

Pre-emptive Oral Pregabalin versus Oral Clonidine for Postoperative Analgesia Following Lower Limb Orthopaedic Surgery under Spinal Anaesthesia: A Prospective Randomized Double-Blind Placebo-Controlled Trial

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ABSTRACT

Background: Effective postoperative pain control is essential after lower limb orthopaedic surgery to facilitate early mobilization, improve patient comfort, and reduce analgesic-related complications. Pregabalin and clonidine have been used as pre-emptive analgesic agents; however, evidence directly comparing their efficacy in patients undergoing spinal anaesthesia remains limited. This study compared the postoperative analgesic efficacy of oral pregabalin and oral clonidine in lower limb orthopaedic surgery performed under spinal anaesthesia.

Methods: This prospective, randomized, double-blind, placebo-controlled study included 90 ASA physical status I–II patients aged 18–65 years undergoing elective lower limb orthopaedic surgery. Patients were randomly allocated into three equal groups (n=30 each): Group A received oral clonidine 150 µg, Group B received oral pregabalin 150 mg, and Group C received placebo one hour before surgery. All patients underwent spinal anaesthesia with 3 mL of 0.5% hyperbaric bupivacaine. Postoperative pain was assessed using the Visual Analogue Scale (VAS). Duration of analgesia, time to first rescue analgesia, total diclofenac consumption, sedation scores, and adverse effects were recorded during the first 24 postoperative hours.

Results: Baseline demographic characteristics and spinal block parameters were comparable among the three groups (p>0.05). Patients receiving pregabalin demonstrated significantly lower postoperative VAS scores throughout the study period compared with clonidine and placebo (p<0.05). The duration of analgesia was longest in the pregabalin group (689±136 min), followed by the clonidine (517±107 min) and placebo groups (381±100 min) (p<0.001). Time to first rescue analgesia was significantly prolonged with pregabalin (572±136 min) compared with clonidine (400±106 min) and placebo (264±102 min) (p<0.001). Total postoperative diclofenac consumption was lowest with pregabalin (80.0±19.0 mg), compared with clonidine (110.0±38.1 mg) and placebo (182.5±37.8 mg) (p<0.001). Adverse effects were mild and comparable across all groups.

Conclusion: Preoperative oral pregabalin (150 mg) provided superior postoperative analgesia compared with oral clonidine (150 µg) and placebo by reducing pain intensity, prolonging analgesia, delaying rescue analgesic requirement, and decreasing postoperative analgesic consumption without increasing clinically significant adverse effects. Oral pregabalin may therefore be considered an effective component of multimodal analgesia for lower limb orthopaedic surgery performed under spinal anaesthesia.

Keywords: Pregabalin; Clonidine; Spinal anaesthesia; Postoperative pain; Orthopaedic surgery; Multimodal analgesia; Premedication.

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INTRODUCTION

Effective postoperative pain management remains a fundamental component of perioperative care, particularly following lower limb orthopaedic surgeries, where moderate-to-severe pain may delay early mobilization, prolong hospital stay, impair functional recovery, and increase the risk of chronic postsurgical pain. Despite advances in perioperative analgesic strategies, inadequate pain control continues to affect approximately 40–60% of surgical patients worldwide, emphasizing the need for effective opioid-sparing analgesic techniques.¹

Spinal anaesthesia using hyperbaric bupivacaine is widely regarded as the anaesthetic technique of choice for lower limb orthopaedic procedures because of its rapid onset, excellent intraoperative analgesia, reduced blood loss, and lower incidence of thromboembolic complications. However, its relatively short duration of postoperative analgesia necessitates the use of adjunctive analgesic strategies to improve pain control after regression of the neuraxial block. Consequently, Enhanced Recovery After Surgery (ERAS) protocols strongly advocate multimodal analgesia, combining drugs with different mechanisms of action to improve analgesic efficacy while minimizing opioid consumption and opioid-related adverse effects.^{2,3}

Pregabalin, a structural analogue of γ -aminobutyric acid (GABA), exerts its analgesic effect by selectively binding to the $\alpha_2\delta$ subunit of presynaptic voltage-gated calcium channels, thereby reducing calcium influx and suppressing the release of excitatory neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide. This mechanism attenuates central sensitization and postoperative hyperalgesia without directly acting on GABA receptors. Several randomized controlled trials and systematic reviews have demonstrated that preoperative administration of pregabalin significantly reduces postoperative pain scores, prolongs analgesia, decreases opioid consumption, and improves patient satisfaction following orthopaedic surgery.^{4–6}

Clonidine, a selective α_2 -adrenergic receptor agonist, produces analgesia through activation of descending noradrenergic inhibitory pathways and inhibition of nociceptive neurotransmission within the dorsal horn of the spinal cord. In addition to its analgesic properties, clonidine provides perioperative sympatholysis, anxiolysis, sedation, and improved haemodynamic stability. Previous studies have reported that oral clonidine administered before spinal anaesthesia prolongs sensory blockade, delays postoperative analgesic requirements, and decreases perioperative opioid consumption while maintaining an acceptable safety profile.^{7,8}

Although both pregabalin and clonidine have individually demonstrated efficacy as pre-emptive analgesic agents, evidence directly comparing these two oral premedications in patients undergoing lower

limb orthopaedic surgery under spinal anaesthesia remains limited. Most published studies have evaluated each drug separately or compared them in heterogeneous surgical populations, making it difficult to determine the optimal oral adjunct for this specific clinical setting. Furthermore, comparative data regarding postoperative pain intensity, duration of analgesia, rescue analgesic requirements, sedation profile, and adverse effects remain scarce.

Therefore, the present prospective, randomized, double-blind, placebo-controlled study was designed to compare the postoperative analgesic efficacy of oral pregabalin (150 mg) and oral clonidine (150 μ g), administered one hour before surgery, in patients undergoing elective lower limb orthopaedic procedures under spinal anaesthesia. The primary objective was to compare postoperative pain intensity using the Visual Analogue Scale (VAS), duration of analgesia, and time to first rescue analgesic requirement. Secondary objectives included evaluation of total postoperative analgesic consumption, sedation scores, spinal block characteristics, haemodynamic stability, and drug-related adverse effects.

MATERIALS AND METHODS

Study Design and Ethical Approval

This prospective, randomized, double-blind, placebo-controlled clinical trial was conducted in the Department of Anaesthesiology and Critical Care, Sri Guru Ram Das Institute of Medical Sciences and Research (SGRDIMSAR), Amritsar, Punjab, India, between July 2024 and December 2025. The study protocol was approved by the Institutional Ethics Committee (Approval No. SGRD/IEC/2024-314) and prospectively registered with the Clinical Trials Registry–India (CTRI/2024/11/076206). The study was performed in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants in their vernacular language before enrolment.

The sample size was calculated using G*Power software (version 3.1.9.7) based on the primary outcome of time to first rescue analgesia reported by Bala et al.⁵ Assuming an alpha error of 0.05, a study power of 85%, and an anticipated dropout rate of approximately 3%, a minimum sample size of 90 patients (30 per group) was determined.

Study Population

Ninety adult patients of either sex, aged 18–65 years, belonging to the American Society of Anesthesiologists (ASA) physical status I or II and scheduled for elective lower limb orthopaedic surgery under spinal anaesthesia, were enrolled.

Inclusion Criteria

Age between 18 and 65 years, ASA physical status I or II, Elective lower limb surgery planned under spinal anaesthesia.

Exclusion Criteria

Patients were excluded if they had: Known hypersensitivity to pregabalin, clonidine, local anaesthetics, or study medications. Coagulation disorders or anticoagulant therapy. Contraindications to spinal anaesthesia, including local infection at the puncture site, spinal deformity, raised intracranial pressure, or hypovolaemic shock. Pre-existing neurological disorders or peripheral neuropathy. Chronic pain syndromes or regular opioid use. Severe hepatic, renal, cardiovascular, or psychiatric illness and pregnancy or lactation.

Randomization and Blinding

Eligible patients were randomly assigned in a 1:1:1 ratio to one of three study groups using a computer-generated randomization sequence. Allocation concealment was achieved using sequentially numbered, sealed opaque envelopes prepared by an investigator who was not involved in patient recruitment or outcome assessment. On the day of surgery, the attending anaesthesiologist opened the envelope immediately before drug administration. The study followed a double-blind design. Both the patients and the investigator responsible for perioperative assessment and postoperative data collection were unaware of group allocation. The study medications were prepared and dispensed in identical containers to maintain blinding throughout the study.

Study Groups

Participants received the allocated oral medication approximately one hour before induction of spinal anaesthesia.

Group A (Clonidine group): Oral clonidine 150 µg.

Group B (Pregabalin group): Oral pregabalin 150 mg.

Group C (Placebo group): Oral multivitamin tablet (placebo).

All patients subsequently received spinal anaesthesia with 3 mL of 0.5% hyperbaric bupivacaine.

Anaesthetic Technique

All patients underwent a standardized pre-anaesthetic evaluation and routine laboratory investigations. They were instructed to remain fasting for at least six hours before surgery.

After arrival in the operating room, standard monitoring, including electrocardiography, non-invasive blood pressure, pulse oximetry, and respiratory rate, was instituted. An 18- or 20-gauge intravenous cannula was secured, and patients received co-loading with Ringer's lactate or normal saline according to institutional protocol.

Baseline heart rate, systolic and diastolic blood pressure, mean arterial pressure, respiratory rate, and oxygen saturation were recorded before spinal anaesthesia.

Under strict aseptic precautions, spinal anaesthesia was performed in the sitting position at the L3–L4 intervertebral space using a midline approach. After local infiltration with 2 mL of 2% lignocaine, a subarachnoid block was administered using 3 mL of

0.5% hyperbaric bupivacaine following confirmation of free cerebrospinal fluid flow. Patients were immediately placed supine after intrathecal injection. Intraoperative haemodynamic variables were recorded every two minutes during the first ten minutes and every five minutes thereafter until completion of surgery.

Assessment of Block Characteristics

Sensory block onset was assessed using the pinprick method at one-minute intervals until the highest dermatome level was achieved. The time required to attain the maximum sensory block and the duration until two-segment sensory regression were recorded.

Motor block was evaluated using the Modified Bromage Scale. The time to onset of complete motor block and the time to regression by one Bromage grade were documented.

Patients with failed or inadequate spinal anaesthesia requiring conversion to general anaesthesia were excluded from the final analysis.

Postoperative Assessment

Postoperative pain intensity was assessed using a 10-cm Visual Analogue Scale (VAS), where 0 represented "no pain" and 10 represented "worst imaginable pain." Pain scores were recorded at 2, 4, 6, 8, 12, and 24 hours after surgery.

Rescue analgesia consisting of intramuscular diclofenac sodium 75 mg was administered whenever the VAS score exceeded 4. The time to first rescue analgesia, duration of analgesia, and total postoperative diclofenac consumption during the first 24 hours were recorded.

Sedation was assessed at predetermined postoperative intervals using the Ramsay Sedation Scale. Drug-related adverse events, including nausea, vomiting, dry mouth, hypotension, bradycardia, excessive sedation, and respiratory depression (respiratory rate <8 breaths/min), were documented throughout the observation period.

OUTCOME MEASURES

Primary Outcomes

Postoperative pain intensity (VAS score).

Duration of postoperative analgesia.

Time to first rescue analgesic requirement.

Secondary Outcomes

Sensory and motor block characteristics.

Total postoperative diclofenac consumption.

Postoperative sedation scores.

Haemodynamic changes.

Incidence of adverse events.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Normality of continuous data was assessed using the Shapiro–Wilk test. Intergroup comparisons of normally distributed variables were

performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. Categorical variables were analysed using the Chi-square test or Fisher's exact test, as appropriate. A two-sided p-value <0.05 was considered statistically significant, while p<0.001 was considered highly statistically significant.

RESULTS

Figure 1 illustrates the CONSORT flow diagram and 90 eligible patients were randomized equally into clonidine, pregabalin, and placebo groups (30 each). All participants received the allocated intervention, completed follow-up, and were included in the final analysis, with no losses to follow-up or protocol deviations.

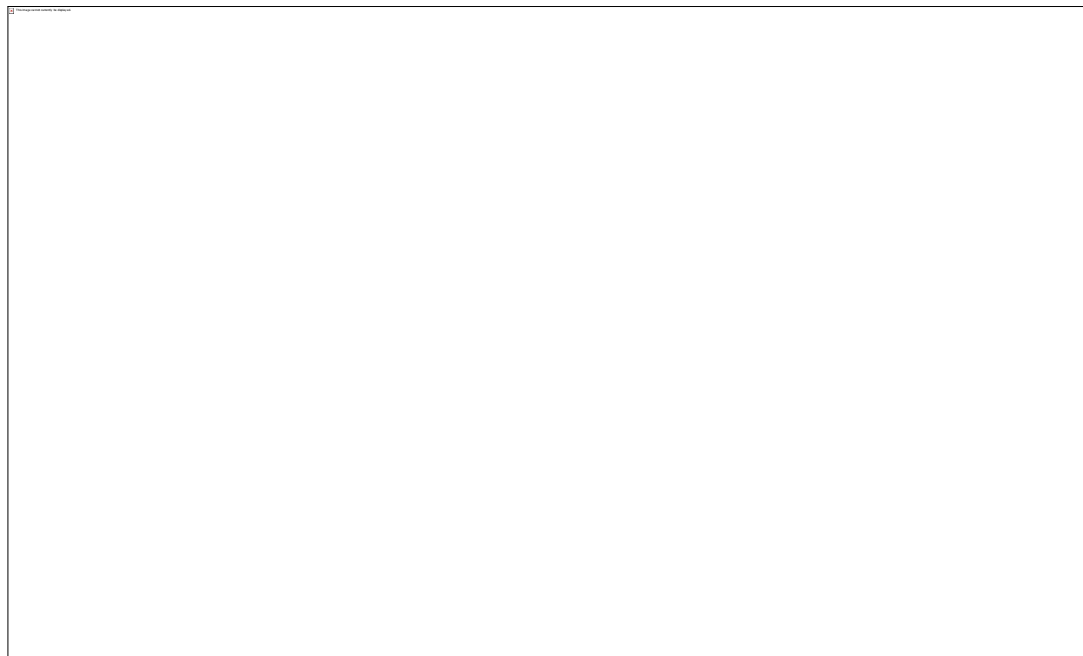


Figure 1. CONSORT flow diagram showing patient enrolment, randomization, allocation, follow-up, and analysis of patients receiving oral clonidine (Group A), oral pregabalin (Group B), and oral placebo (Group C) before lower limb surgery under spinal anaesthesia.

Table 1 demonstrates that the three study groups were comparable with respect to baseline demographic and clinical characteristics, including age, body weight, sex distribution, and ASA physical status. No

statistically significant intergroup differences were observed (all $p>0.05$), indicating successful randomization and minimizing baseline confounding between the treatment groups.

Table 1. Comparison of baseline demographic and clinical characteristics among the clonidine, pregabalin, and placebo groups.

Variable	Group A (Clonidine) n=30	Group B (Pregabalin) n=30	Group C (Placebo) n=30	p-value
Age (years)	38.10 ± 17.91	43.07 ± 13.13	45.00 ± 14.69	0.206
Weight (kg)	67.47 ± 11.24	71.40 ± 7.41	71.90 ± 8.21	0.124
Male, n (%)	22 (73.3)	22 (73.3)	23 (76.7)	0.936
Female, n (%)	8 (26.7)	8 (26.7)	7 (23.3)	
ASA I, n (%)	29 (96.7)	30 (100)	27 (90.0)	0.127
ASA II, n (%)	1 (3.3)	0	3 (10.0)	

Table 2 shows that sensory and motor block characteristics were comparable among the three groups. The onset and regression of sensory and motor blockade did not differ significantly between

clonidine, pregabalin, and placebo groups (all $p>0.05$), indicating that neither premedication altered the characteristics of spinal anaesthesia produced by hyperbaric bupivacaine.

Table 2. Comparison of sensory and motor block characteristics following spinal anaesthesia among the three study groups

Variable	Group A	Group B	Group C	p-value
Sensory onset (min)	4.27±1.55	3.93±1.34	4.13±1.57	0.685
Maximum sensory level (min)	6.60±1.40	6.40±1.43	6.40±1.33	0.813

Two-segment regression (min)	119.83±28.02	117.67±26.58	111.50±19.92	0.414
Motor onset (min)	7.07±2.21	7.00±2.15	6.80±2.01	0.880
Motor regression (min)	126.00±26.96	125.83±36.20	116.33±24.10	0.353

Figure 2 shows that postoperative sedation scores were significantly higher in the clonidine and pregabalin groups during the early postoperative period (2 and 4 hours), with clonidine producing the

greatest sedation. Sedation scores became comparable across all groups from 6 hours onward, indicating only a transient sedative effect of the study medications.

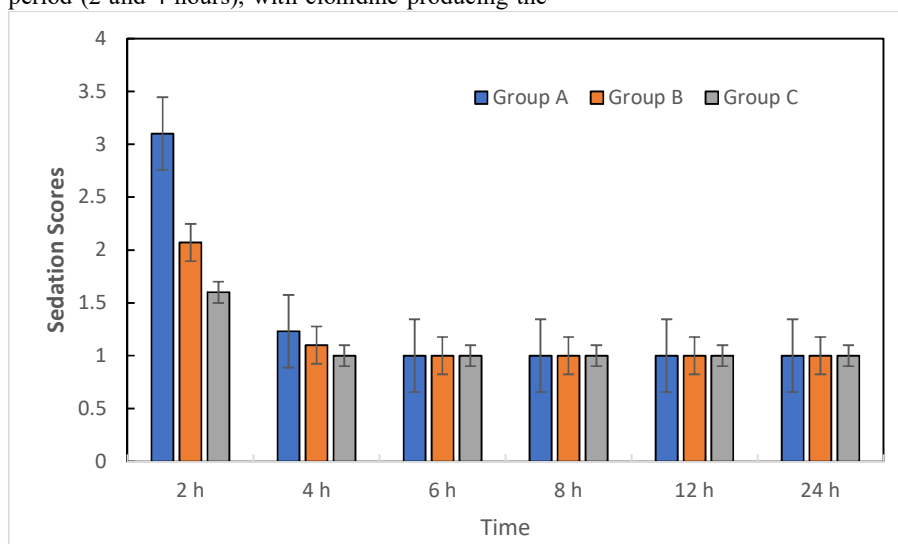


Figure 2. Comparison of postoperative Ramsay sedation scores at different time intervals among the clonidine, pregabalin, and placebo groups. Data are presented as mean $\pm$ standard deviation (SD). Statistical significance was assessed using one-way ANOVA.

Figure 3 demonstrates that patients receiving pregabalin consistently had the lowest postoperative VAS scores at all assessment intervals. Significant intergroup differences were observed throughout the 24-hour postoperative period (all $p < 0.05$), indicating

superior analgesic efficacy of pregabalin compared with clonidine and placebo following lower limb surgery under spinal anaesthesia.

The pairwise comparisons demonstrated significantly lower postoperative pain scores in the pregabalin group than the placebo group at all time points. Compared with clonidine, pregabalin provided significantly better analgesia from 4 to 8 hours postoperatively, while clonidine also produced lower pain scores than placebo during the early postoperative period.

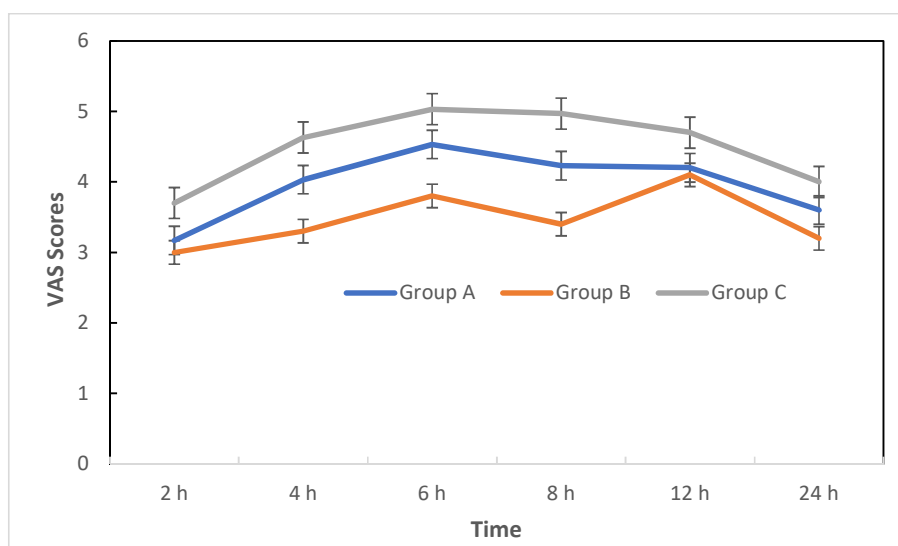


Figure 3. Comparison of postoperative pain intensity measured by the Visual Analogue Scale (VAS) at predetermined time intervals among the three study groups. Values are expressed as mean $\pm$ standard deviation (SD). Overall intergroup comparisons were performed using one-way ANOVA followed by Tukey's post hoc test.

Table 3. Comparison of total postoperative diclofenac consumption during the first 24 hours among the clonidine, pregabalin, and placebo groups.

Outcome	Group A	Group B	Group C	p-value
Duration of analgesia (min)	517 $\pm$ 106.7	689 $\pm$ 136.0	381 $\pm$ 100.1	<0.001
First rescue analgesia (min)	400 $\pm$ 106.1	572 $\pm$ 136.2	264 $\pm$ 101.6	<0.001
Total diclofenac (mg)	110 $\pm$ 38.1	80 $\pm$ 19.0	182.5 $\pm$ 37.8	<0.001

Table 4 shows that the incidence of postoperative adverse effects was low and comparable among the three groups. Nausea and vomiting were the most common complications, whereas dry mouth occurred

Table 3 demonstrates that patients receiving pregabalin experienced the longest duration of postoperative analgesia, the greatest delay in first rescue analgesic requirement, and the lowest total diclofenac consumption. These differences were highly statistically significant ($p < 0.001$), confirming the superior postoperative analgesic efficacy of pregabalin compared with clonidine and placebo.

infrequently. No patient developed respiratory depression, and there were no statistically significant differences in adverse events between the treatment groups ($p > 0.05$).

Table 4. Comparison of the incidence of postoperative adverse effects among the three study groups.

Adverse Effect	Group A n (%)	Group B n (%)	Group C n (%)	p-value
Nausea/Vomiting	11 (36.7)	9 (30.0)	8 (26.7)	0.706
Dry Mouth	2 (6.7)	2 (6.7)	1 (3.3)	0.806
Respiratory Depression	0	0	0	—

DISCUSSION

Effective postoperative pain management remains a cornerstone of perioperative care following lower limb orthopaedic surgery, as inadequate analgesia may delay early ambulation, prolong hospital stay, impair functional recovery, and increase the likelihood of chronic postsurgical pain. The present randomized, double-blind, placebo-controlled study compared the analgesic efficacy of oral pregabalin and oral clonidine administered before spinal anaesthesia. The principal findings demonstrated that preoperative pregabalin provided superior postoperative analgesia compared with clonidine and placebo by significantly reducing postoperative pain scores, prolonging the duration of analgesia, delaying the requirement for rescue analgesia, and reducing postoperative analgesic consumption without increasing adverse effects.

The three study groups were comparable with respect to demographic characteristics, ASA physical status, and baseline clinical variables, thereby minimizing the influence of potential confounding factors on postoperative outcomes. Similar baseline comparability has been reported by Prasad et al.⁹ and Baghel et al.¹⁰, supporting the adequacy of randomization and strengthening the internal validity of the present study.

The characteristics of spinal blockade, including onset of sensory block, time to achieve the maximum sensory level, duration of sensory block, onset of motor block, and motor recovery, were comparable among the three groups. These findings suggest that

neither oral pregabalin nor oral clonidine altered the pharmacodynamic profile of intrathecal hyperbaric bupivacaine. Comparable observations have been reported by Prasad et al.¹¹ and Bagle and Garud,¹² who also demonstrated no significant influence of oral premedication on the onset or regression of spinal blockade. In contrast, Adegboye et al.¹³ observed prolonged sensory blockade following oral clonidine premedication. The discrepancy may be attributed to differences in clonidine dosage, study population, surgical procedures, and assessment protocols.

Postoperative sedation scores were significantly higher in the clonidine and pregabalin groups during the early postoperative period, particularly during the first four hours, but returned to baseline thereafter. The greater sedation observed with clonidine is consistent with its central α_2 -adrenergic agonist activity, whereas pregabalin produces mild sedation through attenuation of neuronal excitability. Importantly, the degree of sedation observed in the present study was transient, did not interfere with postoperative monitoring or recovery, and was not associated with respiratory depression. Similar postoperative sedation profiles have been reported by Bala et al.,⁵ confirming the acceptable safety of both medications when administered as oral premedication.

Pain intensity assessed using the Visual Analogue Scale was significantly lower in the pregabalin group throughout the postoperative observation period. The most pronounced differences were observed during the early postoperative hours (2–8 hours), when central sensitization is greatest following surgical

tissue injury. Pregabalin demonstrated significantly lower VAS scores than both clonidine and placebo, indicating superior attenuation of postoperative nociceptive transmission. Although pain scores gradually converged after 12 hours because of rescue analgesic administration, pregabalin continued to provide better analgesic control than placebo throughout the 24-hour study period.

The superior analgesic efficacy of pregabalin is biologically plausible. By binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, pregabalin reduces presynaptic calcium influx and suppresses the release of excitatory neurotransmitters such as glutamate and substance P, thereby limiting central sensitization and postoperative hyperalgesia. This mechanism differs from that of clonidine, which primarily produces analgesia through activation of spinal α_2 -adrenoceptors and enhancement of descending inhibitory pathways. Consequently, pregabalin appears to provide more sustained postoperative analgesia without adversely affecting spinal block characteristics.

One of the most clinically relevant findings of the present study was the significantly prolonged duration of postoperative analgesia in the pregabalin group. Patients receiving pregabalin experienced a mean analgesic duration of 689 ± 136 minutes, compared with 517 ± 107 minutes in the clonidine group and 381 ± 100 minutes in the placebo group ($p < 0.001$). Similarly, the time to first rescue analgesic was significantly delayed in patients receiving pregabalin (572 ± 136 minutes) compared with clonidine (400 ± 106 minutes) and placebo (264 ± 102 minutes). These findings indicate that pregabalin provides more sustained postoperative pain relief and decreases the need for early supplemental analgesia.

Another important outcome was the marked reduction in postoperative diclofenac consumption among patients receiving pregabalin. The mean total analgesic requirement during the first 24 postoperative hours was only 80.0 ± 19.0 mg in the pregabalin group compared with 110.0 ± 38.1 mg in the clonidine group and 182.5 ± 37.8 mg in the placebo group. This substantial reduction in rescue analgesic requirement demonstrates the opioid- and NSAID-sparing potential of pregabalin and supports its incorporation into multimodal analgesic protocols. The present findings are consistent with previous randomized controlled trials. Prasad et al.¹¹ demonstrated significantly lower postoperative pain scores, prolonged analgesia, delayed rescue analgesic requirement, and reduced postoperative analgesic consumption with pregabalin compared with clonidine. Likewise, Bala et al.⁵ reported superior postoperative analgesia and reduced rescue analgesic requirements with pregabalin in patients undergoing thoracolumbar spine surgery. Although the surgical procedures differed from the present study, both investigations support the concept that preoperative

pregabalin effectively attenuates central sensitization and enhances postoperative analgesia.

The incidence of adverse effects was low and comparable among the three groups. Nausea and vomiting were the most frequently observed complications, whereas dry mouth occurred infrequently and no episode of respiratory depression was recorded. The absence of clinically significant respiratory compromise is particularly reassuring, as respiratory depression remains one of the principal concerns associated with postoperative opioid administration. The favourable safety profile observed in the present study is consistent with previous systematic reviews demonstrating that low-dose pregabalin and clonidine provide effective postoperative analgesia with acceptable tolerability when used as components of multimodal analgesia.¹⁴⁻¹⁵

The present study has several strengths, including its prospective randomized double-blind design, standardized anaesthetic technique, uniform surgical population, and comprehensive assessment of postoperative analgesic outcomes. Nevertheless, certain limitations should be acknowledged. This was a single-centre study with a relatively modest sample size, and postoperative outcomes were evaluated only during the first 24 hours. Long-term functional recovery, patient satisfaction, chronic pain development, and quality-of-recovery scores were not assessed. Multicentre trials with larger sample sizes and longer follow-up are warranted to confirm these findings and establish the optimal dose of pregabalin for different orthopaedic procedures.

Overall, the findings of the present study demonstrate that oral pregabalin administered before spinal anaesthesia offers superior postoperative analgesia compared with oral clonidine and placebo. Its ability to reduce pain intensity, prolong analgesia, delay rescue analgesic requirement, and decrease postoperative analgesic consumption, while maintaining an acceptable safety profile, supports its routine incorporation into multimodal analgesic protocols for lower limb orthopaedic surgery.

CONCLUSION

Preoperative administration of oral pregabalin (150 mg) one hour before lower limb orthopaedic surgery under spinal anaesthesia resulted in superior postoperative analgesia compared with oral clonidine (150 μ g) and placebo. Patients receiving pregabalin experienced lower postoperative pain scores, a longer duration of effective analgesia, delayed requirement for rescue analgesia, and reduced postoperative analgesic consumption during the first 24 hours. Both pregabalin and clonidine were well tolerated, with no increase in clinically significant adverse effects. These findings suggest that oral pregabalin is a safe and effective pre-emptive analgesic and can be incorporated as part of a multimodal analgesic strategy to optimize postoperative pain management

and facilitate enhanced recovery following lower limb orthopaedic procedures.

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Conflict of interest : None

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