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Efficacy and safety of intranasal tapentadol versus intravenous tramadol for post-operative analgesia

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Abstract:
Post-operative pain management is a vital aspect of perioperative management, especially in the management of pain following major surgery of the lower limb and hip. Good pain management will make the patient more comfortable, help get the patient moving early and help prevent complications. Hence, this prospective randomized study compares the efficacy and safety of intranasal tapentadol and intravenous tramadol for post-operative analgesia in 100 patients under regional anesthesia. Patients were split into two groups: one that received intranasal tapentadol and the other intravenous tramadol at a fixed time interval. The Visual Analogue Scale (VAS) was used to evaluate pain, and hemodynamic parameters, adverse effects and patient satisfaction were monitored. Thus, we compare the efficacy, safety, and patient satisfaction of IN tapentadol to IV tramadol.

Keywords: Intranasal tapentadol; intravenous tramadol; patient satisfaction; post-operative analgesia; regional anesthesia; vas score

Background:
Despite the development of new anesthetic and analgesic techniques, post-operative pain is a major clinical problem which is always accompanied by surgical trauma. Poor pain management may result in delayed recovery, longer hospital stay, higher morbidity and lower patient satisfaction **[1].** Post-operative pain is therefore critical for the patient's comfort, as well as for better recovery and prevention of chronic pain syndromes **[2].** Opioids remain the mainstay of moderate to severe post-operative pain management. Tramadol is a commonly used opioid that has been broadly employed because of its dual mechanism of action, as a weak μ-opioid receptor agonist and as a norepinephrine and serotonin reuptake inhibitor **[3].** The IV form of tramadol is often used in the post-operative setting because it is easily titrated and has a quick onset of action. It does, however, have side effects like nausea, vomiting, dizziness, and respiratory depression that can make it difficult to tolerate **[4].** Tapentadol is a newer centrally acting analgesic drug that has a dual mechanism of action, by inhibiting the reuptake of norepinephrine and by acting as a μ-opioid receptor agonist **[5].** Tapentadol is more predictable in its pharmacokinetic profile, has a quicker onset of action and has fewer gastrointestinal side effects than tramadol **[6].** Intranasal drug delivery has traditionally been given orally, and new opportunities are now emerging for quick and non-invasive drug delivery. The intranasal route of drug delivery has been brought to the fore because of its special characteristics such as rapid absorption through the highly vascular nasal mucosa, bypass of first-pass metabolism and the ease of patient compliance **[7].** Intranasal analgesics have been shown to be effective in acute pain, especially in the emergency and post-operative setting **[8].** This may be particularly useful in patients in whom IV access is challenging or undesirable. Intranasal opioids like fentanyl and ketamine have been assessed in a few studies for post-operative pain control and have been found to be as effective as intravenous administration **[9, 10].** But there is little information available on the use of intranasal tapentadol for post-operative pain. Intranasal tapentadol could offer effective pain relief, with less systemic side effects, due to its pharmacological benefits. Another important parameter during post-operative care is hemodynamic stability. Cardiovascular and respiratory parameters may be affected by opioids, so it is important to compare their safety profiles **[11].** In addition, patient satisfaction has become an important outcome measure and is a measure of the overall effectiveness of the analgesic regimens **[12].** Therefore, it is of interest to evaluate the efficacy of the analgesics by using VAS scores, and the secondary goals were to evaluate the hemodynamic parameters, adverse effects, and patient satisfaction.

Materials and Methods:
The study was a prospective, randomized comparative study carried out in the Department of Anaesthesiology, Shyam Shah Medical College and Associated Hospitals, Rewa, Madhya Pradesh, India for one year. A total of 100 patients undergoing major surgery of lower limb and hip under spinal anesthesia were included in the study.

Study design:
A prospective, randomized, comparative clinical study was conducted.

Sample size:
The minimum sample size calculated was 38 patients per group based on the assumptions used in the statistics. A total of 100

patients were included (50 patients in each group) to increase the reliability and statistical power of the study.

Study population:
The study included adult patients aged 18-60 years with American Society of Anesthesiologists (ASA) physical status I and II.

Inclusion criteria:
[1] Patients aged 18–60 years
[2] The ASA grades are I and II.ASA grades are I and II.
[3] Patients who are having a major surgery on the lower leg or hip under regional anesthesia

Exclusion criteria:
[1] Refusal to participate
[2] Presence of psychological disorders
[3] Pathology in the nose which impairs drug absorption
[4] Liver or renal function tests are abnormal
[5] Children under 12 years of age
[6] Patients with significant respiratory illness

Preoperative assessment:
Pre-anesthetic assessment was carried out in detail for all patients, which included history taking, physical examination, airway assessment and appropriate laboratory investigations. Patients were given information about the Visual Analogue Scale (VAS) and patient satisfaction scoring system. Written informed consent was obtained prior to inclusion in the study.

Randomization and group allocation:
Using a chit based randomisation method; patients were randomly allocated to two groups:
[1] Group B: Acetaminophen + hydrocodone
[2] Group B: Intravenous tramadol

Allocation bias was avoided by randomizing the allocation by an independent staff member. Because of the different methods of drug administration, blinding was not possible.

Intervention Protocol:
Standard intraoperative monitoring was performed in all patients, such as heart rate, blood pressure, oxygen saturation (SpO_2), and respiratory rate. Baseline parameters were taken before giving analgesics.

Group A (Intranasal Tapentadol): At the end of surgery, 22.5 mg of tapentadol was administered to each nostril, and then repeated every 8 hours for 72 hours.
Group B (Intravenous Tramadol): At the end of surgery, patients were given 50 mg of tramadol intravenously, followed by tramadol 50 mg every 8 hours for 72 hours.

Intraoperative intravenous dexamethasone (8 mg) and ondansetron post-operatively were used for all patients as prophylaxis for post-operative nausea and vomiting.

Outcome measures:
Pain assessment:
The intensity of pain was assessed on the Visual Analogue Scale (VAS) ranging from 0 (no pain) to 10 (maximum pain imaginable).

Assessments were performed:
[1] Every 4 hours on post-operative day (POD) 1
[2] At 0, 4, 8, 16, and 24 hours on POD 2
[3] Every 8 hours on POD 3

Hemodynamic parameters:
Heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation were measured at specific time points.

Rescue analgesia:
Rescue analgesia of injection paracetamol 1000 mg was given if VAS score was ≥ 5.

Patient satisfaction:
Patient satisfaction was evaluated 24 hours after the procedure on a 5-point Likert scale from highly satisfied to highly dissatisfied.

Adverse effects:
Side effects were observed, including nausea, vomiting, sedation, respiratory depression and nasal irritation.

Data collection:
A structured proforma was used to record the data which included demographic details, intraoperative variables, post-operative pain scores, hemodynamic parameters and adverse effects.

Statistical analysis:
Microsoft Excel and IBM SPSS (version 20) were used for data entry and analysis. The data of continuous variables was represented as mean ± standard deviation and categorical variables as frequencies and percentages. The unpaired t-test was used for comparison of means between groups, and the chi-square test was used for categorical variables. A p value of < 0.05 was deemed statistically significant.

Results:
The present prospective randomized study was conducted on 100 patients undergoing major lower limb and hip surgeries under regional anesthesia. Patients were equally divided into two groups: Group A (intranasal tapentadol) and Group B (intravenous tramadol). Various parameters including demographic profile, hemodynamic variables, pain scores, adverse effects, and patient satisfaction were analyzed. The baseline demographic variables between the two groups were statistically comparable. The mean age difference was not significant (p=0.2279), indicating homogeneity in age distribution. Although Group A had a higher proportion of males (82%) compared to Group B (66%), the difference was not

statistically significant (p=0.111). Similarly, the duration of surgery was nearly identical between both groups (p=0.747). This confirms that both groups were well matched, minimizing confounding bias and allowing reliable comparison of outcomes **(Table 1).** Pain intensity, assessed using the Visual Analogue Scale (VAS), showed a gradual decline in both groups over time, indicating effective post-operative analgesia. During the initial post-operative hours (4–12 hours), both groups demonstrated comparable pain relief (p>0.05). However, statistically significant differences were observed at 20 hours on Day 1 (p=0.0096) and 0 hours on Day 2 (p=0.0280), where Group B (tramadol) reported higher pain scores compared to Group A. This suggests that intranasal tapentadol provided superior analgesic efficacy during these specific intervals. By Day 3, pain scores in both groups were minimal and comparable (p>0.05), indicating that both drugs were effective in long-term pain control. Overall, intranasal tapentadol demonstrated slightly better analgesic efficacy during the early post-operative period **(Table 2)**. Patient satisfaction was markedly higher in Group A, where 62% of patients were highly satisfied, compared to only 6% in Group B. Additionally, no patients in Group A reported dissatisfaction, whereas 36% of patients in Group B expressed dissatisfaction or high dissatisfaction. This difference highlights the better acceptability and patient comfort associated with intranasal administration. In terms of adverse effects, systemic side effects such as nausea and vomiting were more common in Group B (6% and 4%) compared to Group A (2% each). However, Group A showed route-specific side effects such as nasal irritation and bleeding (16%). Conversely, injection site pain was significantly higher in Group B (30%), reflecting discomfort associated with intravenous administration. Overall, intranasal tapentadol showed a favorable safety and tolerability profile, despite minor local nasal side effects **(Table 3).** Both intranasal tapentadol and intravenous tramadol demonstrated comparable safety profiles. Hemodynamic and respiratory parameters remained stable throughout the study in both groups, indicating good tolerability. Although fewer patients in the tapentadol group required rescue analgesia (10% vs. 18%), the difference was not statistically significant (p=0.387), suggesting similar overall analgesic adequacy **(Table 4)**.

Table 1: Baseline Characteristics of Study Population

Parameter	Group A (n=50)	Group B (n=50)	p-value
Age (years)	36.02 ± 13.80	38.18 ± 15.02	0.2279
Male (%)	82%	66%	0.111
Female (%)	18%	34%	
Duration of surgery (min)	80.5 ± 21.84	79.4 ± 15.75	0.747

Table 2: Comparison of VAS Scores (Pain Intensity)

Time Interval	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
4 hrs	3.5 ± 0.70	3.38 ± 0.66	0.3847
8 hrs	2.72 ± 0.64	2.92 ± 0.66	0.1288
12 hrs	2.26 ± 0.66	2.42 ± 0.49	0.1763
20 hrs	1.08 ± 0.75	1.48 ± 0.76	**0.0096**
Day 2 (0 hr)	0.74 ± 0.63	1.02 ± 0.62	**0.028**

Table 3: Patient Satisfaction and Adverse Effects

Satisfaction Level	Group A (%)	Group B (%)
Highly satisfied	62%	6%
Satisfied	34%	48%
Neutral	4%	10%
Dissatisfied	0%	32%
Highly dissatisfied	0%	4%
Adverse Effect	**Group A (%)**	**Group B (%)**
Nausea	2%	6%
Vomiting	2%	4%
Nasal irritation/bleeding	16%	0%
Injection site pain	0%	30%

Table 4: Summary of Additional Clinical Findings

Parameter	Group A (Tapentadol)	Group B (Tramadol)	p-value
Hemodynamic parameters (HR, SBP, DBP, SpO_2)	Stable	Stable	>0.05 (most intervals)
Respiratory rate	Within normal limits	Within normal limits	>0.05
Rescue analgesia requirement	5 patients (10%)	9 patients (18%)	0.387

Discussion:

Post-operative pain management is a fundamental element of perioperative care, especially in orthopedic surgeries where pain levels tend to be significant. This current study compared intranasal tapentadol to intravenous tramadol, specifically in terms of efficacy, safety, and patient satisfaction. Both groups were similar in terms of demographic characteristics, which ensured internal validity. Previous studies have reported similar results, highlighting the need for the uniformity of baseline characteristics in analgesic trials **[2].** Both intranasal tapentadol and intravenous tramadol were effective analgesics as demonstrated by pain assessment using VAS scores. Tapentadol, however, was more effective at certain early post-operative time points (20 hours on Day 1 and 0 hours on Day 2). This may be explained by the dual mechanism of action of tapentadol, a μ-opioid receptor agonist and a norepinephrine reuptake inhibitor, which results in a greater analgesic effect **[4].** Tramadol is a commonly prescribed drug, but it is not as potent as other opioids and requires metabolic activation for its analgesic effect, which can lead to differences in response to the drug **[5].** This limitation in pharmacology could be the reason for the higher VAS scores seen in the tramadol group at some time points. The intranasal route has several advantages such as rapid absorption through the nasal mucosa and bypass of first-pass metabolism. Intranasal opioids like fentanyl have been shown to be equally or more effective at providing analgesia than intravenous **[7].** This study is consistent with these results and shows that intranasal tapentadol is an effective alternative to IV analgesics. The hemodynamic stability of both groups is consistent with previous reports of minimal cardiovascular effects in therapeutic doses of both tapentadol and tramadol **[8].** There were no clinically significant differences in heart rate and blood pressure between the two drugs, further confirming their safety. There was no evidence of respiratory depression and respiratory parameters were stable in both groups. This is in line with previous research indicating that tapentadol is less likely to

cause respiratory depression than traditional opioids **[9].** Patient satisfaction is an important indicator of overall treatment success. Tapentadol was associated with significantly greater levels of satisfaction in this study. This is due to improved pain management, ease of administration and elimination of injection discomfort. The same results have been obtained in trials assessing non-invasive routes of analgesia **[10].** The groups had different adverse effect profiles. In line with previous reports **[11]** tramadol was linked to increased nausea and vomiting. Tapentadol, however, showed less systemic side effects and was linked with local nasal irritation. The results indicate a balance between systemic and local negative effects. Pain at the injection site was noted only in the tramadol group (30%) and had a significant effect on patient comfort and satisfaction. This highlights the benefits of intranasal delivery in terms of patient experience **[12].** There was no significant difference between the groups in terms of the need for rescue analgesia. This indicates that both medications are effective at keeping the pain level at an adequate level, with a slight benefit to tapentadol. In summary, the results of this study are consistent with the literature that shows tapentadol to be an effective and tolerated analgesic **[13–15].** The intranasal route also makes it more clinically useful, as it is a non-invasive route of administration that is patient-friendly.

Conclusion:

Intranasal tapentadol is effective and safe alternative to IV tramadol for post-operative analgesia. It offers similar, and sometimes greater, pain relief, greater patient satisfaction and fewer systemic side effects. It is associated with mild nasal side effects, but it is well tolerated and is a promising method for post-operative pain management due to its non-invasive delivery.

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