Comparison of Meperidine, Ketamine, Magnesium Sulphate, and Ondansetron for Post-spinal Shivering Prevention during Transurethral Resection of Prostate

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Abstract

Purpose: Shivering during surgery is a relatively frequent consequence. Although perioperative shivering and its impacts are well understood, prophylaxis is often disregarded. In order to assess the effectiveness and safety of meperidine, low-dose ketamine, magnesium sulphate, and ondansetron in avoiding perioperative tremor in patients having transurethral resection of prostate under subarachnoid block, this research was conducted.

Method: In this randomized controlled investigation, 200 patients aged 60 to 70 years were divided equally into one of four groups. meperidine 0.3mg\kg (group M), Ketamine 0.25 mg\ kg (Group K), magnesium sulphate 40mg\kg diluted in 100ml normal saline over 10min. (Group MS), and Ondansetron 0.1 mg\kg (Group O). There have been reports of side effects including hypotension, sedation, nausea and vomiting, hallucinations, and respiratory depression.

Results. Postoperative shivering (POS)was observed in 8 (16%), 10 (20%), 22 (44%), and 26 (52%) of group M, K, MS, and O, respectively. The frequency of hypothermia did not vary across groups (P = 0.217). There were no discernible intergroup variations in the prevalence of bradycardia (P=0.190). In the K group, there were considerably fewer cases of hypotension (8%). Sex, and two patients from groups MS and K, respectively, had RAMSAY sedation scores of 4 recorded. In group K, 4%,12%, and 12% of the patients were found to have headache, hallucination, and nystagmus respectively. In none of the four research groups was there a case of respiratory depression.

Conclusion. Low-dose meperidine, low-dose ketamine, magnesium sulphate, or ondansetron given as a preventative measure all had a strong anti-shivering effect with few side effects. Low dosage ketamine, however, has the benefit of being less likely to cause hypotension, nausea, and vomiting than meperidine.

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1-INTRODUCTION

A repeated, spontaneous, and involuntary muscle activity is what is meant when someone shivers. Due to vasodilation, one of the common issues during and after subarachnoid anesthesia is that it might encourage rapid heat loss and produce a peripheral redistribution of body heat, ultimately leading to hypothermia that reduces the shivering threshold.[1,2]

In individuals with a history of cardiac or pulmonary disorders, shivering may potentially lead to serious problems including elevated oxygen demand that causes lactic acidosis, hypoxemia, and elevated carbon dioxide generation. Shivering is not a deadly occurrence. Additionally, it enhances wound pain, worsens intraocular and intracerebral pressure, may be irritating for patients, hinders blood pressure, pulse oximetry, and ECG monitoring, which may represent a risk to patient safety.[3,4]

Due to coexisting medical conditions, patients having transurethral resection of the prostate (TURP) are at significant cardiac risk.[5]

Geriatric people are more susceptible to the danger of hypothermia-induced shivering while under anesthesia because their lower core temperatures do not trigger protective autonomic response. By inhibiting vasomotor and shivering responses and the associated transfer of heat from the center of the body to the peripheral tissue, neuraxial blockade gravely hampers the control of body temperature.[6]

There are several pharmacological and non-pharmacological approaches that may be used to treat intraoperative shivering. [7]

Shivering may be treated with pethidine, which has been done for many years. [8]

It is thought that ketamine, a competitive N-methyl-D-aspartate receptor antagonist, inhibits postoperative shivering by causing non-shivering thermogenesis through either effect on the hypothalamus or the norepinephrine-induced beta-adrenergic impact.[9]

Magnesium sulfate is a naturally occurring calcium antagonist and a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors. It has been

utilized as an adjuvant analgesic to decrease the usage of opioids in anesthesia, as a bronchodilator, neuroprotective, or antiarrhythmic drug to enhance onset of effect and lessen the requirement for muscular relaxation. [10]

Ondansetron's anti-shivering action operates independently of the intraoperative core temperature due to a central mechanism that inhibits the shivering response.[11]

In this research, we examine how meperidine, ketamine, magnesium sulphate, or ondansetron affect patients having TURP under spinal anesthesia in terms of preventing intraoperative and postoperative shivering.

2-METHODS

2.1 *study population*

A prospective, randomized, interventional control trial was carried out at Alzahraa university hospital from the period of January 2022 to March 2023. Patients provided written informed permission after the hospital's ethical committee approved it.

2.2 Participants

We include 200 patients divided into 4 equal groups (50 each), named meperidine group (group M), Ketamine group (group K), magnesium sulfate group (group MS), and Ondansetron group (group O).

2.3 Inclusion criteria

A group of patients between the ages of 60 and 70 who were having TURP under subarachnoid block (SAB) received an anesthesia level of I, II, or III from the American Society of Anesthesiologists.

2.4 Exclusion criteria

Exclusion criteria for the trial included those with known thyroid, Addison's, Parkinson's, Raynaud's syndrome, cardiac, liver, or renal problems, a history of convulsions or epilepsy, bronchial asthma, or a history of allergy to the study's interventional agents. patients who need blood transfusions during surgery or who initially have a fever in the axilla below 36.0°C or above 37.5°C, the usage of sedative-hypnotic drugs, vasodilators, antidepressant medication with monoamine oxidase and selective serotonin reuptake inhibitors, and benzodiazepines. Patients with contraindications to SAB or insufficient SAB needing general anesthetic augmentation were also excluded from the research.

2.5 Randomization.

The computer-generated randomization map allocated the patients to one of four groups. Each trial drug was prepared blindly and administered by a blinded anesthesiologist for group prescription immediately after SAB. Group M patients received meperidine 0.3mg\kg, (Group K) Ketamine 0.25 mg\ kg, (Group MS) magnesium sulphate 40mg\kg diluted in 100ml normal saline over 10min, and (Group O) Ondansetron 0.1 mg\kg.

2.6 Study protocol.

Each subject received 15 mL of room-temperature lactated Ringer's solution per kilogram of ideal body weight (IBW) before SAB. SAB was injected using a 25G sharp spinal needle and 2.5ml of hyperbaric bupivacaine+25ug fentanyl under stringent aseptic circumstances at the L4-5 or L3-4 interspace. A nasal canula was used to provide more oxygen throughout the process, beginning with the SAB injection. Automated noninvasive blood pressure, pulse oximetry (SpO2), and ECG monitoring are performed on all trial participants. Blood pressure, heart rate, pulse, and oxygen saturation were all monitored at baseline. The significant benefit of infrared thermometry is that it can measure temperature at a distance. The body temperature was tracked using a tympanic membrane probe and recorded every 10 minutes until the procedure was complete. Scores for shivering were recorded every 10 minutes during surgery and every 10 minutes for 90 minutes after.

The primary operating room's temperature was kept between 20 and 22 degrees Celsius. All surgical patients have a standard blanket placed over their chest and belly throughout the procedure. Additionally, a surface heater that blows hot air below the patient's blanket has been included. The standard saline irrigation solution was maintained at room temperature throughout the procedure.

2.7 Measurement

At 10-minute intervals during the process, the onset and intensity of shivering were noted. According to Wrench, shivering was scored on a four-point scale (table 1). [12]

Table 1: Wrench shivering four-point scale.

Grade of shivering	Clinical signs
Grade 0	There is no shivering
Grade 1	any one or more of the following Without any discernible muscular movement, a piloerection, peripheral cyanosis, and vasoconstriction
Grade 2	one muscle type alone showing visible muscle activity
Grade 3	many muscle units that are clearly active
Grade 4	All-over body movement using large muscles

If a shivering score ≥3 was achieved at any time within 15 min after SAB, the trial medication was thought to be unsuccessful and tramadol O.5 mg\kg was injected as rescue in these patients.
Sedation was reported based on RAMSAY sedation Scale (table 2).[13]

Table 2: Ramsay sedation score.

Level	***Response***
1	awake and tense, riled up, or restless
2	awake, obedient, willing to receive ventilation, oriented, or at peace
3	Awake, only reacts to orders
4	Sleep, rapid eye movement, glabellar tapping, or loud noises
5	Unresponsive to light, the glabella tapping, or loud noises when dozing off
6	Unresponsive to loud noises, glabella taps, or light while asleep

When the tympanic temperature is regularly checked, hypothermia is defined as a body temperature below 35.5°C at any point during operation.
A fall in mean arterial pressure (MAP) of greater than 20% from the initial value is regarded as hypotension. Any MAP measurement below 65 mm Hg or a decline in MAP of more than 25% was regarded as severe hypotension. Ephedrine 6 mg incremental IV boluses were used to treat episodes of severe hypotension, followed by further IV infusions of Ringer's lactate as required. Any patient complaints, such as nausea , vomiting, or fits, were noted. A decrease in SpO2 below 92% saturation or a respiratory rate of less than 8 per minute is regarded as respiratory depression. Hypotension, hallucinations, nausea and vomiting, drowsiness, and respiratory depression were all noted as adverse effects.

2.8 Primary and secondary results

Meperidine, ketamine, magnesium sulphate, and ondansetron were evaluated and compared for their effectiveness and safety in preventing POS in patients undergoing TURP surgery under SAB. The secondary outcomes included research on the adverse effects of these medications (respiratory depression, hallucinations, sedation, nausea, and hypotension).

Sample size calculation

The sample size was determined utilizing MedCalc version 11.3.0.0 and in accordance with a prior investigation conducted by Jabalameli et al. (2021) who stated in his study that the four groups' average shivering severity was 1.33 ±0.5, 0.17± 0.8, 1.09± 0.4, and 1.13± 0.39, respectively. The variations between the four groups were considerable (P = 0.005) after adjusting the confidence interval to 95%, the test's power to 90%, and the required minimum sample size of 12 patients per group was discovered.

STATISTICAL ANALYSIS

The resulting data were gathered, updated, coded, and input into the SPSS software version 23 (IBM, USA) statistical package for social science. provided quantitatively as mean ± SD and range and qualitatively as numbers and percentages. Chi square test is utilized to compare groups based on qualitative criteria. just one ANOVA for comparing quantitative parameters between groups using a parametric distribution. Comparing groups based on quantitative parameters with a non-parametric distribution utilizing the Kruskal-Wallis test. The p-value was regarded as significant at the level of <0.05, and the confidence interval was set at 95%.

RESULTS

In 200 patients receiving elective TURP under SAB, the effectiveness of prophylactic meperidine, ketamine, magnesium sulphate, and ondansetron in avoiding post spinal shivering was examined. The demographic information can be seen in Table 3. Age, ASA, and body mass index (BMI) did not significantly vary across groups. Last but not least, 200 patients were examined in groups M (n = 50), K (n = 50), MS (n = 50), and O (n = 50).

Table 3: Demographic data of the four study groups

	Group M No. = 50	Group K No. = 50	Group MS No. = 50	Group O No. = 50	Test value	P-value
Age (mean ± SD)	66.26±6.33	65.38±5.26	65.15±6.02	64.92±5.66	0.505•	0.679
BMI (mean ± SD)	25.83±4.83	26.31±3.37	25.82±3.84	26.65±3.34	0.536•	0.658
ASA class n (%)						
ASA I	17 (34%)	18 (36%)	16 (32%)	18 (36%)	1.276*	0.972
ASA II	18 (36%)	16 (32%)	16 (32%)	20 (40%)		
ASA III	15 (30%)	16 (32%)	18 (36%)	14 (28%)		

Data were presented as mean ± SD and numbers with percentages.; •: One Way ANOVA; *: Chi-square test.

Ringer lactate preloading volumes varied from 825 to 1260 mL (15 mL kg-1 of IBW).

The frequency of hypothermia did not vary across groups (P value was 0.217) (Table 4). Groups K and M saw a very significant decline in POS (P< 0.001) (Figure 1). Groups K and M had the least severe shivering (Table 4). Nevertheless, there was a statistically substantial increase in the frequency of shivering in the intergroup comparison of group O and MS with groups K and M.

Table 4: Incidence of hypothermia, postoperative shivering, and shivering scale of the four study groups

	Group M No. = 50	Group K No. = 50	Group MS No. = 50	Group O No. = 50	Test value	P-value
Hypothermia	42 (84%)	44 (88%)	48 (96%)	46 (92%)	4.444	0.217
Postoperative shivering	8 (16.0%)	10 (20%)	22 (44.0%)	26 (52.0%)	21.257	<0.001
Shivering Scale						
Median (IQR)	0 (0 – 0)	0 (0 – 0)	0 (0 – 1)	1 (0 – 2)		
Mean ± SD	0.22 ± 0.55	0.30 ± 0.68	0.76 ± 1.08	1.08 ± 1.31	23.511	<0.001
Range	0 – 2	0 – 3	0 – 4	0 – 4		
0	42 (84%)	40 (80%)	28 (56%)	24 (48%)		
1	5 (10%)	6 (12%)	12 (24%)	10 (20%)		
2	3 (6%)	3 (6%)	6 (12%)	8 (16%)	19.535	0.021
3	0 (0%)	1 (2%)	2 (4%)	4 (8%)		
4	0 (0%)	0 (0%)	2 (4%)	4 (8%)		

Numbers and percentages were used to portray the data.; •: One Way ANOVA; *: Chi-square test.

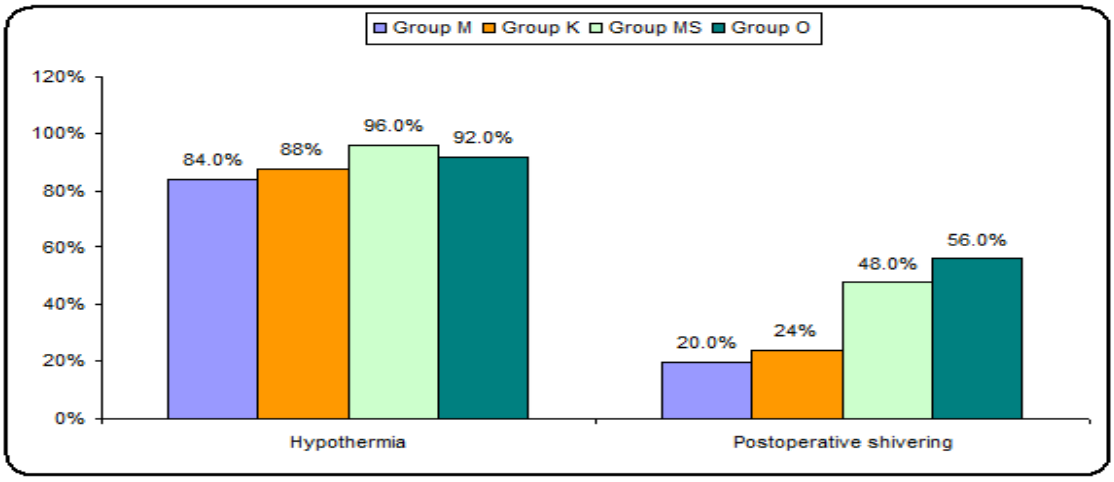

Figure 1: Incidence of hypothermia, postoperative shivering, and shivering scale of the four study groups

Regarding variations in blood pressure, group K showed a substantially decreased frequency of hypotension (Table 5). There were no discernible intergroup variations in the prevalence of

bradycardia (P=0.190) (Table 5). In group O, there was no occurrence of nausea or vomiting, while group K had a lower incidence. According to table 5, 4%, 12%, and 12% of the patients in group K, respectively, had headaches, hallucinations, and nystagmus (Figure 2). In none of the four research groups was there a case of respiratory depression.

Table 5: comparison of the four study groups as regard side effects

Side effects	Group M, n (%)	Group K, n (%)	Group MS, n (%)	Group O, n (%)	Test value*	P-value
Bradycardia	8 (16%)	4 (8%)	12 (24%)	8 (16%)	4.762	0.190
Hypotension	20 (40%)	4 (8%)	24 (48%)	12 (24%)	22.476	<0.001
Nausea &vomiting	24 (48%)	4 (8%)	8 (16%)	0 (0%)	44.986	<0.001
Headache	0 (0%)	6 (12%)	0 (0%)	0 (0%)	18.557	<0.001
Hallucination	0 (0%)	12 (24%)	0 (0%)	0 (0%)	38.298	<0.001
Nystagmus	0 (0%)	12 (24%)	0 (0%)	0 (0%)	38.298	<0.001

*: Chi-square test

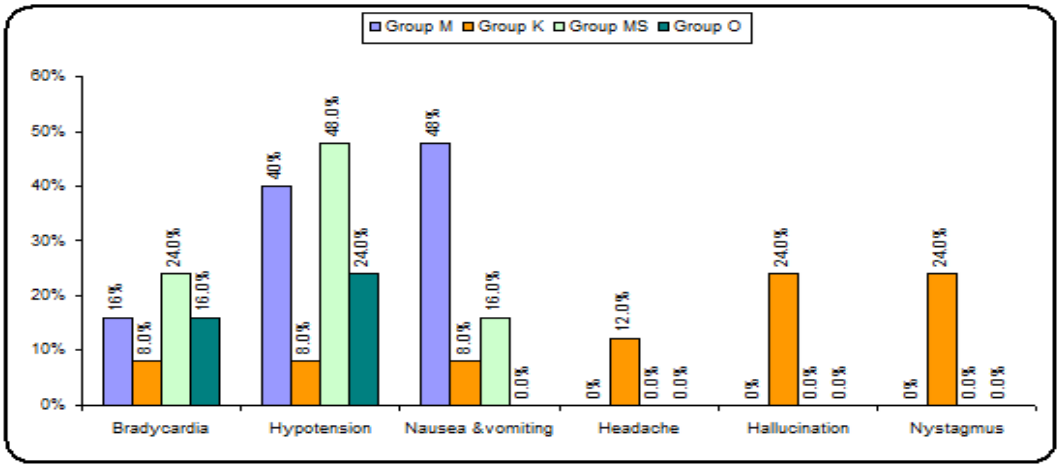

Figure 2: comparison of the four study groups as regard side effects

Comparing the total sedation score among the four research groups revealed substantial differences. No patient in either group had a sedation score of 5 or 6 (table 6). A RAMSAY sedation score of 4 was recorded for 6, and 2 patients, respectively, in the groups MS and K (Figure 3).

Table 6: Comparison of the research groups' RAMSAY sedation scores

RAMSAY sedation scores	Group M	Group K	Group MS	Group O	Test value	P-value
Median (IQR) Mean±SD Range	2 (2 – 2) 1.92 ± 0.49 1 – 3	2 (2 – 3) 2.20 ± 0.69 1 – 4	2 (2 – 3) 2.56 ± 0.76 1 – 4	2 (2 – 2) 1.68 ± 0.62 0 - 2	40.264≠	<0.001
Score 0 Score 1 Score 2 Score 3 Score 4 Score 5 Score 6	0 (0%) 8 (16%) 38 (76%) 4 (8%) 0 (0%) 0 (0%) 0 (0%)	0 (0%) 6 (12%) 30 (60%) 12 (24%) 2 (4%) 0 (0%) 0 (0%)	0 (0%) 2 (4%) 24 (48%) 18 (36%) 6 (12%) 0 (0%) 0 (0%)	4 (8%) 8 (16%) 38 (76%) 0 (0%) 0 (0%) 0 (0%) 0 (0%)	55.218*	<0.001

P>0.05: Non-significant (NS); P <0.05: substantial (S); P <0.01: Highly substantial (HS); ≠: Kruskall-Wallis test; *: Chi-square test

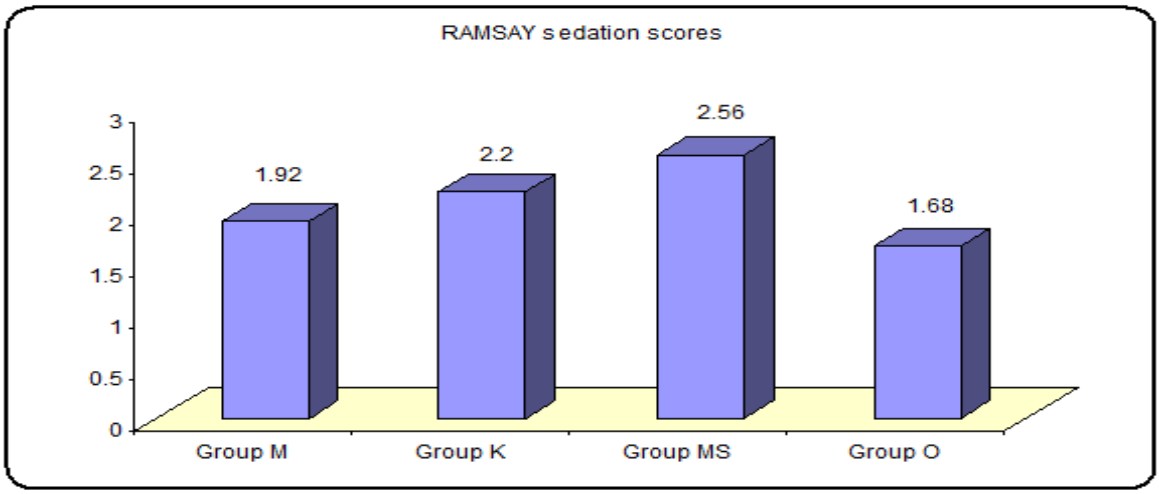

Figure 3: Comparison of the research groups' RAMSAY sedation scores

DISCUSSION

The fact that shivering was much less common in all treatments groups was a notable result of our research. According to the literature, the reported prevalence of shivering ranges from 41% to 60% if preventive measures are not used. [13,14,15] As a result, the risk of shivering was substantially reduced in the intervention group. It was recorded that there were 16% in group M, 20% in group K, 44% in group MS, and 52% in group O.

A different incidence has been observed in some studies using 5-HT3 antagonists to reduce shivering during spinal anesthesia. *Noaman et al* compared the tremor preventing effect of ondansetron 4mg with meperidine in spinal anesthesia, found a similar anti-tremor impact and documented a tremor incidence of approximately 15% in the ondansetron group.[16]

Nallam et al utilized a greater dose of 8mg ondansetron to prevent tremors during SAB low segment caesarean section in their study of Indian patients and recorded a tremor incidence of 10%.[17] Other authors have observed similar results. *18-20.* In our research, a lower dose of 0.25 mg kg-1 of ketamine was utilized to reduce its side impacts and maximize potential benefits. In a study performed under general anesthesia, *Corredor et al.* tremors were present in 28% and 13% of patients receiving ketamine 0.5 mg kg-1 and meperidine 0.4 mg kg-1, respectively, but none of the patient's receiving meperidine experienced severe tremors.[21] A similar prophylactic dose was also used by *Sagir et al* (0.5 mg kg-1) ketamine IV, but in patients receiving SAB has been shown to be efficient in preventing POS.[18] Utilizing a lower dose, *Elmawgood et al.* Low doses of ketamine (0.25 mg kg-1) and hydrocortisone (2 mg kg-1) were found in a study of patients undergoing corrective surgery for posterior vaginal Prolapse. Tremor frequency reduced in the ketamine group from 60% in the control group to 20%**.** [22]

A randomized control trial (RCT) study done by *Ibrahim et al* Prophylactic MgSO4 was successful in lowering the likelihood of shivering in 120 patients, but therapeutic MgSO4 was more effective in controlling shivering once it had started, as demonstrated by the use of rescue meperidine, which was more common in Groups P (20%) and C (50%) compared to none in Group T. The study's findings, which included the recommendation that 50 mg/kg of IV MgSO4 be used to treat grade 2 shivering, showed that preventive and therapeutic MgSO4 infusion reduced the risk of shivering and is employed as an effective therapy with few adverse effects.[23]

An RCT study by *Elsonbaty et al.* an IV MgSO4 dosage of 50 mg/kg was shown to be beneficial for treating a moderate type of shivering without causing any substantial negative impacts in 50 individuals scheduled for elective knee arthroscopy. Additionally, it is suggested that it could take the place of Meperidine in middle-aged individuals receiving spinal anesthetic.[24] Similar findings were made by *Faizshr et al*, who demonstrated that Female patients undergoing planned cesarean sections had less perioperative shivering after receiving a 25 mg intrathecal injection of MgSO4. [25].

We used meperidine as the test drug and considered it as the baseline drug for this study because it is one of the best-known drugs for postoperative shivering prevention. In the study of *Kelsaka E et al*, an intravenous injection of meperidine 0.4 mg/ kg has been utilized as a prophylaxis for POS. In the meperidine group, there was a drop in the prevalence of SOP to 8%.[26] Although statistically insignificant, a decreased risk of hypothermia was seen in the ketamine group than in the other groups, which may be related to the drug's vasoconstrictive effects. This is in line with earlier research, in which *Sagir et al.* noted that in comparison to the control group, there was a higher frequency of core temperature reduction in

the ketamine (0.5 mg kg1) group. While ketamine interacts with the brain's thermoregulatory control processes, limiting shivering, pethidine disproportionately lowers the shivering threshold in relation to its impact on the vasoconstriction threshold.[18] systematic review and meta-analysis conducted recently by *H. Kawamikami et al.* revealed that IV Shivering is significantly reduced by magnesium, and administration of magnesium has a negligible frequency of side effects. [27]

In the ketamine group, there were considerably fewer cases of hypotension (4%). The ketamine group also had a considerably decreased incidence of serious hypotension, which necessitated the use of ephedrine. *Salah et al*. discovered findings comparable to ours, which revealed a considerably reduced occurrence of hypotension in the ketamine group compared with the control group, despite the fact that the majority of studies utilizing ketamine and other drugs have shown similar hemodynamic profiles.[18] This is brought on by ketamine's sympathetic and vasoconstrictor actions.

Ondansetron and ketamine users reported much less postoperative nausea and vomiting. In our research, 24% of the meperidine group had nausea and vomiting. Meperidine has been shown to produce substantial adverse effects, including nausea and vomiting. Low dosages of meperidine (0.3 mg/kg) nonetheless decreased the look. Due in part to its effective anti-emetic qualities, ondansetron is recognized to prevent nausea and vomiting. In earlier investigations, similar decreases in the frequency of nausea and vomiting were seen. *Ejiro et al.* in research of ondansetron for POS prevention after caesarean surgery in the context of SAB, ondansetron at a dosage of 4 mg was shown to have a considerably greater probability of nausea and vomiting than tramadol. [29]

Despite the fact that the magnesium sulfate and ketamine groups had much greater rates of sedation, this was statistically insignificant. Ketamine is known to have a sedative effect, although at modest dosages (0.25 mg kg), this impact was not particularly noticeable. In earlier research by *Sagir et al.*, When compared to granisetron and the control group, most patients who received ketamine 0.5 mg/kg for the prevention of tremor had significant degrees of drowsiness (grade 4 or above).[18]

This study has certain limitations. Although the shivering scale we employed was the most commonly utilized, it was not appropriate for assessing patients with a SAB since grade 4 tremor (generalized tremor) can never be detected owing to the immobility of the lower body in SAB. Additionally, intraoperative hypotension might be affected by preoperative volume status; thus, patient intravascular volumes should be evaluated before surgery using any measuring method.

CONCLUSION

We concluded that Low-dose meperidine, low-dose ketamine, magnesium sulphate, or ondansetron were administered prophylactically, and each had a strong anti-shivering impact with little negative side impacts. Low dosage ketamine, however, has the benefit of being less likely to cause hypotension, nausea, and vomiting than meperidine.

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