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Original Research Article

A comparison of oral tramadol and oral tapentadol for prevention of perioperative shivering during subarachnoid block in patients undergoing transurethral resection of prostate: A randomized control trial

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ABSTRACT

Background: Postanaesthetic shivering is a frequent complication after subarachnoid block, particularly in elderly patients, and can lead to discomfort and adverse effects. Prophylactic interventions are needed to mitigate this issue and enhance patient comfort during surgery.

Aim & Objective: This randomized controlled trial (RCT) aimed to compare the efficacy of oral tramadol and tapentadol as premedications for the prevention of perioperative shivering following subarachnoid block in geriatric patients undergoing transurethral resection of the prostate (TURP).

Materials and Methods: A total of 150 elderly patients scheduled for TURP under subarachnoid block were enrolled in the study. Patients were randomized into two groups: Group A (n=75) received 50 mg of oral tramadol, and Group B (n=75) received 50 mg of oral tapentadol 90 minutes before surgery. After achieving an adequate block, body temperature (forehead and tympanic membrane), shivering grades, sedation scores, and the incidence of nausea and vomiting were recorded at regular intervals throughout the perioperative period. Data were analyzed using ANOVA, Student's t-test, test of proportions, and Fisher's exact test where appropriate. A p-value of <0.05 was considered statistically significant.

Results: There were no significant differences between the two groups in the incidence of shivering. Mean body temperature measurements (forehead and tympanic membrane) were comparable across both groups throughout the observation period. The sedation scores between Group A and Group B showed no statistically significant differences. Four patients in Group A experienced nausea, while no such incidents were reported in Group B.

Conclusion: Both oral tramadol and oral tapentadol are equally effective as premedications for the prevention of perioperative shivering following subarachnoid block in elderly patients. However, tapentadol may be associated with a lower incidence of nausea compared to tramadol.

1. Introduction

Perioperative shivering is a frequent but significant complication in patients undergoing urological procedures under subarachnoid block.[1] Patients often report shivering as remarkably unpleasant and even experience the accompanying cold thermal sensation more distressing than surgical pain. Shivering has a spectrum of physiological consequences, including increased oxygen consumption, hypoxemia, hypercarbia, lactic acidosis, and raised intracranial and intraocular pressures. On many occasions, shivering interferes with the monitoring techniques contributing to measurement errors.[2–4]

The exact etiology of postanaesthetic shivering is poorly understood. Both thermoregulatory and non-thermoregulatory factors may contribute to perioperative

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shivering. The high incidence of postanaesthetic shivering is directly related to intraoperative hypothermia produced as a result of heat loss from the body surfaces and redistribution of heat from the core to the peripheries.[5–7]

Maintenance of normothermia and prevention of shivering is advisable during the perioperative period to minimize adverse consequences. So, different pharmacologic interventions have been identified and studied considering their role in the modulation of shivering. Opioids have demonstrated significant anti-shivering properties and are used frequently both for the prevention and treatment of postanaesthetic shivering.[8] The associated adverse effects like sedation, pruritus, respiratory depression, nausea, and vomiting have limited their use. The oral formulation of tramadol is easily available, economical, and used extensively. Tramadol is readily absorbed following oral administration and is associated with a high safety profile and weak sedative properties, particularly in patients with poor cardiorespiratory reserve.[9–11]

Tapentadol is a novel, FDA-approved central-acting opioid analgesic with a dual mechanism of action, combining agonism at μ receptors and inhibition of noradrenaline reuptake. Currently, tapentadol is available exclusively in oral formulation and is used in the treatment of acute, chronic, and neuropathic pain. Tapentadol is associated with an opioid-sparing effect contributing to the reduction of typical opioid-related side effects and resulting in improved patient acceptance and compliance.[12–14] In this study we test the hypothesis that oral tapentadol possesses a similar potential of anti shivering agent as that of oral tramadol administered during the perioperative period.

This randomized control trial was conducted to investigate the anti-shivering properties of oral tapentadol and compare its effects with oral tramadol following subarachnoid block in geriatric patients.

2. Materials and Methods

After obtaining approval from the institutional ethics committee for human subjects (MDC/JNMCIEC/144 and CTRI – India (CTRI/2023/07/055415), this prospective randomized control trial was carried out on 150 geriatric patients aged between 60-80years (American Society of Anaesthesiologists [ASA] physical status I, II, and III) undergoing transurethral resection of prostate under subarachnoid block. Patients were excluded in the presence of obesity with body mass index (BMI) $\geq$ 30, presence of febrile illness, known allergy to either of the study drugs, ischaemic heart disease, neuro-behavioral disorders, thyroid dysfunction, severe diabetic/autonomic neuropathy, and patients on vasodilator medications.

Allocation of patients was conducted in a randomized manner by opening a sealed envelope method into two groups, a) group A (tramadol, n=75) and b) group B (tapentadol, n=75). Informed and written consent was obtained from all study participants during pre-anaesthetic evaluation one day before surgery. Group A received an oral formulation of tramadol 50mg, while Group B received an oral formulation of tapentadol 50mg with sips of water 90 minutes before surgery. Patients and treating anaesthesiologists were unaware of the preparations administered.

Under strict aseptic precautions, a subarachnoid block was achieved with a sensory block up to T9-10 level using hyperbaric levobupivacaine (0.5%) 3ml. All surgeries were carried out in the same operation theatre maintained with constant humidity and ambient temperature of 25°C. The operating room selected during the study was not equipped for the provision of laminar flow. No measures of active rewarming were used unless deemed essential for rescue therapy. Pre-warmed intravenous fluids and irrigating glycine were used during the study period.

Skin temperature (forehead, using the Braun BNT400 thermometer) and core temperature (tympanic membrane, using the Braun Thermoscan5 thermometer) were recorded every 5min from the baseline (5 minutes before the subarachnoid block) for 1 hour followed by every 10min for the rest of the observation period. Shivering grades were assessed by the attending anaesthesiologist at a period of 0, 1, 5, 10, 15, 30, 45, 60, and 90 minutes from the baseline according to the Wrench grading scale (Table 1).

Perioperatively shivering if present was managed by reassurance, the use of a forced air warming blanket, or injection of intravenous pethidine depending on the intensity of shivering. Adverse effects such as nausea and vomiting were treated with intravenous ondansetron. Perioperative sedation was assessed using the Filos four-point sedation score (Table 2).

2.1. Statistical analysis

The sample size was calculated based on the incidence of shivering of 40% following subarachnoid block derived from pilot study results of 60 patients in the same institute (using a formula for comparing two proportions).

$$n = \frac{(z_\alpha + z_\beta)^2\, p\,(1-p)}{d^2}$$

where p_1 and p_2 are the proportions of the two groups.

$$p = \frac{p_1 + p_2}{2}$$

and $d = p_1 - p_2$

z_α is linked with the significance level and z_β is linked with the power of the test. For a 5% significance level, z_α = 1.96 and z_β = 0.84 for 80% power of the test. Considering the proportions p_1 = 37.5% and p_2 = 17.0% (incidence of shivering among both the comparison groups), the sample size obtained was 75 in each group.

Study participants from the pilot study were excluded from the sample recruited for the actual study. MS-Excel sheets were used to enter collected data and statistical

analysis was performed by using SPSS (Statistical Package for Social Sciences) version 20.0 software. All data results were expressed as mean ± standard deviation and percentages in tabulations. Parametric data were analyzed using a student t-test and analysis of variance (ANOVA) while non-parametric data were analyzed using a test of proportions. Fischer exact test was used to compare incidences among both groups. A p-value of less than 0.05 was considered statistically significant.

3. Results

A sum of 150 geriatric patients scheduled to undergo transurethral resection of the prostate under subarachnoid block were assessed for the study (Diagram 1). The demographic and clinical characteristics were similar among both groups (Table 3).

Both skin and core body temperature recordings were comparable among the two groups throughout the period of observation (Figures 1 and 2). All patients of both groups demonstrated downward trends of skin and core temperatures during the course of surgery and were statistically insignificant ($p > 0.05$). The incidence of shivering showed no significant differences between the groups. At baseline, all participants had a shivering grade of 0. Over time, the majority of patients maintained a shivering grade of 0, with no clinically significant differences between Group A and Group B ($p = 0.771$). At 15 minutes, 33.33% of Group A participants and 30.67% of Group B participants experienced grade 1 shivering ($p = 0.744$). At 30 minutes, 13.33% of Group A participants and 17.33% of Group B participants manifested grade 2 shivering ($p = 0.499$). By 60 minutes, 97.33% of both groups demonstrated shivering grade 0 ($p = 0.999$). None among the groups exhibited grade 4 shivering (Figure 3). The distribution of the need for additional rescue measures was comparable among both groups. Patients with shivering grade 1 were managed by reassurance whereas patients with shivering grade 2 and 3 were managed by use of forced warming blankets in both the groups. None of the patients in either group required parenteral medication.

In group A, 4 patients suffered nausea after 20 minutes of ingestion of the study drug and were treated with antiemetics. There was no incidence of nausea or vomiting noticed among group B patients. Sedation scores among both groups were comparable and statistically insignificant ($p = 0.999$). At the end of 10 minutes and 60 minutes, only 10% and 37.4% of patients demonstrated a sedation score of 2 respectively. There were no differences in the incidence of drug-related adverse events among both groups.

4. Discussion

The core temperature of the human body ranges between 97.7°F and 99.5°F. The autonomic nervous system

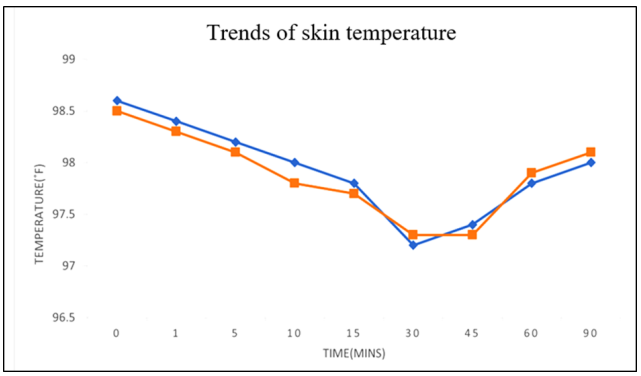

Figure 1: Trends of skin temperature changes following subarachnoid block

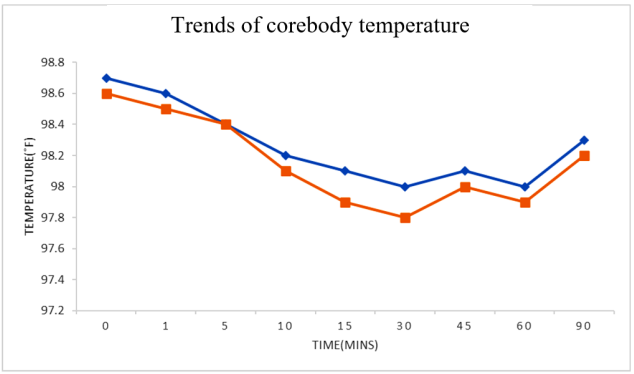

Figure 2: Trends of core body temperature changes following subarachnoid block

Table 1: Grading of shivering (Wrench et al.)[15]

Grades	Observation
0	No observable shivering
1	Piloerection; peripheral cyanosis without other specific cause and no visible muscle movements
2	Visible muscle contractions limited to one muscle group
3	Visible tremors involving more than one muscle groups
4	Gross muscular activity involving whole body

Table 2: Sedation score (Filos et al.)[16]

Score	Level of sedation
1	Awake, alert, and cooperative
2	Drowsy but responsive to verbal commands
3	Drowsy but arousable to physical stimuli
4	No response

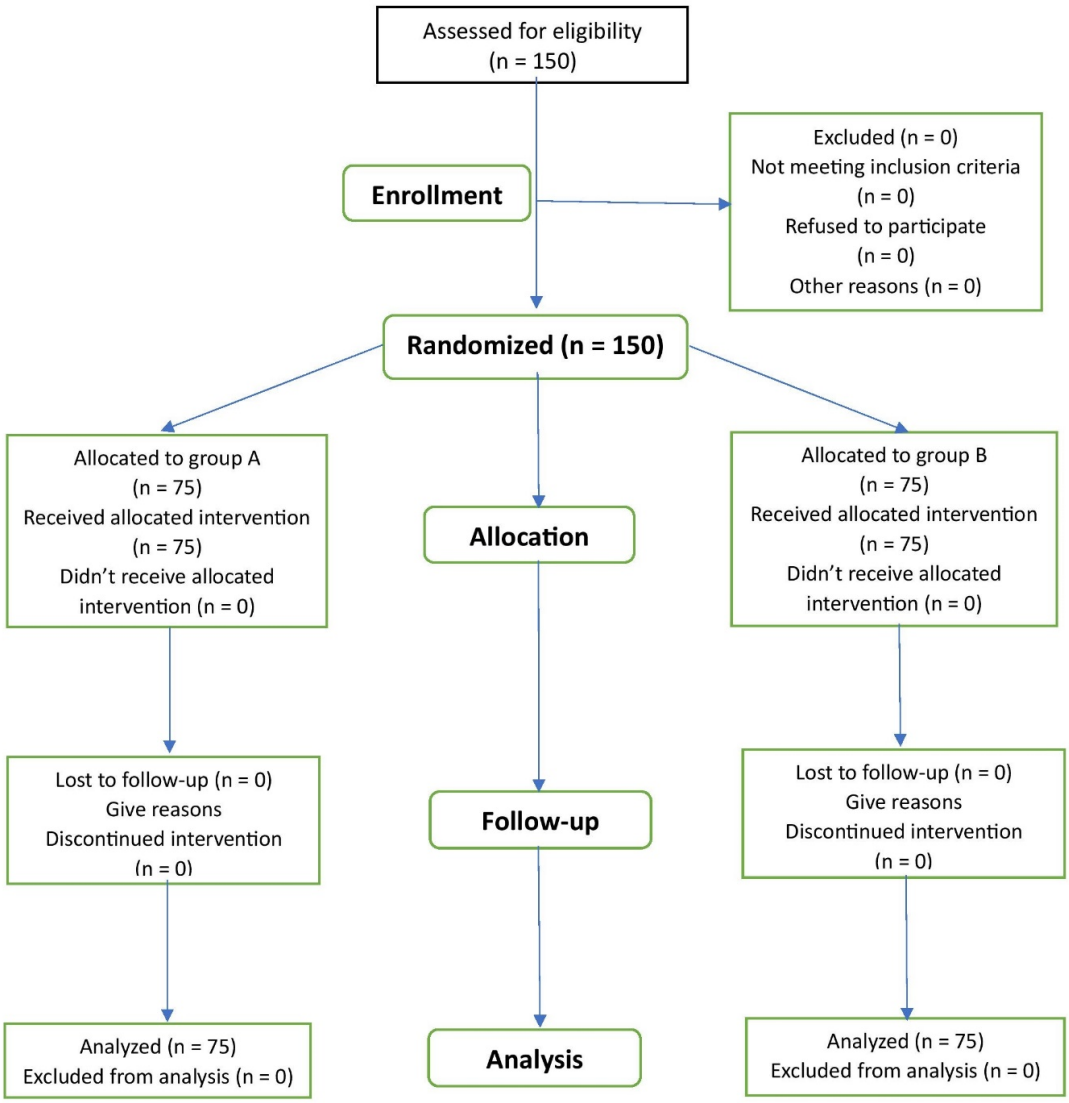

Diagram 1: Consort flow chart

Table 3: Demographic and clinical characteristics

Parameter	Group A	Group B	p value
Age (Years)	68.41 ± 6.98	69.15 ± 5.42	0.411
Weight (Kgs)	71.97 ± 7.09	74.2 ± 7.56	0.093
Height (Cms)	172.53 ± 6.44	173.85 ± 6.59	0.108
BMI	24.16 ± 1.83	24.5 ± 1.39	0.157
ASA Status			
I	15(20%)	10(13.33%)	0.273
II	60(80%)	65(86.67%)	
Duration of surgery (Mins)	61.33 ± 7.9	61.73 ± 9.13	0.726

maintains the core temperature by appropriate tuning of behavioral and physiological responses. Subarachnoid block impairs thermoregulation by abolishing tonic vasoconstriction below the blocked segments and also redistributes body heat from center to periphery leading to intraoperative hypothermia and shivering.[17,18]

Numerous modalities of therapy for the prevention and treatment of perioperative shivering exist. Unfortunately, the established guidelines for treatment options are rarely found in the available literature data. Among all pharmacological and non-pharmacological methods, ASA recommendations on the use of forced air warming and pethidine have been

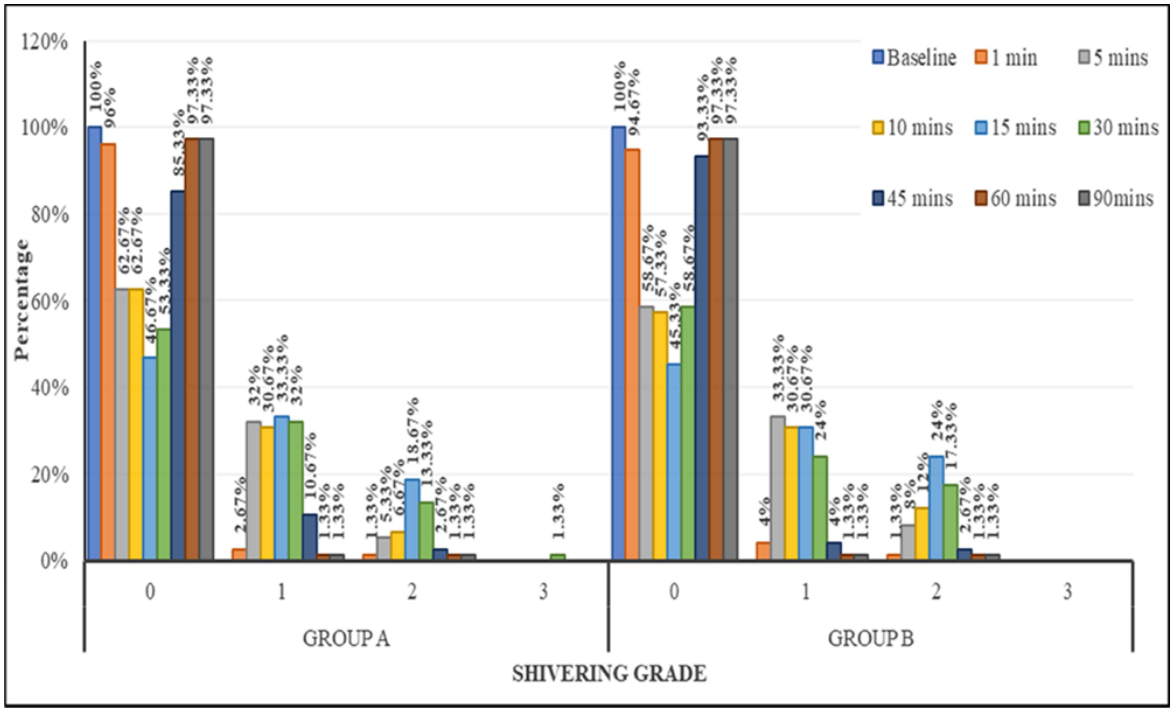

Figure 3: Distribution of shivering grades over time and groups

considered reliable and acceptable strategies.[19]

Apart from pethidine, various other opioid medications have been studied and suggested for the management of shivering, but they have associated potential and frequent side effects like sedation, nausea, vomiting, hypotension, and respiratory depression.[2,5,8,9] Many reports suggesting the use of a lower dose of intravenous tramadol administered immediately after the establishment of subarachnoid block for prevention and treatment of shivering have proven its efficacy with fewer side-effect profiles.[10,12,20] Oral tramadol is a simple, cost-effective, and readily available preparation, being considered for clinical trials as a prophylactic measure against intraoperative shivering following subarachnoid block.[1,21]

Tramadol is a synthetic opioid displaying dual action of being a mu receptor agonist and weak inhibitor of norepinephrine and 5-hydroxytryptamine (5-HT) neuronal uptake. After oral administration, the bioavailability of tramadol in adults is 68% and it is 20% protein-bound. Numerous well-established reviews are narrating the role of 5-hydroxytryptamine receptors in the thermoregulation mechanisms in humans. The preoptic nucleus of the hypothalamus releases 5-HT3 to activate heat production thereby increasing body temperature. 5-HT antagonists like tramadol prevent perioperative shivering by inhibiting the reuptake of 5-HT in the preoptic areas of the brain.[8,9,22] Tramadol also reportedly inhibits NMDA receptors at clinically useful concentrations.[8] Hereby we assume that tramadol also has effects in decreasing core to peripheral heat distribution.

The newer opioid analog tapentadol available exclusively in oral form has a mechanism of action similar to tramadol on noradrenaline reuptake and is approximately five times less potent than tramadol on 5-HT reuptake. In vitro studies suggest that dual actions of tramadol contribute to its analgesic properties whereas the noradrenergic activity of tapentadol likely to be more important than serotonergic activity. However, in vivo studies in humans suggest tapentadol is said to be as potent as tramadol with greater gastrointestinal tolerability.[23,24]

In our study, most episodes of shivering occurred within the first 30 minutes of subarachnoid block, and shivering lasted for the next 15 to 30 minutes. Maximal redistribution of heat from the center to the periphery takes place within the first 1 hour following the subarachnoid block.[25] This results in intraoperative hypothermia and shivering thermogenesis. The study drugs used do not have any thermogenic properties. So, their anti-shivering effects may be related to lowering the threshold of shivering. Ram et al. conducted a comparative study between tapentadol and tramadol on 60 patients for postoperative analgesia following lumbar laminectomy under general anaesthesia. None of the patients in both groups experienced post-anaesthesia shivering.[26] In contrast to this study, our results showed a comparable degree of shivering among both groups. Clinically we observed that incidence as well as degree of shivering was significantly reduced by premedication with study drugs.

In another observational single-center trial on 1385 adult patients, Eberhart et al. identified four independent potential risk factors for post-anaesthesia shivering; age, core temperature, duration of surgery, and type of surgery. They suggested that post-anaesthetic shivering can be predicted with acceptable accuracy using these four risk factors and it helps clinicians to rationally administer prophylactic anti-shivering agents.[27] Premedication with either tramadol or tapentadol is beneficial in elderly patients with a high risk of shivering during TURP due to decreased core temperature resulting from sympathetic blockade, cold ambient temperature, and/or cold irrigating fluids. Moreover, elderly patients are not able to initiate protective autonomic responses to cold.[1,5] Prophylaxis against shivering has proven to prevent postoperative morbidity and lead to shorter hospital stays for geriatric patients.

Tramadol, like other opioid analgesics, is frequently associated with nausea and vomiting, however, this study did not report any clinically significant adverse effects following oral administration of tramadol. Similarly, it was evident that the incidence of nausea or vomiting was significantly lower with tapentadol. None of the patients in either group experienced respiratory depression. Both medications demonstrated better tolerability than traditional strong opioids. Although the results on the efficacy and safety of tramadol and tapentadol in the study population are reassuring, there is still insufficient evidence to support their use in vulnerable geriatric patients.

5. Limitation

Although advanced age and extent of the subarachnoid block are critical factors for prediction of hypothermia, several other factors like ambient temperature, body composition, amount of blood loss, duration of surgical procedure, and volume of transurethral irrigation fluids are significant for determining the magnitude of hypothermia. A fixed dose of study drugs was used as a premedication for the whole study population. However, this might not have confounded the results considering the statistically comparable BMI among both groups.

6. Conclusion

In conclusion, both oral tramadol and oral tapentadol are equally effective in the prevention of perioperative shivering following subarachnoid block during transurethral resection of the prostate.

7. Source of Funding

None.

8. Conflict of interest

None.

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