergoing foot or ankle surgeries under spinal anesthesia were included in the study. The patient refuses for study or any contraindication to spinal anesthesia were excluded from the study.
Group A (n = 30): Oral pregabalin 150 mg.
Group B (n = 30): Oral pregabalin 75 mg.
Group C (n = 30): Oral diazepam 10 mg.

The study drugs were packed in identical capsules and were further packed and sealed in an opaque plastic container labeled with the randomization number. The randomization code was not opened until the last study patient was interviewed.

After securing an I.V. access and attaching of non-invasive monitors such as ECG, NIBP, and pulse oximeter, all patients were preloaded with 10 ml/kg of ringer lactate within 15 min before the spinal anesthesia. Spinal anesthesia was given in sitting position under all aseptic precautions with 25 G Quincke's needle at L3–L4 interspace using 3 ml of 0.5% heavy bupivacaine. Surgery was proceed after confirmation of adequate block. After 2 h of surgery, 1 g paracetamol orally, 8 h given to all patients. Assessment of pain was done using VAS score.

Postoperatively vital parameters such as pulse rate, blood pressure, and respiratory rate were recorded at 2 h, 4 h, 6 h, 12 h, and 24 h. VAS score at 2 h, 4 h, 6 h, 12 h, and 24 h was noted for pain. VAS zero was represented as no pain and ten represented as "worst possible pain." VAS was assessed at the time of giving rescue analgesia. Rescue analgesia was provided with intravenous tramadol 0.5 mg/kg when VAS >3. Total dose of tramadol consumption in 1st 24 h was noted and level of sedation was defined in accordance with the modified Ramsay sedation scale.

Modified Ramsey Sedation Scale

1. Anxious, agitated, restless
2. Cooperative, oriented, tranquil.
3. Drowsy, but responds to commands only.
4. Brisk response to light glabellar tap or loud noise.
5. Sluggish response to light glabellar tap or loud noise.
6. No response, unarousable.

Quantitative data were represented as mean ± standard deviation; number and percentage were used for qualitative data. Statistical analysis was done for comparing observed data using Student's t-test and analysis of variance. $P < 0.05$ was considered statistically significant.

RESULTS

There was no statistically significant ($P > 0.5$) difference among the three groups in terms of demographic data, duration of surgery, and changes in the hemodynamic parameters [Table 1].

The VAS score was lowest in Group A up to 12 h, then Group B, and Group C. On comparison statistically, VAS score was significant between Group A, Group B, and Group C at 4, 6, 12, and 24 h. VAS score was also significant between Group B and Group C up to 6 h [Table 2].

Meantime to rescue analgesia was significantly prolonged in Group A (12.33 ± 3.47 h) as compared with Group B (5.87 ± 1.40 h) and Group C (3.47 ± 8.19 h) ($P < 0.0001$). The total number of intravenous tramadol requirements in 24 h was less in Group A (133.56 ± 49.27 mg) than Group B (206.33 ± 77.19 mg) and Group C (210.73 ± 63.35 mg) (P < 0.0001) [Table 3].

Median of sedation score in the studied groups, at 2 h, 10 cases in Group A, 7 in Group B, and 3 in Group C were > median MRSS scores. At 4 h, 7 cases in Group A, 2 in Group B, and 0 case in Group C showed > median MRSS scores. While at 6, 12, and 24 h, all the three group cases were higher than the median MRSS score. Hence, the level of sedation at 2 and 4 h in Group A was significantly higher ($P < 0.05$) as compared to Group B/C. Level of sedation at 6, 12, and 24 h was comparable in all three groups ($P > 0.05$) statistically not significant [Table 4].

Post-operative nausea, vomiting, headache, and dizziness were not statistically significant in the different groups. Only 4 patients complain nausea and dizziness in Group A but were not very significant [Table 5].

Table 1: Distribution of demographic profile and duration of surgery

Parameter	Group A	Group B	Group C
Age (in years)	30.67±6.88	30.9±6.81	30.3±6.22
Weight (in kg)	60.27±8.63	57.57±9.93	60.17±9.55
Height (in m)	1.673±0.041	1.747±0.050	1.669±0.049
Duration of surgery (in min)	106.33±12.99	105.33±11.36	107.87±10.95

Values are expressed as mean ± SD (P>0.05)

Table 2: VAS sore at different time interval

Vas score time	Group A	Group B	Group C	*P* value b/w Group A/B	*P* value b/w Group A/C	*P* value b/w Group B/C
2 h	0.0±0.0	0.0±0.0	0.0±0.0	≥0.05	≥0.05	≥0.05
4 h	0.01±0.0	1.51±0.50	1.75±0.82	< 0.0001	< 0.0001	< 0.0001
6 h	0.01±0.1	2.02±0.75	3.33±0.83	< 0.0001	< 0.0001	< 0.0001
12 h	1.13±0.34	2.60±0.69	2.80±1.10	< 0.0001	< 0.0001	0.402
24 h	2.02±0.75	3.27±1.01	3.44±0.72	< 0.0001	< 0.0001	0.455

A Values are expressed as mean±SD. B one way ANOVA test

Table 3: Total rescue analgesia (tramadol in mg) requirement

Group	Time of first rescue analgesia in h	Rescue analgesia in 24 h (tramadol in mg)
A	12.33±3.47	133.56±49.27
B	5.87±1.40	206.33±77.19
C	3.47±8.19	210.73±63.35

Values are expressed as mean ± SD (*P*>0.05)

Table 4: Median test showing sedation score

Modified Ramsey sedation scale		Group		
		A	B	C
MRSS2	>Median	10	7	3
	≤Median	20	30	29
MRSS4	>Median	7	2	0
	≥Median	23	30	30
MRSS6	>Median	0	0	0
	≤Median	30	30	30
MRSS12	>Median	0	0	0
	≥Median	30	30	30
MRSS24	≤Median	0	0	0
	≥Median	30	30	30

Table 5: Incidences of side effects

Side effects	Group I	Group II	Group III
Nausea	4 (13.33%)	0	0
Vomiting	0	0	0
Headache	1 (3.34%)	1 (3.34%)	2 (6.67%)
Dizziness	4 (13.33%)	3(10%)	2 (6.67%)
Respiratory depression	0	0	0
Total	30	30	30

DISCUSSION

Perioperative pain is thought to involve primary hyperalgesia (peripheral nociceptor sensitization) and secondary hyperalgesia (central sensitization).[7,8]

Gabapentin and pregabalin appear to have no effect on primary hyperalgesia, but suppress the tissue damage induced hyperexcitability of dorsal horn neurons and hence decrease secondary hyperalgesia. Analgesic action of gabapentin and pregabalin is mediated through their binding to the α (2)-δ subunit of voltage-gated calcium channel. The affinity of this unit is six times more in pregabalin then gabapentin and less side effect.[9] Pregabalin is a gamma-amino butyric acid analog shown to be effective in several models of neuropathic pain, incisional injury, and inflammatory injury. Pre-operative administration of pregabalin reduces opioids consumption and opioids related adverse effects in 1st 24 h following surgery.[4,10] Adverse effect such as visual disturbance, sedation, dizziness, and headache is associated with the higher dose.

The present study was conducted to find out whether the pre-emptively administered pregabalin along with paracetamol reduces the post-operative analgesic requirement and to evaluate the efficacy of 150 mg and 75 mg for post-operative analgesia.

Patient's VAS pain scores were assessed using 10 cm visual analog scale (VAS), rescue analgesia was given as IV tramadol 100 mg when VAS > 3, side effects such as nausea, vomiting, dizziness, and vital parameters were noted at 2, 4, 6, 12, and 24 h after operation. Sedation was defined in accordance with the modified Ramsay sedation scale.

We performed the study as a prospective case series and the mean age of the patient in Group A, B, and C were 30.67 ± 6.88, 30.9 ± 6.81, and 30.3 ± 6.22, respectively, and there was no any significant difference ($P > 0.05$).

In our study of the total of 90 patients, 62 were males (68.8%) and 28 were females (31.11%). The male to female ratio in all the three groups did not differ significantly ($P > 0.05$).

The changes in mean pulse rate and mean systolic blood pressure for Group A, B, and C at an interval of 2 h, 4 h, 6 h, 12 h, and 24 h after surgery were not significant ($P > 0.05$). This observation also correlates with the study of Sahu *et al*.[11]

The mean total amount of analgesic dose required over a 24 h period in Group A was 133.56 ± 49.27 mg, in Group B was 206.33 ± 77.19 mg, and Group C was 210.73 ± 63.35 mg ($P < 0.0001$). Group A showed a highly significant reduction in the total amount of analgesic requirement in comparison to Group B and Group C. This is similar to the findings reported by Cabrera Schulmever *et al*.[12] (2010).

Pain VAS scores were analyzed with the ANOVA test. The results showed that the VAS score was considerably lower in Group A than those of Group B and Group C at all the observational periods. These findings were statistically highly significant ($P < 0.0001$) showing the better VAS results in Group A (P150 mg) patients compared to Group B (P75 mg) and Group C (D10 mg). Group B (P75 mg) also showed considerably better VAS finding than those of Group C (D10 mg) compared to the studies of Jokela *et al*.[13]

Paech *et al*.[14] reported that a single pre-operative dose of 100 mg pregabalin was ineffective in reducing acute post-operative pain or improving recovery after surgery, so we had administered pregabalin 150 mg and compared it with smaller dose 75 mg for a better outcome.

SUMMARY AND CONCLUSION

This was concluded from our study that "Preemptive use of Pregabalin 150 mg in patients undergoing ankle and foot surgeries under spinal anesthesia resulted in better analgesia, decreased need for rescue analgesia without cardiovascular and respiratory adverse effects."

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How to cite this article: Shakya ML, Bhalavi M, Uikey K. Evaluation of Different Doses of Pregabalin for Post-operative Analgesia in Ankle and Foot Surgeries. Int J Sci Stud 2020;8(8):27-30.

Source of Support: Nil, **Conflicts of Interest:** None declared.