

Comparative Study between Tramadol, Dexmedetomidine & Ketamine for Prevention of Post Spinal Shivering

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Abstract: **Background:** Post-operative shivering are one of the commonest problems after giving spinal anaesthesia worldwide. Hypothermia and prolonged surgeries along with cold OT temperature & IV fluids leads to the post operative shivering. The aim of our study is to decrease the incidence of post-operative shivering by comparing 3 drugs i.e. IV Tramadol, IV Dexmedetomidine and IV Ketamine. **Methodology:** 192 cases were selected on the basis of inclusion criteria & divided into three groups of 64 each. Spinal anaesthesia was given to all 192 patients & Inj. Tramadol was given to 64 patients, Inj. Dexmedetomidine was given to 64 patients and Inj. Ketamine was given to 64 patients. The duration of study was 18 months. The duration of Post-operative shivering, complications, Level of satisfaction was documented. **Result:** Post-operative shivering was commonly seen in all 192 patients but incidence of post operative shivering was minimum in Inj. Tramadol group, while incidence of recurrence of shivering was least in dexmedetomidine group. **Conclusion:** On comparing all the three groups, incidence of shivering was least in tramadol group as compare to other 2 drugs.

Keywords: Post-operative Shivering, Tramadol, Dexmedetomidine, Ketamine

1. Introduction

Spinal anaesthesia is mostly used for patients who require surgical anaesthesia for procedures of known duration involving either the lower extremities, perineum, pelvic girdle, or lower abdomen^[1-3]. Spinal anaesthesia may be useful when patients wish to remain conscious or when comorbidities such as severe respiratory disease or a difficult airway increase the risks of using general anaesthesia^[3,4]. Regional anaesthesia impairs both central and peripheral thermoregulatory control, thereby causing hypothermia during the intra- and post-operative periods^[5]. In addition to the anaesthetic procedures, surgery predisposes to peri-operative hypothermia by uncovered body surface areas exposing the skin to low temperature; exposed operating sites contribute to heat loss; insufflation of cold gases and irrigation fluids; lastly, by the administration of OT temperature intravenous fluids^[6]. Depending on the peri-operative conditions, the incidence of peri-operative hypothermia varies widely and ranges from 7% to more than 60%^[5]. Hypothermia during the surgery under spinal anaesthesia does not provoke as much thermal discomfort, consequently, patients do not complaint of feeling of cold, even when they are hypothermic^[7]. Therefore, hypothermia tends to progress throughout the surgery. Due to its more rapid onset, hypothermia occurs more quickly in the spinal than in epidural anaesthesia^[7].

Furthermore, the extent of hypothermia is directly dependent on the height of the blockade by spinal anaesthesia^[7]. Even mild hypothermia increases the incidence of complications like wound infection, post-operative ischaemic myocardial events, and blood loss during surgery, and it prolongs postoperative recovery^[8]. Collectively, these consequences

of peri-operative hypothermia delay the recovery, thereby, increasing the peri-operative costs. Therefore, maintaining normo-thermia is important for optimal surgical results as well as for patient safety and satisfaction. Hence, a team approach between surgery and anaesthesia is desirable to minimize loss of heat and promote active warming therapy.

Shivering-like tremor is common during neuraxial anaesthesia and has at least four potential aetiologies, nevertheless, hypothermia is responsible for post spinal shivering in most patients^[9]. Given significant muscle mass, a young adult male seems to be at the highest risk of developing post spinal shivering^[7-9]. Other risk factors for post spinal shivering are the length and type of the anaesthesia, length and type of surgery and whether an active peri-operative re-warming procedure was used or not. In conclusion, the more serious the hypothermia, the higher the probability (and severity) of post spinal shivering^[7-9]. Shivering causes an increase in pain secondary to muscular contractions on the operated site^[10]. The main pathophysiological effect of post spinal shivering is the increase in oxygen consumption. By affecting several muscular groups, post spinal shivering triggers an increase in metabolic demand. The post spinal shivering increases oxygen consumption by 40 to 100%, additionally, plasma catecholamine's and cardiac output increase in response to raised metabolic activity^[11]. Lastly, shivering movements may interfere with monitoring of blood pressure, electrocardiogram, and pulse oximetry.

Prevention of peri-operative hypothermia by preoperative skin surface rewarming efficiently limits the effects of internal heat redistribution. Covering the patient with a forced-air warmer for 30 minutes before the induction of

anaesthesia is enough to eliminate the phenomenon of internal redistribution^[12-14]. As patients mainly lose calories through radiation and convection on the skin surface, it also helps to raise the operating room temperature ($>23^{\circ}\text{C}$)^[12-14]. Indeed, simply covering the patient with the surgical drapes (excellent insulators), is sufficient to significantly reduce the loss of heat from the skin. When perfusion of a large volume of crystalloid or colloid or cold blood products is needed, intravenous solution warming to normal body temperature prevents the patient from hypothermia. The phenomenon of post spinal shivering is tending to decline thanks to a systematic approach for the prevention of hypothermia in the perioperative stage^[16,18-20]. However, if shivering occurs, it must be treated aggressively. On the contrary, a variety of pharmacological agents have been used (some without any evidence) for preventing or treating post spinal shivering. These include α_2 -agonists, opiates, tramadol, ketamine, magnesium sulphate, physostigmine, methylphenidate, nefopam, and serotonin 5-HT₃ antagonists.

The shivering centre is under the inhibiting control of the preoptic anterior hypothalamic region^[21]. The α_2 -agonists have been shown to possess the ability to prevent/reduce post spinal anaesthesia by acting on the central thermoregulatory framework. Dexmedetomidine is a highly selective α_2 -agonist that has been shown to have sedative, analgesic, and anaesthetic-sparing effects without significant respiratory depression. Dexmedetomidine lowers the threshold for vasoconstriction and shivering without changing the sweating threshold^[22-23]. Ketamine is a non-competitive NMDA receptor antagonist with the effect of thermoregulation. It may prevent post spinal shivering by decreasing core-to peripheral heat distribution. The effect of ketamine on post spinal shivering remained equally beneficial for both spinal and general types of anaesthesia^[24]. Tramadol, a centrally acting analgesic drug, is effective in the treatment of post-anaesthetic shivering after general and neuraxial anaesthesia. It inhibits the neuronal reuptake of noradrenaline and 5-hydroxytryptamine (5-HT), facilitates the 5-HT release and activates the μ -opioid receptors. Each of these actions is likely to influence thermoregulatory control^[25-26].

Tramadol, Dexmedetomidine, and Ketamine are common drugs used in diverse types of surgical and anaesthesia procedures. Although many published works of literature have investigated the potential effects of these three drugs for the prevention of post-anaesthetic shivering, there is no consensus on the appropriateness of these drugs, especially about the side effect profile. Thus, an evidence-based understanding and comparison of the benefits and risks of the effectiveness of these three drugs would aid in their rational and best use during spinal anaesthesia. Therefore, we undertook this to study the effectiveness of these commonly used drugs in anaesthesia to prevent post-spinal anaesthesia shivering along with their side effect profile.

2. Methodology

This was an observational, cross-sectional study conducted at a single centre. The present study was conducted at L.N. Medical College, Bhopal which is a tertiary health care centre. The data collection for this study was initiated after

the research protocol for this study was approved by the Institute's Ethical Committee on Human Research. This study was conducted at the Department of Anaesthesiology, LN Medical College Bhopal. It is a tertiary care institute. In the year 2019, a total of 2980 surgeries were assisted by the department. Further, a total of 1824 patients were given spinal anaesthesia in the same period. The total duration of the study was 18 months; from 1st December 2019 to May 2021. The recruitment of the participants and primary data collection was initiated once the protocol was approved by the Institute's ethical committee. The participants were recruited into the study after verifying that they fulfilled the Inclusion Criteria (Patients who gave written informed consent, Patients who were to undergo lower abdominal surgical procedures, to be performed under spinal anaesthesia - hernia, hydrocele, open appendectomy only, Patients who were categorised as belonging to grades I and II of the American Society of Anaesthesiologists (ASA), Patients of all genders, between 18-60 years. Those come under exclusion criteria were excluded (Patient's refusal to take part in the study, Patients with contraindication to spinal anaesthesia, Patients with ASA physical status III or more, Allergy to medicines to be used during the procedure and study, Failed spinal anaesthesia, Intra-operative patient temperature <35.5 , Patients with a history of alcohol or drug abuse, History of psychoactive medication, Intra-operative blood transfusion). All participants who fulfilled the selection criteria were recruited into the present study until the desired sample size in each group was completed. The participants were divided into three study groups according to the study drugs given by anaesthesiologist, Group T(n=64) (0.5mg/kg Tramadol diluted to 5ml with NS), Group D(n=64) (0.5mcg/kg Dexmedetomidine diluted to 5ml with NS), Group K(n=64) (0.5mg/kg Ketamine diluted to 5ml with NS). All study participants were visited one day before the surgery. A detailed pre-anaesthetic evaluation was completed one day before the surgery. Appropriate laboratory and radiological investigations were conducted. All patients were kept nil-per-oral from midnight before the day of surgery and were given tablet ranitidine 150 mg as premedication. The patient was shifted in the operation theatre and monitor was attached for peri-operative period vital monitoring including pulse rate, non-invasive blood pressure, pulse oximetry, 3-lead ECG, core body temperature. The body temperature warmed fluid therapy was done according to 4-2-1 formula (4 ml/kg/h for the first 10 kg of body weight, 2 ml/kg/h for the second 10 kg of body weight, and 1 ml/kg/h for the third hour 10 kg of body weight). Before the onset of anaesthesia, all subjects were preloaded with 10 ml/kg of Ringer Lactate solution over 30 minutes with the remaining dose of drugs compared in the study viz. Ketamine, Tramadol, and Dexmedetomidine. Under aseptic precaution, spinal anaesthesia was given at either L4-L5 or L3-L4 of the spinal cord using 25-gauge Quincke's spinal needle, midline, and in a sitting position. After the free flow of CSF was verified, a total of 3.0 ml of bupivacaine (heavy 0.5%) was injected within 10 seconds. Then, the patient, at once was immediately placed in the supine position and the patient's head was put $15-20^{\circ}$ above the horizon and no analgesic drug was given to the patient. The level of sensory block was verified using a bilateral blunted pin-prick test in the mid-clavicular line. When the level of block reached the desired level, the lower abdomen

surgery was started. Basal values were recorded 10 minutes before administering spinal anaesthesia. For the study, we recorded vital parameters every 5 minutes for the first 1 hour and thereafter every 15 minutes for the rest of the duration of surgery. The temperature of the operating room had been kept at 21–24°C, with a constant humidity of 70% and non-operative parts were covered by a layer of drapes (not pre-warmed), intravenous fluids, and drugs were kept at room temperature (37°C). After the surgery, the whole body was covered by a layer of cotton blanket and then, the patients were transferred to the recovery room. The temperature of the recovery room was similar for all patients, and no heating device was used for any patients. The body temperature was measured soon after shifting the patient to the recovery room and thereafter every 15 minutes till the effect of spinal anaesthesia weaned off.

Primary parameters are Core body temperature during Pre-, Intra-, and Postoperative period, Incidence of shivering, Intensity of shivering, Duration of shivering, Time after administering spinal at which shivering started, Recurrence of shivering, Response of shivering to medication, Side Effects (Nausea, Vomiting, Bradycardia, Hypotension, Sedation level), Any statistical difference between the two proportions was estimated using the Chi-square test. Any statistical difference between the two means was estimated using the T-test. Non-Parametric tests (e.g., Friedman test) were used to make a statistical inference in case the data were not normally distributed. A p-value <0.05 was considered statistically significant.

3. Result

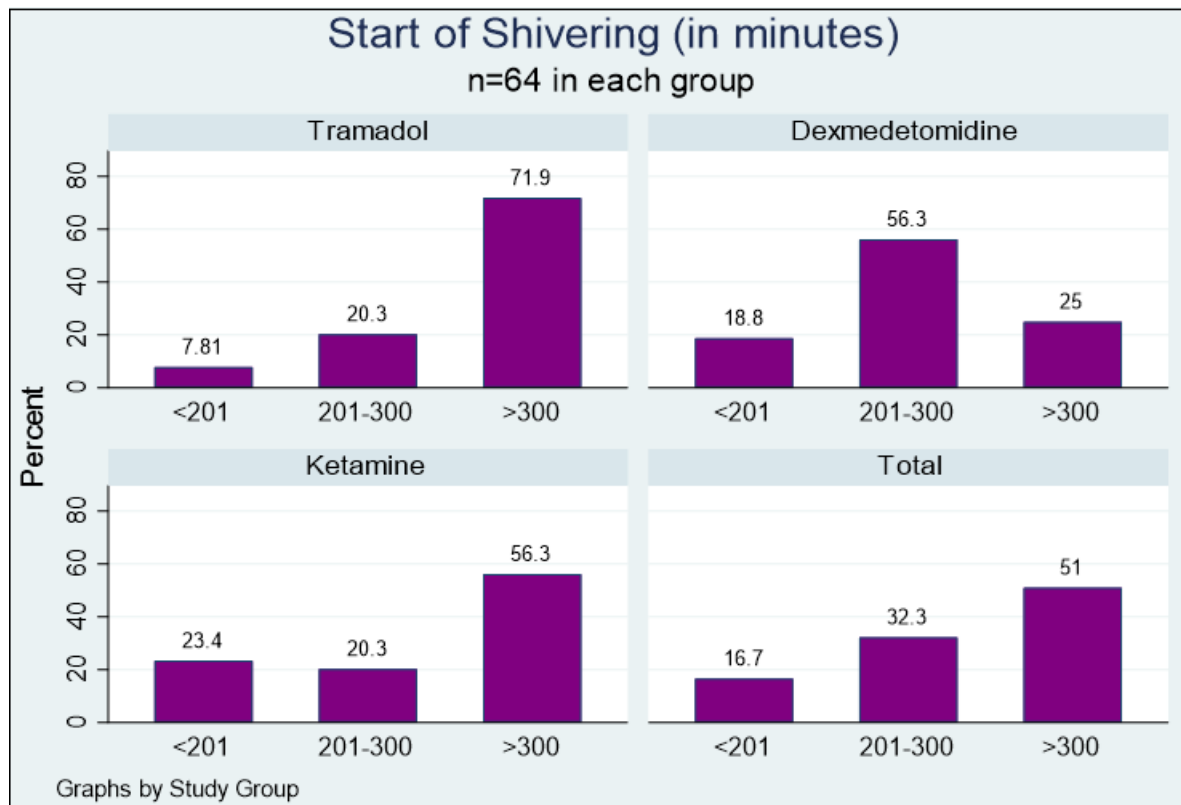
In our study, a total of 192 participants were enrolled: 64 participants in each of the three study groups i.e. Tramadol, Dexmedetomidine, and Ketamine. Overall, a maximum of 35.9% of participants belonged to the age group 51-60 years and a minimum of 12.5% of participants belonged to the age group 31-40. The mean age of the participants in the group Tramadol, Dexmedetomidine, and Ketamine was 42.9, 44.7, and 44.7 years, respectively. There was no statistically significant difference between the three study groups in terms of mean age. Overall, there were approximately four times as many male participants in comparison to female participants. There was no statistically significant difference between the three study groups in terms of the gender of participants. The mean weight of the participants in the group Tramadol, Dexmedetomidine, and Ketamine was 61.5, 62.6, and 61.1 kilograms, respectively. On comparison between the three groups, the difference in mean weight of participants was statistically not significant between any of the three-drug pairs. Overall, hernioplasty (54%) was the most common followed by hydrocelectomy (23%), and open appendectomy was the least common type of surgery. Similarly, in each of the study groups, hernioplasty was the most common type of surgery.

The prevalence of nausea in the Tramadol, Dexmedetomidine, and Ketamine groups was 18%, 1.5%, and 3% respectively. The difference in the proportion of

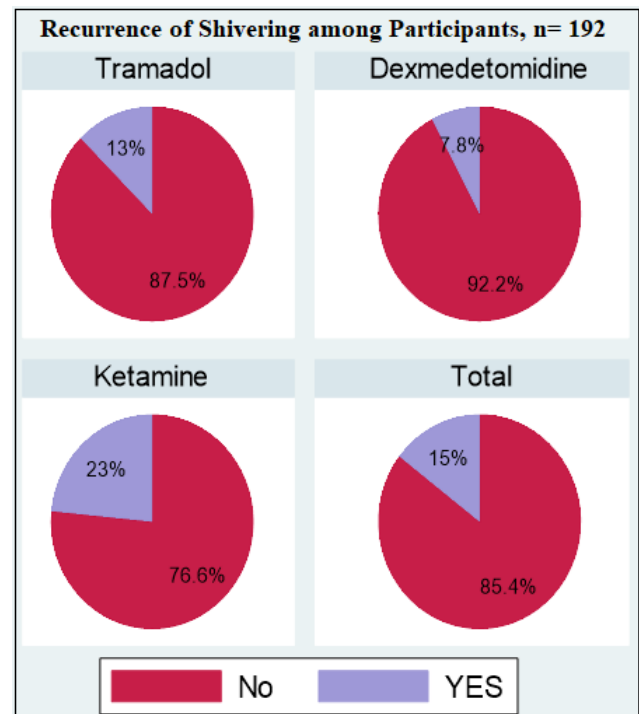
participants who experienced nausea was statistically significant between the first two pairwise comparison study groups. The prevalence of vomiting in the Tramadol, Dexmedetomidine, and Ketamine groups was 21%, 1.5%, and 6% respectively. The difference in the proportion of participants who experienced vomiting was statistically significant between each of the three study groups.

Overall, 5.7% of the participants experienced hypotension during the period of observation. Group-wise: 3.1%, 9.3% and 4.6% participants in Tramadol, Dexmedetomidine, and Ketamine group, respectively had an episode of hypotension during the period of observation. The occurrence of hypotension was statistically significant between dexmedetomidine and the other two drug groups. The occurrence of hypotension was statistically not significant between Tramadol and Ketamine ($p=0.099$). Comparatively, only 4.6% of the participants experienced bradycardia during the period of observation. Group-wise: 1.5%, 7.8% and 4.6% participants in Tramadol, Dexmedetomidine, and Ketamine groups, respectively, had an episode of bradycardia during the period of observation. On pairwise comparison between the three study groups, the occurrence of bradycardia was statistically significant only between Tramadol and Dexmedetomidine. Overall, 14.5% of the participants experienced sedation during the period of observation. Group-wise: 1.5 %, 20.3% and 21.8% participants in Tramadol, Dexmedetomidine, and Ketamine groups, respectively experienced sedation. The occurrence of sedation was statistically significant between Tramadol and the other two groups. The occurrence of sedation was statistically not significant between Dexmedetomidine and Ketamine ($p=0.068$).

Overall, the test drugs failed to prevent the occurrence of shivering in only 3.13% of participants. Groupwise, the occurrence of shivering was seen in 1.5%, 3.13% and 4.69% participants in group Tramadol, Dexmedetomidine, and Ketamine, respectively. On pairwise comparison, the difference in the occurrence of shivering was statistically not significant between any group. Overall, only 14.5% of participants had a recurrence of shivering during the period of observation. Group-wise: 12.5%, 7.8% and 23.4% participants in Tramadol, Dexmedetomidine, and Ketamine groups, respectively had a recurrence of shivering during the period of observation. On pairwise comparison between the three study groups, the recurrence of shivering was statistically significant between dexmedetomidine and ketamine only ($p= 0.015$), it was more in K group. The time for the 'end of effect' of the drug as measured by the modified Bromage scale score to be 0. Group-wise, the meantime for the 'end of effect' of the drug was longest among patients given Tramadol and it was shortest among patients given ketamine. However, the difference in the meantime for the end of effect was statistically significant only between Tramadol and Ketamine ($p= 0.0043$). Further, when comparing the median time for the 'end of effect' of the drug, then it was shortest among patients given dexmedetomidine. The range of end of the effect of the drug was almost the same across three-study groups.



At baseline, the mean heart rate was lowest in group K and highest among group T participants, however, this difference was not statistically significant. In each of the three study groups, there was a significant decline in the pulse rate around 10 minutes after giving spinal anaesthesia. None of the participants in our study had an episode of either bradycardia or tachycardia during observation. In Group T, the maximum decline (-4.7%) from the baseline was observed 10 minutes after giving SA. In the first hour after giving SA, the maximum increase in heart rate (5.8%) was seen after 15 minutes. At 60 minutes after giving SA, the heart rate was 4.4% higher than the baseline value. In Group: D, the maximum change (increase) from the baseline was observed at 15 and 60 minutes after SA. The heart rate increased gradually during most of the observation period in group D. A decline in heart rate, as seen in group T, was not seen at any time point among participants in group D. In Group: K, the maximum increase (11.7%) from the baseline was observed at 15 and 60 minutes after SA. The heart rate increased gradually during most of the observation period in group K. A decline in heart rate, as seen in group T, was also seen at 10 minutes among participants in group K.



The body temperature among participants in each of the three groups either remained constant around baseline or decreased slightly but did not increase significantly. The change in the body temperature in each of the three study groups during the first 150 minutes of the surgery was statistically not-significant (Friedman Test: $p > 0.05$). The body temperature among participants in each of the three groups either remained constant around baseline or decreased slightly but did not increase significantly. The body temperature of the participants became equal to baseline temperature about five and half-hour after surgery. The change in the body temperature in each of the three

study groups during the first 150 minutes of the surgery was statistically not-significant (Friedman Test: $p > 0.05$).

4. Discussion

In a large survey of patients given spinal or epidural anaesthesia, more than two-thirds of participants reported that shivering during the post-operative period was among the most annoying/discomforting experience. Several studies have reported that the incidence of shivering in the post-spinal period ranges from 40% to 100%. Fern et al. reported that 59% of participants in their study reported grade 3 or more severe shivering^[27]. Mittal G et al. reported that grade 3 shivering during/after spinal anaesthesia was seen among 100% of participants undergoing lower abdominal surgeries^[28]. Wason et al. reported that 72% of participants in their control group experienced shivering^[29]. As mentioned earlier, shivering is not only uncomfortable to patients but does have physiological consequences. Further, if shivering is either very severe or prolonged or both, it leads to pathological consequences. Given the near-universal incidence of shivering in the post-spinal period and its pathological consequences, it is, therefore, of paramount importance for any anaesthesiologist to prevent (preferentially) or to treat it at the earliest. In the present study, we assessed the effectiveness of three popularly used drugs i.e. Tramadol, Dexmedetomidine & Ketamine for preventing the incidence of shivering during/after spinal anaesthesia.

In our study, we conducted an observational study to determine the effectiveness of prophylactic doses of tramadol (0.5mg/kg), dexmedetomidine (0.5mcg/kg), and ketamine (0.5mg/kg) in preventing the post-spinal anaesthesia shivering among patients undergoing lower abdominal surgery. We enrolled a total of 192 participants with sixty-four participants in each group. Azam M et al. conducted a study to compare the prophylactic use of tramadol and ketamine on the incidence of post-spinal anaesthesia shivering among patients undergoing caesarean section^[30]. They conducted a randomized study involving four hundred women: (0.5mg/kg) Ketamine and (2mg/kg) tramadol. Bozgeyik S et al. conducted a study to evaluate the effectiveness of dexmedetomidine and tramadol in preventing post-spinal anaesthesia shivering^[31]. A total of 90 participants were randomised to either receive dexmedetomidine (0.5µg/kg), tramadol (100 mg) or 100 ml NS alone. Lema GF et al. conducted a study to compare the efficacy of intravenous ketamine with tramadol for the prevention of shivering in patients who underwent caesarean delivery under spinal anaesthesia^[32]. They enrolled a total of 123 patients: group S received saline, group K received ketamine (0.2 mg/kg) and group T received tramadol (0.5 mg/kg). Wason R et al. conducted a trial to evaluate the effectiveness of prophylactic doses of intravenous ketamine, clonidine, and tramadol for the prevention of shivering^[33]. They enrolled a total of 200 participants: saline as a placebo (group P), ketamine (0.5 mg/kg), Clonidine (75 mcg) and Tramadol (0.5 mg/kg). Usta B et al. conducted a randomised controlled trial to evaluate the efficacy of dexmedetomidine in the prevention of shivering after spinal anaesthesia^[34]. A total of 60 participants were randomised to receive either dexmedetomidine (1µg/kg followed by 0.4µg/kg IV infusion

till the end of surgery) or a placebo (normal saline)^[33]. Sathya Moorthy V et al. conducted an observational comparative study to assess the effectiveness of dexmedetomidine and tramadol in preventing shivering in patients undergoing lower abdominal surgeries under subarachnoid block^[35]. A total of 80 patients were included: Group D (dexmedetomidine) and Group T (tramadol).

Fern and Misiran conducted a study to determine the effectiveness of dexmedetomidine, pethidine, and tramadol for the treatment of shivering during spinal anaesthesia by enrolling a total of 60 participants^[36]. In the study, Dexmedetomidine was administered at a dose of 0.5µg/kg, pethidine at 0.5mg/kg and tramadol at 0.5mg/kg. Kundra TS et al. conducted a study to compare the efficacy of dexmedetomidine and tramadol in the treatment of post-spinal anaesthesia shivering^[37]. They conducted a randomized controlled trial by enrolling a total of one hundred patients with shivering after spinal anaesthesia. Mittal G et al. conducted a study among 50 participants comparing the efficacy of dexmedetomidine and tramadol in the treatment of post-spinal anaesthesia shivering: dexmedetomidine (0.5µg/kg) or tramadol (0.5mg/kg)^[38]. Lakhe G et al. conducted a study to evaluate the efficacy of ondansetron, ketamine, and tramadol for the prevention of shivering^[39]. They conducted a randomized controlled study by enrolling a total of 120 participants into 4 groups; Normal saline, Ondansetron (4mg), Ketamine (0.25mg/kg), and Tramadol (0.5mg/kg).

In our study, overall 14.5% of the participants experienced sedation during the period of observation. Group-wise: 1.5 %, 20.3% and 21.8% participants in Tramadol, Dexmedetomidine, and Ketamine groups, respectively experienced sedation. The occurrence of sedation was statistically significant between Tramadol and the other two groups. The occurrence of sedation was statistically not significant between Dexmedetomidine and Ketamine. Bozgeyik S et al., reported that participants receiving dexmedetomidine were more sedated in comparison to participants in the tramadol group and this difference was statistically significant^[40]. Fern et al. reported that none of the participants' given tramadol was sedated^[41]. Kundra et al. reported that participants receiving dexmedetomidine were more sedated than participants receiving tramadol ($P < 0.001$)^[42]. In their study, about three-fourths of the total participants given dexmedetomidine had a sedation score of 4. In comparison, all participants receiving tramadol had sedation of Grade 2. They further reported that the increased sedation was beneficial for the participants as it decreased anxiety, thereby making recovery more comfortable. In our study, the incidence of shivering was compared among the three groups. & overall, the test drugs failed to prevent the occurrence of shivering in only 3.13% of participants. Individually, the occurrence of shivering was seen in 1.5%, 3.13% and 4.69% participants in group Tramadol, Dexmedetomidine, and Ketamine, respectively. On pairwise comparison, the difference in the occurrence of shivering was statistically not significant between any group.

5. Conclusion

We concluded that, the incidence of shivering was 3.13% among all participants. The highest incidence of shivering was seen in Ketamine and lowest incidence of shivering was seen in Tramadol group. The highest rate of recurrence of shivering was seen among participants given Ketamine and lowest incidence of recurrence of shivering was seen among Dexmedetomidine group.

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