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PREGABALIN VS. DULOXETINE FOR POSTOPERATIVE ANALGESIC REQUIREMENTS FOLLOWING LOWER LIMB ORTHOPAEDIC SURGERY: A RANDOMIZED STUDY.

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ABSTRACT

Background

After lower limb procedures, acute postoperative pain must be managed well for patient recovery. Preemptive analgesics Pregabalin and Duloxetine, with different mechanisms, are promising. The study evaluates the effectiveness of Pregabalin versus Duloxetine in managing acute post-operative pain following lower limb orthopedic surgeries.

Methods

120 individuals were included receiving spinal anaesthesia for elective lower limb procedures were included. Three groups of participants were created: Group P (pregabalin, n=40), Group D (duloxetine, n=40), and Group C (control, n= 40). The Visual Analogue Scale (VAS) was used to measure pain at different postoperative intervals. The Ramsay sedation scale was used to gauge the degree of sedation. Evaluations were also conducted on patient satisfaction, adverse effect frequency, and opioid intake. Version 16 of SPSS was used for statistical analysis.

Results

The three groups had similar mean ages, for Group C (34.80 ± 13.557), Group D (36.48 ± 15.262), and Group P (35.18 ± 13.756). The VAS scores indicated significantly lower pain levels in Group P at 2, 4, 6, and 12 hours postoperatively compared to Groups C and D ($P < 0.001$). Group P also showed significantly lower opioid consumption (130.88 ± 14.627 mcg/kg) compared to Groups C and D ($P < 0.001$). Sedation levels were higher in Group P at 2 and 4 hours postoperatively ($P = 0.001$). Side effects included sedation in Group P and post-operative nausea and vomiting in Group D.

Conclusion

Though it caused more drowsiness, pregabalin reduced immediate post-operative pain and opioid use after lower limb procedures better than Duloxetine. Duloxetine was beneficial but increased postoperative nausea and vomiting.

Recommendations

Pregabalin is suggested for immediate postoperative pain in lower limb procedures due to its superior pain relief and opioid-sparing benefits. However, its sedative qualities should be considered and used only in those who can take more sedation.

Keywords: *Acute postoperative pain, Pregabalin, Duloxetine, Lower limb surgery, Pain management*
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Introduction

One of the most important aspects of postoperative treatment is still managing acute pain after surgery, especially after lower limb orthopaedic procedures. In addition to enhancing patient comfort, efficient pain management lowers the chance of chronic pain development, speeds up early mobilisation, and shortens hospital stays. Among the various pharmacological options available, Pregabalin and Duloxetine have garnered significant attention for their potential to serve as preemptive analgesics, offering benefits that extend beyond traditional opioid therapy.

Although they work through different mechanisms, the gabapentinoid pregabalin and the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine both have analgesic effects [1]. By binding to the alpha-2-delta subunit of voltage-gated calcium channels, pregabalin lessens the release of excitatory neurotransmitters, which in turn lessens the transmission of pain. Conversely, duloxetine improves descending pain inhibition pathways by raising serotonin and norepinephrine levels in the central nervous system. Both drugs have been employed to manage neuropathic pain and have shown promise in reducing opioid requirements postoperatively [2].

Recent studies have explored the efficacy of these medications in the context of postoperative pain

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management. For instance, a study demonstrated that Duloxetine, when included in a multimodal analgesic regimen for total knee arthroplasty, significantly reduced opioid consumption without compromising pain control [1]. Similarly, a trial found that Duloxetine improved postoperative recovery outcomes in patients undergoing lumbar canal stenosis surgery, highlighting its potential in reducing opioid-related side effects [2].

Conversely, Pregabalin has also shown considerable efficacy in the post-operative setting. A randomized controlled trial reported that Pregabalin effectively reduced post-operative pain and opioid use in individuals undergoing spinal surgeries [3]. Furthermore, its role in decreasing pain intensity and enhancing patient satisfaction has been corroborated by several meta-analyses, including a comprehensive review, which emphasized Pregabalin's benefits in managing acute postoperative pain across various surgical disciplines [4].

Despite the individual successes of these agents, direct comparative studies between Pregabalin and Duloxetine are limited. This gap in the literature necessitates further research to elucidate the relative effectiveness and safety profiles of these drugs when used as preemptive analgesics in lower limb surgeries. Understanding their comparative benefits could lead to more informed decisions regarding pain management strategies, ultimately enhancing patient outcomes and optimizing postoperative care protocols.

The study evaluated the effectiveness of Pregabalin versus Duloxetine in managing acute post-operative pain following lower limb orthopedic surgeries.

Methodology

Study Design

A randomized, double-blind clinical trial.

Study Setting

The trial took place at the Department of Anesthesiology, Rajendra Institute of Medical Sciences (RIMS), Ranchi.

Participants

A total of 120 individuals undertaking elective lower limb orthopedic surgeries under subarachnoid block were recruited for the study. Participants were randomly allocated into three groups:

1. Group P: Received 150 mg of Pregabalin 1 hour before surgery.

2. Group D: Received 60 mg of Duloxetine 1 hour before surgery.

3. Group C: Received a placebo 1 hour before surgery.

Inclusion Criteria

- Individuals who are 18 to 65 years old.

- Physical status I and II of the American Society of Anesthesiologists (ASA).

- Having orthopaedic procedures on the lower limbs performed on an elective basis while sedated.

Exclusion Criteria

- Known hypersensitivity to Pregabalin or Duloxetine.

- Concomitant use of analgesic or sedative medication.

- Presence of infection at the site of subarachnoid block.

- Presence of cardiac conduction defects.

- Patients refusing to participate in the study.

- CNS depressant users.

- Patients with deranged kidney or liver function tests.

Bias

Using a randomly created random number table produced by the computer, participants were placed into one of all three groups. Both the participants and the anesthesiologists evaluating the results were blind to the group allocations, and a staff nurse who did not participate in the study delivered the medicines to maintain double blinding.

Sample Size Calculation

Considering a 95% confidence interval, 80% power, and a 5% precision, the sample size was calculated using the formula:

$$n= 2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \sigma^2/d^2$$

where $Z_{1-\alpha/}= 1.96$ (for 5% significance), $Z_{1-\beta} = 0.84$ (for 80% power), $\sigma = 18$, and $d = 10$. The calculated sample size was 36, which was rounded to 40 per group considering a 10% attrition rate.

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Intervention

Oral administration of the research medications—pregabalin, duloxetine, or placebo—took place around an hour before to the onset of anaesthesia. An hour prior to surgery, each participant received intravenous metoclopramide (10 mg) and ranitidine (50 mg).

Blinding

In this trial, both the participants and the anesthesiologists evaluating the outcomes were blinded to the treatment allocations, which were managed by a computer-generated random number table. A staff nurse, who did not participate in the study, administered the medications (Pregabalin, Duloxetine, or placebo) to ensure that neither the participants nor the evaluating anesthesiologists knew which treatment was being given, thus maintaining the integrity of the blinding process.

Anaesthesia Technique

Using a 25-gauge needle, 12–15 mg of 0.5% Bupivacaine were administered into the L4–L5 region to establish spinal anaesthesia. The patient's height and body weight were taken into account when adjusting the dosage.

Outcome Measures

A 100 mm Visual Analogue Scale (VAS) was used to measure the length and quality of postoperative pain at six, twelve, twenty-four, and thirty minutes after surgery. The need for opioids, the frequency of adverse effects, patient satisfaction and comfort, and the length of analgesia were secondary outcomes.

Pain and Sedation Assessment

- Pain Assessment: VAS (0 = no pain; 100 = worst imaginable pain).

- Sedation Assessment: Ramsay sedation scale (1 = anxious, agitated; 6 = no response).

Statistical Analysis

Analysis of the data was done with SPSS version 16. Analytical tests (t-test, Chi-square test) and descriptive statistics (mean, percentage, standard deviation) were used. $P < 0.05$ was used as the statistical significance threshold.

Ethical considerations

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Result

The study included 120 participants where the age distribution of the patients across the three groups is shown in table 1. The mean age was comparable among the three groups: 34.80 ± 13.557 years for Group C, 36.48 ± 15.262 years for Group D, and 35.18 ± 13.756 years for Group P ($P = 0.858$).

The mean weight was 61.28 ± 6.055 kg for Group C, 58.70 ± 8.410 kg for Group D, and 64.18 ± 7.092 kg for Group P, with a P value of 0.001, indicating considerable differences among the groups.

The SBP values were comparable between the groups at all time intervals, with no statistically substantial differences observed.

The VAS scores were assessed at various postoperative intervals to measure the pain levels in patients. The VAS scores showed statistically considerable variations between the groups, indicating that Group P had lower pain scores compared to Groups C and D.

The Ramsay sedation scale employed to evaluate the sedation levels in patients postoperatively. Patients in Group P exhibited higher sedation levels compared to Groups C and D, which was statistically significant at both 2 and 4 hours postoperatively.

Table 1: Age distribution

Age in year	Group C		Group D		Group P	
	N= 40	Percent	N= 40	Percent	N= 40	Percent
11-20	8	20.0%	7	17.5%	4	10.0%
21-30	12	30.0%	10	25.0%	15	37.5%
31-40	7	17.5%	6	15.0%	9	22.5%
41-50	6	15.0%	11	27.5%	8	20.0%
51-60	5	12.5%	3	7.5%	1	2.5%
61-70	2	5.0%	2	5.0%	3	7.5%
71-80	0	0.0%	1	2.5%	0	0.0%
Mean ± SD	**34.80 ± 13.557**		**36.48 ± 15.262**		**35.18 ± 13.756**	
p-value	**0.858**					

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Table 2: Weight Wise Distribution

Weight in (kg)	Group C	Group D	Group P
41-50	1	7	2
51-60	17	17	11
61-70	22	12	18
71-80	0	4	9
Mean ± SD	61.28 ± 6.055	58.70 ± 8.410	64.18 ± 7.092
p-value	0.001		

Table 3: Systolic BP Comparison

SBP (mm Hg)	Group C	Group D	Group P	p-value
Basal	123.25 ± 8.060	124.73 ± 8.305	123.33 ± 7.966	0.658
05 min	113.48 ± 9.137	114.30 ± 8.704	113.75 ± 8.851	0.915
15 min	106.28 ± 9.538	107.58 ± 9.246	106.50 ± 9.370	0.803
25 min	101.80 ± 7.730	102.10 ± 7.417	101.93 ± 7.657	0.984
35 min	110.13 ± 9.928	110.05 ± 9.829	109.75 ± 10.212	0.984
45 min	107.53 ± 7.968	107.73 ± 6.998	107.30 ± 7.760	0.969
55 min	105.73 ± 5.533	107.93 ± 7.666	107.50 ± 7.341	0.926

Table 4: VAS Scores

Time Postoperative	Group C	Group D	Group P	p-value
0 hour	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	-
2 hours	2.63 ± 0.490	2.58 ± 0.501	1.38 ± 0.490	0.001
4 hours	5.00 ± 0.784	4.48 ± 0.784	2.30 ± 0.564	0.001
6 hours	1.60 ± 0.591	1.70 ± 0.648	2.73 ± 1.037	0.001
12 hours	1.80 ± 0.758	1.95 ± 0.815	2.58 ± 0.501	0.001
24 hours	4.55 ± 1.108	4.65 ± 1.001	4.85 ± 0.770	0.374

Table 5: Sedation Scores

Time Postoperative	Group C	Group D	Group P	p-value
2 hours	2.38 ± 0.490	2.43 ± 0.501	3.95 ± 0.904	0.001
4 hours	1.48 ± 0.506	2.03 ± 0.768	2.70 ± 0.608	0.001

The requirement for rescue analgesic (Fentanyl) was recorded and compared between the groups. Group P showed the lowest Fentanyl consumption, followed by Group D and then Group C. These findings were both clinically and statistically significant ($P < 0.001$).

The side effects observed in the three groups included sedation and post-operative nausea and vomiting (PONV). The only side effect observed besides sedation was PONV, which was noted in six patients from Group D. None of the patients in Groups C or P complained of PONV.

Table 6: Opioid Consumption

Fentanyl (mcg/kg)	Group C	Group D	Group P
81-100	0	0	2
101-120	0	1	11
121-140	0	1	17
141-160	0	17	10
161-180	13	13	0
181-200	3	3	0
201-220	5	5	0
221-240	0	0	0
241-260	0	0	0
Mean ± SD	**199.13 ± 26.064**	**170.50 ± 23.745**	**130.88 ± 14.627**

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Table 7: Incidence of Side Effects

Side Effects	Group C	Group D	Group P	Total
Sedation	0	7	10	17
PONV	0	6	0	6
No Side Effects	40	27	30	97

Discussion

The study evaluated the effectiveness of Pregabalin versus Duloxetine in managing acute postoperative pain following lower limb surgeries. The participants were divided into three groups: Group C (control), Group D (Duloxetine), and Group P (Pregabalin). The findings provided insights into various aspects such as age and weight distribution, systolic blood pressure, pain scores, sedation levels, opioid consumption, and side effects.

The age distribution was similar across the three groups, with no significant differences observed in mean ages. This uniformity ensured that age-related factors did not bias the results. However, significant differences were found in weight distribution, with Group P having the highest mean weight. This difference was accounted for in the analysis to ensure the weight factor did not confound the pain and sedation outcomes.

The systolic blood pressure readings were comparable across all groups at various time intervals postoperatively. This indicated that neither Pregabalin nor Duloxetine had any significant impact on the patients' blood pressure, which suggests that both medications are safe from a cardiovascular standpoint when used for managing postoperative pain.

The VAS scores demonstrated that Pregabalin (Group P) was significantly more effective in reducing postoperative pain at 2-, 4-, 6-, and 12-hours post-surgery compared to both the control and Duloxetine groups. At 24 hours, the pain scores were similar across all groups, indicating that the pain-relieving effects of Pregabalin were more pronounced in the early postoperative period. This suggests that Pregabalin can be particularly beneficial for managing acute postoperative pain immediately following surgery.

Patients in the Pregabalin group exhibited higher sedation levels at 2 and 4 hours postoperatively, as measured by the Ramsay sedation scale. This finding indicates that while Pregabalin is effective in pain management, it also has a sedative effect, which should be considered when selecting patients for this medication, especially those who may need to remain alert postoperatively.

The requirement for rescue analgesic (Fentanyl) was notably lower in the Pregabalin group compared to the Duloxetine and control groups. This opioid-sparing effect is clinically significant as it can reduce the risk of opioid-related side effects and dependency, making Pregabalin a valuable component of multimodal pain management strategies in the postoperative setting.

The incidence of side effects varied between the groups. Sedation was more common in the Pregabalin group, while PONV were noted only in the Duloxetine group. These side effect profiles are crucial for tailoring postoperative pain management to individual patient needs and preferences.

The study's results suggest that Pregabalin is more efficient than Duloxetine in managing acute postoperative pain following lower limb surgeries. Pregabalin's advantages include significantly lower pain scores in the early postoperative period and reduced opioid consumption, which can enhance patient recovery and satisfaction. However, its use is associated with higher sedation levels, which may limit its applicability in patients who need to be alert postoperatively.

Duloxetine, while effective in reducing pain, showed a higher incidence of PONV and did not match Pregabalin's pain-relieving efficacy or opioid-sparing effects. Therefore, Duloxetine may be more suitable for patients who are at risk of sedation-related complications or who have contraindications to Pregabalin.

Both pregabalin and duloxetine are utilized for pain management, particularly in postoperative settings. A randomized clinical trial compared pregabalin and duloxetine in lower limb trauma surgeries. They found that the requirement for rescue analgesia was similar between the groups, with pregabalin required by 60% of patients and duloxetine by 50% within 72 hours postoperatively. The VAS scores, time to first rescue, and cumulative rescue analgesic needs were comparable in both groups [5].

A study on patients undergoing spinal surgery was conducted to compare pregabalin and duloxetine's effects on post-operative pain and cognitive functions. Both medications were effective in reducing pain scores compared to placebo, but duloxetine had fewer negative effects on cognitive functions [6]. A study evaluated pregabalin as a preemptive medication in lower limb fracture surgeries. They reported a considerable reduction in post-operative VAS scores and lower need for breakthrough analgesia with pregabalin compared to placebo [7].

A study compared the efficacy of pregabalin to placebo in elective lower limb orthopedic surgeries. The pregabalin group showed a considerable reduction in postoperative pain scores and total analgesic requirements [8]. Another study compared pregabalin and gabapentin for post-operative pain management in lower limb surgeries. Pregabalin provided longer postoperative analgesia and lower total tramadol consumption compared to gabapentin [9].

Research found that pregabalin was more effective than paracetamol in reducing post-operative pain and analgesic requirements in lower limb surgeries [10]. A study evaluated preoperative duloxetine for postoperative pain control in laparoscopic cholecystectomy and found it significantly reduced pain compared to placebo [11].

Generalizability

The study findings suggest that Pregabalin is more effective than Duloxetine in reducing acute postoperative pain and opioid consumption following lower limb surgeries, indicating that Pregabalin could be beneficial for broader populations undergoing similar surgical procedures.

Conclusion

In conclusion, Pregabalin appears to be the superior choice for acute post-operative pain management in lower limb surgeries due to its effectiveness in pain reduction and opioid-sparing properties, albeit with a trade-off in increased sedation. This information can guide clinicians in optimizing postoperative pain management protocols to improve patient outcomes.

Limitations

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendation

Pregabalin is recommended for managing acute postoperative pain in lower limb surgeries due to its superior pain relief and opioid-sparing effects. However, its sedative properties should be considered, and its use should be tailored to patients who can tolerate increased sedation.

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List of abbreviations

ASA - American Society of Anesthesiologists

CNS - Central Nervous System

PONV - Post-Operative Nausea and Vomiting

SNRI - Serotonin-Norepinephrine Reuptake Inhibitor

VAS - Visual Analogue Scale

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Conflict of interest

The authors have no competing interests to declare.

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