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Original Research Article

Safety and Tolerability of Transdermal Buprenorphine Compared with Oral Tramadol Following Lower-Limb Surgery under Spinal Anaesthesia

Vikas S. Joshi[1], Jyothi Sheelavantar[2], Nishant Deshpande[3]

[1]Associate Professor, Department of Anaesthesiology, Mahadevappa Rampure Medical College, Kalaburagi, Karnataka, India.
[2]Senior Resident, Department of Anaesthesia, M.R. Medical College, Kalaburagi, Karnataka, India.
[3]Assistant Professor, Department of Anaesthesiology, Khaja Bandanawaz University – Faculty of Medical Sciences, Kalaburagi, Karnataka, India.

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Corresponding author: Dr. Jyothi Sheelavantar
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Abstract

Background: Transdermal buprenorphine may provide sustained postoperative analgesia with fewer adverse effects than oral tramadol. This study compared their safety, tolerability and analgesic efficacy following lower-limb surgery under spinal anaesthesia.

Methods: Sixty ASA I–II patients were divided into two groups of 30. Group A received a transdermal buprenorphine patch 10 µg/hour, while Group B received oral tramadol 50 mg three times daily. Pain scores, rescue analgesic requirements, haemodynamic parameters and adverse effects were assessed for six postoperative days.

Results: Baseline characteristics were comparable. VAS scores were significantly lower in Group A at all postoperative assessments. Rescue analgesia was required by 60.0% of Group A and 100.0% of Group B on Day 1, decreasing to 33.3% and remaining 100.0%, respectively, on Day 6. Adverse effects occurred in 13.3% of Group A and 40.0% of Group B (p=0.040). No respiratory depression or patch-site reaction occurred.

Conclusion: Transdermal buprenorphine provided better analgesia, reduced rescue analgesic use and showed superior tolerability compared with oral tramadol.

Keywords: Buprenorphine Patch; Tramadol; Postoperative Analgesia; Spinal Anaesthesia; Lower-Limb Surgery.

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Introduction

Effective postoperative pain management is an important component of perioperative care because inadequate analgesia may delay mobilisation, impair functional recovery, increase postoperative morbidity and reduce patient satisfaction.[1,2] Pain management following lower-limb surgery may be particularly challenging in elderly patients and those with associated comorbidities, in whom opioid-related sedation, respiratory depression and haemodynamic effects are important concerns. Therefore, an ideal postoperative analgesic regimen should provide sustained pain relief with minimal adverse effects and facilitate early recovery. [3]

Buprenorphine is a potent, centrally acting opioid with high affinity and partial agonist activity at the µ-opioid receptor. Its distinctive pharmacological profile provides effective analgesia with a ceiling effect on respiratory depression, potentially offering a favourable safety margin compared with conventional full opioid agonists.[4,5] The transdermal buprenorphine patch provides continuous systemic drug delivery, stable plasma concentrations and prolonged analgesia while reducing the need for repeated drug administration. Although it is widely used for chronic pain, evidence regarding its safety, tolerability and effectiveness in acute postoperative pain remains comparatively limited. [6,7]

Tramadol is a centrally acting analgesic that produces pain relief through weak µ-opioid receptor agonism and inhibition of serotonin and noradrenaline reuptake. [8,9] It is frequently used for acute musculoskeletal and postoperative pain because of its oral availability and comparatively lower respiratory-depressant effect. However, tramadol may cause nausea, vomiting, dizziness, sedation, constipation and headache. Its analgesic response may vary because of genetic differences

in drug metabolism, while prolonged or inappropriate use may be associated with dependence and misuse. [10] Despite the potential advantages of transdermal buprenorphine, direct comparisons with oral tramadol for postoperative analgesia following lower-limb surgery are limited. Therefore, the present study was undertaken to compare the safety, tolerability and analgesic effectiveness of transdermal buprenorphine with oral tramadol following lower-limb surgery under spinal anaesthesia.

Materials and Methods

Study design and setting: This prospective comparative study was conducted in the Department of Anaesthesiology, Basaveshwar Teaching and General Hospital, attached to Mahadevappa Rampure Medical College, Kalaburagi. The study was conducted over 18 months, from August 1, 2022, to January 31, 2024.

Study population: A total of 60 adult patients scheduled to undergo lower-limb surgery under spinal anaesthesia were included. The patients were divided into two groups of 30 each:

Group A: Transdermal buprenorphine patch, 10 µg/hour

Group B: Oral tramadol, 50 mg three times daily

Sample-size Calculation: The calculated sample size was 29.65 patients per group. Therefore, 30 patients were included in each group, giving a total sample size of 60.

Sampling Procedure: Eligible patients were selected after applying the predefined inclusion and exclusion criteria. Demographic, clinical, intraoperative and postoperative information was collected using a structured study proforma.

Inclusion Criteria: Patients aged 18–80 years, belonging to American Society of Anesthesiologists physical status I or II, and undergoing lower-limb surgery under spinal anaesthesia were included.

Exclusion Criteria: Patients with known hypersensitivity to buprenorphine, tramadol or any study medication were excluded. Patients with hepatic or renal impairment, myasthenia gravis, delirium tremens, dermatitis or skin lesions at the proposed patch-application site, and those with a body mass index greater than 35 kg/m² were also excluded.

Study Procedure: After preoperative evaluation and confirmation of eligibility, patients were assigned to either Group A or Group B. Patients in Group A received a transdermal buprenorphine patch delivering 10 µg/hour, whereas patients in Group B received oral tramadol 50 mg three times daily. The assigned analgesic treatment was initiated one day before surgery.

All patients received oral alprazolam 0.25 mg at bedtime on the night before surgery. Lower-limb surgery was subsequently performed under spinal anaesthesia according to the institutional anaesthetic protocol.

Heart rate, blood pressure, pain intensity and treatment-related adverse effects were assessed at 8-hour intervals preoperatively and postoperatively for six days. Pain intensity was evaluated using the visual analogue scale, ranging from 0, indicating no pain, to 10, indicating the worst imaginable pain.

Rescue analgesia was administered when the visual analogue scale score was 4 or greater. The sequential rescue analgesic protocol included oral diclofenac 50 mg, followed by an additional dose of oral diclofenac 50 mg, oral paracetamol 1 g, an additional dose of oral paracetamol 1 g and, when pain persisted, a regional nerve block. The number of rescue analgesic doses required by each patient was recorded.

Outcome Assessment: The primary outcomes were the safety and tolerability of transdermal buprenorphine compared with oral tramadol. Safety and tolerability were assessed by recording adverse effects such as giddiness, drowsiness, postoperative nausea and vomiting, constipation, respiratory depression and redness or irritation at the patch-application site.

Pain scores and rescue analgesic requirements were assessed as secondary outcomes. Haemodynamic parameters, including heart rate and blood pressure, were also monitored. Bradycardia was defined as a heart rate below 50 beats per minute, while hypotension was defined as blood pressure below 90/60 mmHg.

Statistical Analysis: Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics for Windows, version 20.0. Continuous variables were expressed as mean and standard deviation or median and interquartile range, depending on data distribution. Categorical variables were presented as frequencies and percentages.

Continuous variables between the two groups were compared using the independent-samples Student's t-test or Mann–Whitney U test, as appropriate. Repeated pain and haemodynamic measurements were analysed using repeated-measures analysis of variance or an appropriate non-parametric test. Within-group comparisons were performed using the paired t-test or Wilcoxon signed-rank test. Categorical variables were compared using the chi-square test or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 60 patients undergoing lower-limb surgery under spinal anaesthesia were included in the study, with 30 patients assigned to the transdermal buprenorphine group (Group A) and 30 to the oral tramadol group (Group B). All patients completed the study and were included in the final analysis.

The mean age of patients was 43.50 ± 13.87 years in Group A and 45.13 ± 18.25 years in Group B, with no statistically significant difference between the groups (p=0.434). Group A comprised 19 males (63.3%) and 11 females (36.7%), whereas Group B comprised 20 males (66.7%) and 10 females (33.3%). The sex distribution was comparable between the groups (p=0.786) (Table 1).

Most patients had a BMI of 20–25 kg/m², accounting for 83.3% of Group A and 90.0% of Group B. A BMI of 25.1–30 kg/m² was observed in 16.7% and 6.7% of patients, respectively, while only one patient in Group B had a BMI of 30.1–35 kg/m². The overall BMI distribution was comparable between the two groups (p=0.300) (Table 4). ASA physical status was equally distributed, with 15 patients each classified as ASA I and ASA II in both groups (p=1.000).

Postoperative VAS scores were consistently lower in the transdermal buprenorphine group than in the oral tramadol group at all assessed time points during the six-day postoperative period (Table 2, Figure 1). At 8 hours on postoperative Day 1, the mean VAS score was 5.50 ± 2.28 in Group A compared with 7.73 ± 1.09 in Group B. On Day 2, the corresponding scores were 3.80 ± 1.33 and 6.27 ± 1.31, respectively. Lower pain scores in Group A persisted from Day 3 through Day 6. On Day 6, the mean VAS score at 8 hours was 2.93 ± 0.68 in Group A compared with 5.03 ± 1.62 in Group B. A similar pattern was observed at the 16-hour assessment. On Day 1, the mean VAS score was 4.63 ± 1.99 in Group A and 6.80 ± 1.25 in Group B. By Day 6, the corresponding scores had decreased to 2.93 ± 0.57 and 4.03 ± 1.30, respectively. At 24 hours on Day 1, the mean VAS score was 4.13 ± 1.82 in Group A compared with 6.07 ± 1.12 in Group B. On Day 6, the mean scores were 2.63 ± 0.60 and 3.40 ± 0.80, respectively.

These findings demonstrated consistently better postoperative pain control with transdermal buprenorphine throughout the observation period (Table 2, Figure 1). The requirement for rescue analgesia was significantly lower in Group A than in Group B throughout the six postoperative days (Table 3, Figure 2). On postoperative Day 1, rescue analgesia was required by 18 patients (60.0%) in Group A compared with all 30 patients (100.0%) in Group B (p=0.002). In Group A, the proportion of patients requiring rescue analgesia was 60.0% on Day 2, 50.0% on Days 3 and 4, 40.0% on Day 5 and 33.3% on Day 6. In contrast, all patients in Group B required rescue analgesia on every postoperative day. The between-group differences remained statistically significant throughout the study period (Table 3, Figure 2). No patient in either group required a regional nerve block for persistent postoperative pain.

Most patients in both groups had a BMI of 20–25 kg/m², comprising 25 patients (83.3%) in the transdermal buprenorphine group and 27 patients (90.0%) in the oral tramadol group. A BMI of 25.1–30 kg/m² was observed in 5 patients (16.7%) in Group A and 2 patients (6.7%) in Group B. Only one patient (3.3%) in Group B had a BMI of 30.1–35 kg/m², while no patient in Group A belonged to this category. Overall, the BMI distribution was comparable between the two groups (Table 4).

Treatment-related adverse effects were observed in 4 patients (13.3%) in Group A compared with 12 patients (40.0%) in Group B, indicating significantly better tolerability with transdermal buprenorphine (p=0.040). Nausea was reported in 13.3% of patients in Group A and 33.3% in Group B. Constipation occurred in 3.3% and 10.0%, while dizziness occurred in 3.3% and 6.7% of patients, respectively.

Headache was not observed in Group A but was reported in 23.3% of patients in Group B. Nausea associated with vomiting occurred in 3.3% of Group A and 13.3% of Group B. No cases of respiratory depression or anaphylaxis were observed in both group, and no patch-site reactions occurred among patients receiving transdermal buprenorphine.

The patients underwent a variety of lower-limb surgical procedures. Debridement was the most frequently performed procedure in Group A (26.7%), whereas other procedures constituted the largest category in Group B (36.7%). Wound exploration and repair was performed in 16.7% of Group A and 20.0% of Group B. Fixation and plating, contracture release with grafting, ACL reconstruction and soft-tissue repair were performed in smaller proportions of patients in both groups. Most surgeries lasted between 1.5 and 2 hours. A surgical duration of 1.5 hours was recorded in 43.3% of Group A and 53.3% of Group B, while 46.7% of patients in each group underwent surgery lasting 2 hours. Only three patients in Group A underwent procedures lasting 1 hour (Table 5, Figure 3) Overall, transdermal buprenorphine provided better postoperative analgesia, reduced the requirement for rescue analgesics and was associated with fewer treatment-related adverse effects than oral tramadol.

Table 1: Baseline Characteristics of the Study Groups

Characteristic	Transdermal buprenorphine (n=30)	Oral tramadol (n=30)	p-value
Age, years	43.50 ± 13.87	45.13 ± 18.25	0.434
Male sex	19 (63.3%)	20 (66.7%)	0.786
Female sex	11 (36.7%)	10 (33.3%)	

Table 2: Comparison of Mean Postoperative VAS Scores

Postoperative day	8 hours Group A	8 hours Group B	16 hours Group A	16 hours Group B	24 hours Group A	24 hours Group B
Day 1	5.50 ± 2.28	7.73 ± 1.09	4.63 ± 1.99	6.80 ± 1.25	4.13 ± 1.82	6.07 ± 1.12
Day 2	3.80 ± 1.33	6.27 ± 1.31	3.43 ± 1.23	5.07 ± 1.71	3.53 ± 1.18	4.40 ± 1.43
Day 3	3.10 ± 0.79	6.40 ± 1.02	3.23 ± 1.02	4.43 ± 1.31	2.90 ± 0.87	3.63 ± 0.66
Day 4	3.10 ± 0.91	5.67 ± 1.04	3.17 ± 1.00	4.60 ± 1.23	2.97 ± 0.80	3.87 ± 0.88
Day 5	2.63 ± 0.55	5.07 ± 1.39	2.90 ± 0.75	4.40 ± 1.25	3.03 ± 0.80	3.57 ± 0.84
Day 6	2.93 ± 0.68	5.03 ± 1.62	2.93 ± 0.57	4.03 ± 1.30	2.63 ± 0.60	3.40 ± 0.80

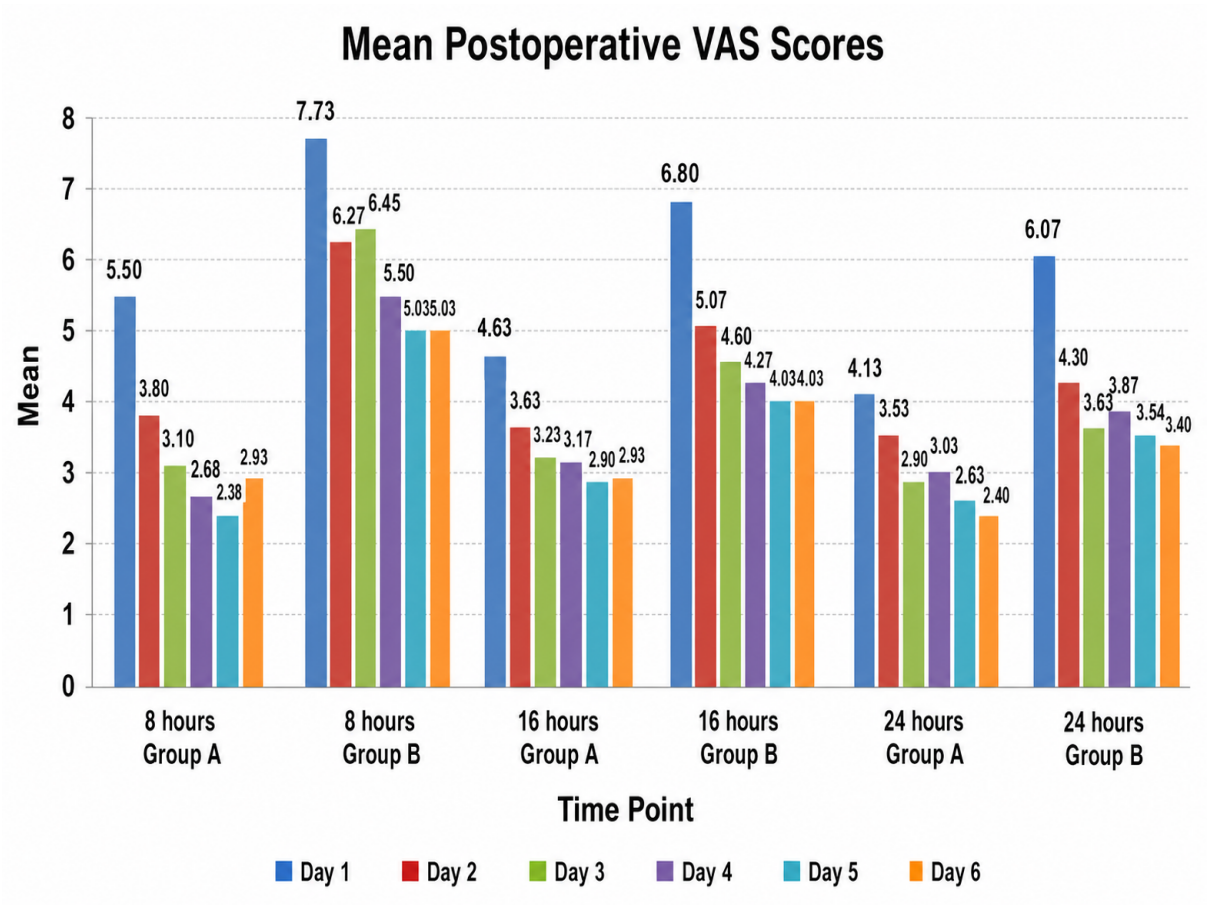

Figure 1: Comparison of Mean Postoperative VAS Scores

Table 3: Comparison of Rescue Analgesic Requirement

Postoperative day	Transdermal buprenorphine, n (%)	Oral tramadol, n (%)	p-value
Day 1	18 (60.0)	30 (100.0)	0.002
Day 2	18 (60.0)	30 (100.0)	0.020
Day 3	15 (50.0)	30 (100.0)	<0.010
Day 4	15 (50.0)	30 (100.0)	<0.010
Day 5	12 (40.0)	30 (100.0)	<0.010
Day 6	10 (33.3)	30 (100.0)	0.040

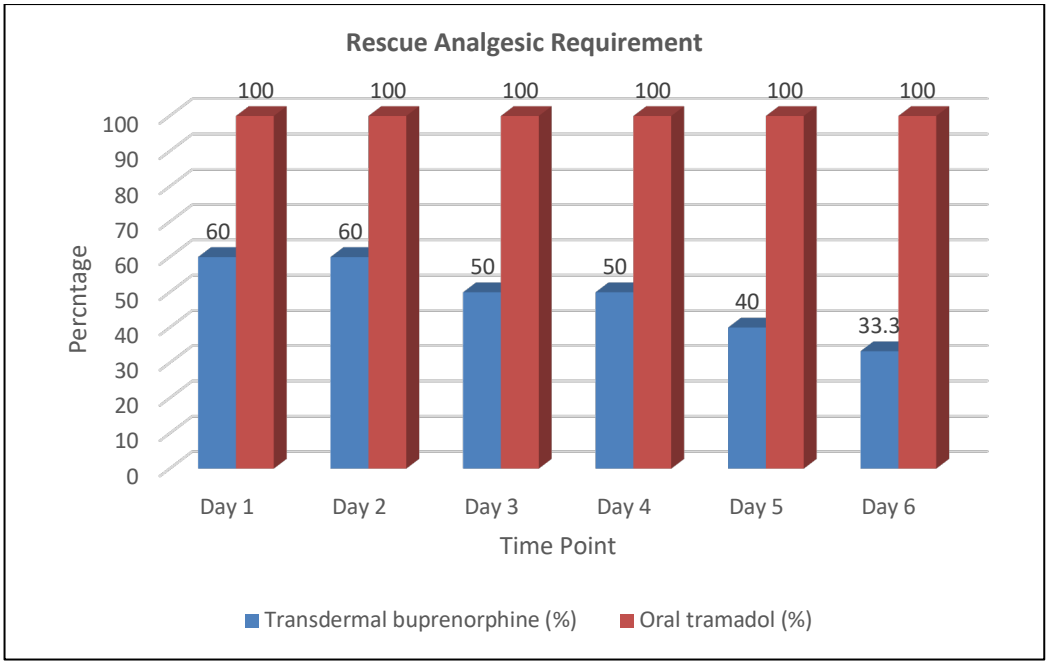

Figure 2: Comparison of Rescue Analgesic Requirement

Table 4: Distribution According to Body Mass Index

BMI category	Group A (n=30)	Group B (n=30)	Total (n=60)
20–25 kg/m²	25 (83.3%)	27 (90.0%)	52 (86.7%)
25.1–30 kg/m²	5 (16.7%)	2 (6.7%)	7 (11.7%)
30.1–35 kg/m²	0	1 (3.3%)	1 (1.7%)
Total	30 (100%)	30 (100%)	60 (100%)

Table 5: Surgical Characteristics

Surgical characteristic	Transdermal buprenorphine (n=30)	Oral tramadol (n=30)
Wound exploration and repair	5 (16.7%)	6 (20.0%)
Debridement	8 (26.7%)	4 (13.3%)
Fixation and plating	4 (13.3%)	3 (10.0%)
Contracture release and grafting	3 (10.0%)	1 (3.3%)
ACL reconstruction	4 (13.3%)	2 (6.7%)
Soft-tissue repair	2 (6.7%)	3 (10.0%)
Other procedures	4 (13.3%)	11 (36.7%)
Surgery duration: 1 hour	3 (10.0%)	0
Surgery duration: 1.5 hours	13 (43.3%)	16 (53.3%)
Surgery duration: 2 hours	14 (46.7%)	14 (46.7%)

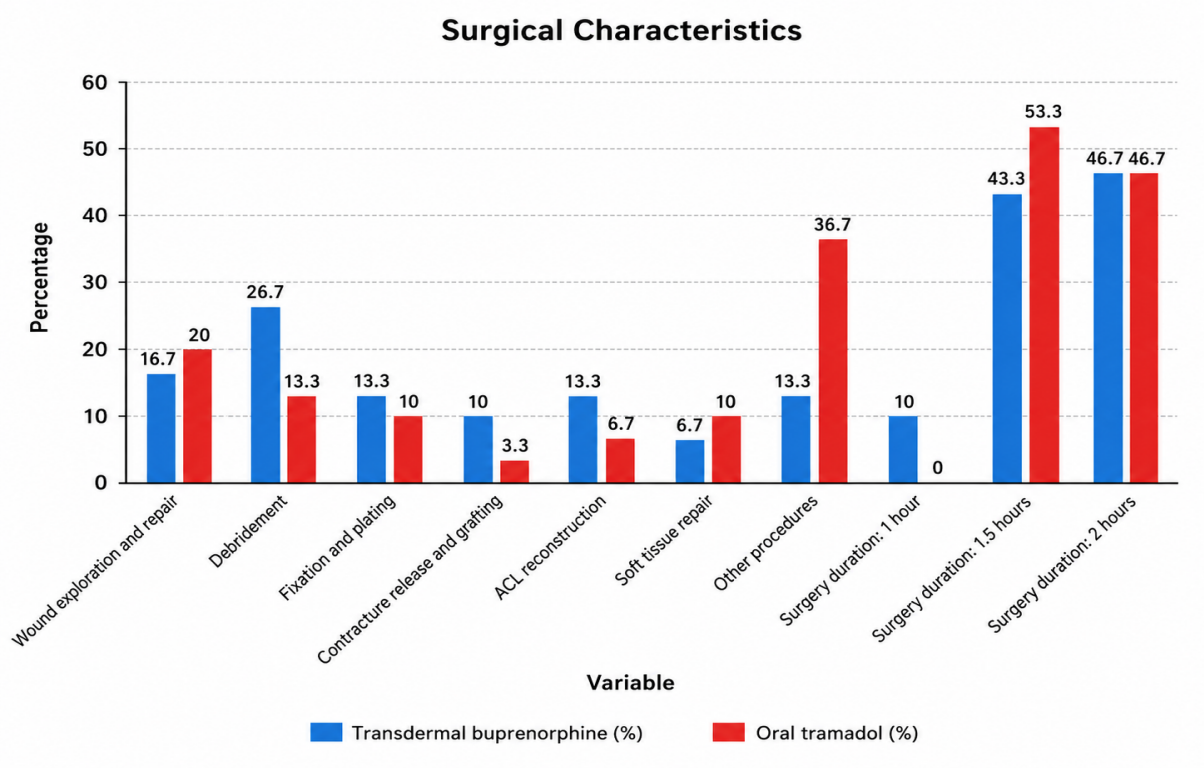

Figure 3: Surgical Characteristics

Discussion

The present prospective comparative study assessed the safety, tolerability and analgesic effectiveness of transdermal buprenorphine 10 µg/hour versus oral tramadol 50 mg three times daily in patients undergoing lower-limb surgery under spinal anaesthesia. Transdermal buprenorphine produced consistently lower postoperative pain scores, reduced rescue analgesic requirements and caused fewer adverse effects than oral tramadol, while haemodynamic parameters remained largely stable in both groups.

The two groups were comparable regarding age, sex, BMI and ASA physical status. The mean age was 43.50 ± 13.87 years in the transdermal buprenorphine group and 45.13 ± 18.25 years in the tramadol group. Comparable baseline characteristics were also reported by Desai et al. [11], Kadapamannil et al. [12] and Hembram et al. [13], supporting that the observed outcome differences were mainly related to the analgesic intervention.

The study included varied lower-limb procedures, with debridement, wound exploration and repair, fixation and ACL reconstruction being common. Most operations lasted 1.5–2 hours. Similar lower-limb procedures and broadly comparable operative durations were reported by Desai et al.[11] and Hembram et al.[13].

Postoperative VAS scores were significantly lower with transdermal buprenorphine at all assessed time points. On Day 1 at 8 hours, the mean VAS score was 5.50 ± 2.28 in Group A compared with 7.73 ± 1.09 in Group B, and this difference persisted throughout the six-day follow-up. John et al. [14] also reported lower pain scores with transdermal buprenorphine than with diclofenac patches. Londhe et al. [15] similarly observed significantly lower pain scores after hemiarthroplasty among patients receiving transdermal buprenorphine. These findings may be attributed to continuous drug delivery and more stable plasma concentrations with the transdermal system.

Rescue analgesic use was significantly lower in the transdermal buprenorphine group. The proportion requiring rescue analgesia decreased from 60.0% on Day 1 to 33.3% on Day 6, whereas all patients receiving tramadol required rescue analgesia throughout the study period. Lee et al.[16] reported fewer rescue medication doses with the buprenorphine transdermal system than with tramadol–acetaminophen after spinal surgery. Karlsson and Berggren [17] also demonstrated lower additional analgesic requirements with transdermal buprenorphine than with prolonged-release tramadol. Treatment-related adverse effects occurred in 13.3% of patients receiving transdermal buprenorphine and 40.0% of those receiving tramadol. Nausea, vomiting, constipation, dizziness and headache were more frequent with tramadol. No respiratory depression, anaphylaxis or patch-site reaction was observed. Karlsson and Berggren [17] reported nausea, constipation and dizziness

with both treatments but greater discontinuation due to adverse effects with tramadol.

Khandelwal et al.[18] also demonstrated acceptable tolerability of buprenorphine patches following arthroscopic lower-limb surgery, while Londhe et al.[15] reported fewer gastrointestinal adverse effects with transdermal buprenorphine than with conventional analgesics.

Blood pressure and pulse rate remained generally stable and comparable between the groups, apart from isolated transient differences. Similar haemodynamic stability with transdermal buprenorphine was reported by Desai et al.[11], Kadapamannil et al.[12] and Hembram et al.[13].

Conclusion

Transdermal buprenorphine provided superior and sustained postoperative analgesia with lower rescue analgesic requirements than oral tramadol following lower-limb surgery under spinal anaesthesia. It was also associated with fewer adverse effects and stable haemodynamic parameters. Therefore, transdermal buprenorphine may be considered a safe and well-tolerated alternative to oral tramadol.

Limitations

The study was conducted at a single centre with a small sample size and included heterogeneous lower-limb surgical procedures.

The short follow-up period and absence of blinding may limit the generalisability of the findings.

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