Original Article

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Comparative Study of Ondansetron versus Low Dose Ketamine in Prevention of Intra Operative Hypotension and Shivering in Patients Undergoing Subarachnoid Block

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Abstract

Context: Subarachnoid block (SAB) is a safe anesthestic technique commonly practiced worldwide. It is associated with hypotension (33%), bradycardia (13%), and shivering due to hypovolemia, sympathetic blockade, and Bezold- zarisch reflex. Hypotension is managed with vasopressors and crystalloids, while drugs and physical methods are useful to control shivering.

Aims: The study aims to evaluate the efficacy of ondansetron versus low dose ketamine to prevent hypotension and shivering during SAB.

Settings and Design: A prospective, randomized comparative study.

Methods: The studywas conducted on 120 patients undergoing elective lower abdominal surgeries under SAB. Patients were randomly allocated into two groups of 60 each. Group K received 0.25 mg/kg ketamine, while Group O received 4 mg of ondansetron as a slow intravenous infusion (IV) 5 min before SAB. Mean arterial pressure (MAP) and Heart rate (HR) were studied at 2 min intervals for the first ten minutes and once in 5 minutes for the next thirty minutes. Shivering scores were measured at 5 min interval for 40 min.

Statistical Analysis: Mean Arterial pressure and heart rate were compared and analyzed using unpaired t-tests. Shivering was compared using contingency tests.

Results: A decrease in HR is significantly lower in group K than in group O after 2 min ($p < 0.001$), 8 min ($p < 0.001$), 15 min ($p < 0.0031$), 25 min ($p < 0.0115$) and 40 min ($p < 0.0037$) of SAB. MAP was increased at 2 min time interval in the Ketamine group comparative with the Ondansetron group with a p-value <0.05 showing a high statistical significance. Group K had grade I ($p < 0.001$) shivering in 70% (42) of the patients compared with 36.7% (22) of patients in group O.

Conclusion: Administration of IV ondansetron and ketamine prevents SAB induced hypotension and shivering effectively.

Keywords: Hypotension, Ketamine, Ondansetron, Shivering, Subarachnoid Block.

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Introduction

Spinal anesthesia is a simple, reliable, and most common anesthetic technique practiced worldwide.[1] Despite its popularity and ease of use, it is frequentlyassociated with hemodynamic instability and shivering. The incidence of hypotension and bradycardia in non-obstetric patients is 33% and 13%, respectively.[2] Vasopressors are highly effective in preventing hypotension but may result in cardiac arrhythmias and myocardial ischemia.

Due to the relative safety and beneficial effects on cardiovascular function, ketamine is an anaesthetic agent of choice for hemodynamically unstable patients. Ketamine increases HR and blood pressure due to sympathetic activation, therefore reduces hypotension and bradycardia following SAB. Ondansetron is a selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonists and thus may be beneficial for preventing bradycardia and hypotension.[3]

Shivering is the "big little problem" during anesthesia. The serotonergic system playsan essential role in the pathogenesis of perioperative shivering.4Apart from physical warming, drugs such as tramadol and pethidine are being used to prevent shivering. Ketamine is used for preventing shivering during anaesthesia in doses of 0.5 to 0.75mg /kg, 5The primary outcome of this study was to evaluate the efficacy of low dose ketamine (0.25 mg/kg) and ondansetron (4 mg) to prevent hypotension and shivering during SAB. The secondary outcome was was to evaluate the side effects of ondansetron and ketamine.

Methods

This prospective randomized comparative study was conducted in a tertiary care hospital from January 2018 to July 2019. After approval from the institutional ethics committee (No: PESIMSR/IHEC/75/28/12/2017), 120 adult patients of ASA physical status I & II aged 18 – 60 years, undergoing elective lower abdominal surgical procedures under SAB were included in this study. Exclusion criteria were patients with thyroid disorders, epilepsy, bronchial asthma, cardiopulmonary, liver and kidney diseases, pregnancy, patients with severe bradycardia and hypotension, allergic to the agents used, and contraindications to SAB.

After explaining the procedure and obtaining written informed consent, the pre-anaesthetic evaluation was done, and patients allotted into two groups (Group K and Group O) of sixty each. The allocation to each group was done randomly using randomization through the random number generator application method. (Random number generator application, Jess tucker, version 1.1.3.2013). Group- K received 0.25mg/kg of IV ketamine and Group- O received 4mg of IV ondansetron five minutes before SAB. All patients received tablet Alprazolam 0.5 mg pre-operative day at night time.Patients were fasting for 8 hours before surgery for solids and 2 hours for clearliquids. The Patients underwent scheduled surgery next day under spinal anaesthesia. The routine monitoring protocols were as per our institution department protocol. Baseline vitals recorded, the operating room temperature maintained at 21°C to 22°C. administered Irrigation and IV Fluids at room temperature (24°C - 26°C) without inline warming. Ringer lactate solution is given at 500 ml/20 min as rapid infusion when spinal anaesthesia was induced and then at 7 ml/kg/h.Instituted subarachnoid block at the L3/4 or L4/5 interspace with 3 ml of 0.5 % hyperbaric bupivacaine.

Patients received respective drugs intravenously just before initiation of SAB. All patients covered with one layer of paper surgical drapes and one layer of a cotton blanket positioned over the thighs and calves. Besides, one layer of a cotton blanket is placed over the chest and arms. No other warming devices were used.

The MAP and heart rate of the patients were studied at different intervals, once in 2 minutes for the first ten minutes and once in 5 minutes for the next thirty minutes. Hypotension was defined as a fall in blood pressure by 20% from the baseline or an absolute mean arterial pressure (MAP) <60 mmHg, managed by increments of intravenous Mephentermine 6 mg. Bradycardia is defined as a decrease in HR by 20% from the baseline value or an absolute HR <50 beats/min, managed by 0.6 mg IV bolus of atropine. Patients with refractory nausea or vomiting were treated with 10 mg metoclopramide IV as a rescue medication. Shivering was graded based on the Bedside Shivering Assessment Scale (BSAS).[6] (Table: 1).

Table: 1 Bedside Shivering Assessment Scale (BSAS).

BSAS 0	None	No Shivering
BSAS 1	Mild	Shivering localized to neck/thorax may be seen only as an artefact on ECG or felt by palpation
BSAS 2	Moderate	Intermittent involvement of the upper extremities +/- thorax
BSAS 3	Severe	Generalized shivering or sustained upper/lower extremity shivering

The incidence and severity of shivering were recorded every five min for the first 40 minutes intraoperatively. If scores were three or higher at 15minutes after spinal anaesthesia, the prophylaxis was regarded as ineffective and were treated withpethidine 0.5 mg/kg IV as a rescue medication.

Power analysis was based on the results of a previous study conducted by Shakya et al. They have shown that hypotension was lowest in the ketamine group (10%) in comparison to the ondansetron group (22.5%) and saline group (20%).[7] The sample size was calculated based on these findings, with a value of 0.055 and an expected prevalence of 0.1(10%). It was calculated that 114 subjects are required for the study. We included (120 subjects) 60 patients in each group for better validation of results. Data were analyzed using STATA 14. Numerical data like MAP and HR were compared and analyzed using unpaired t-tests between the groups. Shivering was compared using contingency tests. The data collected were presented as Mean & SD with 95% confidence intervals for quantitative observations and proportions (%) for qualitative observations.A statistical probability value of <0.05 is considered to be statistically significant. To reject the null hypothesis, the significant level was taken as $p < 0.05$.

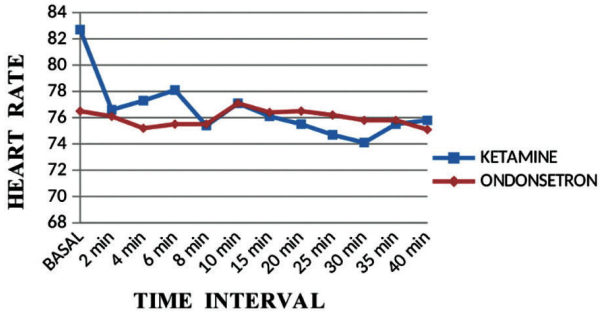
Results

The study was conducted on 120 patients who were posted for elective surgical procedures. The demographic characteristics, such as age, gender, and weight, were comparable in both groups (p> 0.05) (Table: 2). There was no statistical significance in both groups.

Table: 2 Demographic data of study groups.

Variables	Group K (Mean ± SD)	Group O (Mean ± SD)	P value
Age	42.1±10.8	38.6±12.4	0.1128
Weight	61.1±8.3	61.5±9.6	0.8009
Gender (M/F)	29/31	30/30	0.8550

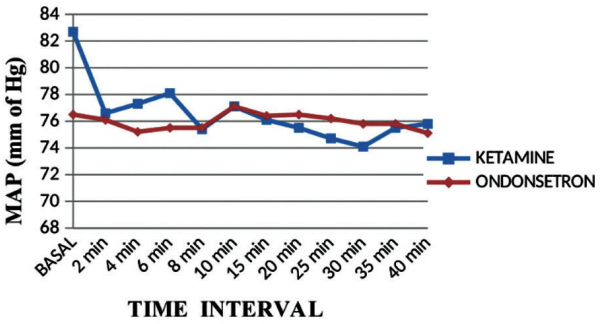
Graph: 1 Comparison of HR between studied groups.



Comparison of heart rate between study groups.

A decrease in HR issignificantly lower in group K than in group O after 2 min (0.001), 8 min (0.001), 15 min (0.0031), 25 min (0.0115) and 40 min (0.0037) of SAB (Graph: 1).Decreases in MAP were significantly lower in group K than group O. patients in group K had significantly fewer vasopressor requirements. There were no statistically significant differences between the two groups after 2 min of SAB. MAP was increased at 2 min time interval in the Ketamine group comparative with the Ondansetron group with a p-value <0.05 showing a high statistical significance (Graph: 2).

Graph: 2 Comparision of MAP between two groups.



Comparison of MAP between study groups.

Table: 3 Comparisonof Shivering Scale.

Shivering Scale	Group					p-value
	Keta Mine		Ondansetron			
	n	%	n	%		
BASAL	0	60	100	60	100	-
5 min	0	60	100	60	100	-
10 min	0	60	100	60	100	-
15min	0	60	100	60	100	-
20 min	0	60	100	60	100	-
25 min	0	18	30	38	63.3	*<0.001
	1	42	70	22	36.7	
30 min	0	30	50	28	46.7	0.715
	1	30	50	32	53.3	
35 min	0	38	63.3	44	73.3	0.239
	1	22	36.7	16	26.7	
40 min	0	30	50	42	70	0.025
	1	30	50	18	30	

* Significant difference

Shivering was not observed in any patient in both the groups within 20 min time interval. While 70 % (42) of patients in group K had shivering with grade 1 ($p< 0.001$) compared to 36.7 % (22) of patients in group O (Table: 3).

Discussion

Hypotension is the most common complication of SAB with an incidence of 20% in the elderly.8 Spinal induced hypotension and bradycardia are multifactorial due to the Bezold–Jarisch reflex, mediated by serotonin receptors within the ventricle wall in response to systemic hypotension. The stimulation of these peripheral 5 hydroxytryptamine subtype 3 (5 HT3) receptors resulted in increased parasympathetic activity and decreased sympathetic activity, resulting in bradycardia, vasodilatation and hypotension.

Ketamine is an NMDA receptor antagonist known to produce dissociative anaesthesia and has a strong analgesic effect. Its acts by noncompetitive antagonism at N-methyl D-aspartate (NMDA) receptors and has a local anaesthetic effect. It increases the blood pressure by central stimulation of the sympathetic nervous system and inhibition of norepinephrine reuptake. Many medical centers use ketamine as an induction agent for potentially hypovolemic trauma patients undergoing rapid-sequence intubation. Ondansetron has been safely used to blunt the Bezold–Jarisch reflex resulting in less bradycardia and hypotension.

Our study investigated the comparative efficacy and safety of a low prophylactic dose of ketamine and ondansetron (with a different mechanism of action) to prevent hypotension and shivering during the subarachnoid block. There was no difference between the two groups concerning hemodynamic parameters. These results were consistent with previous studies by Sagiret al.[9] and Kelsakaet al.10Nallam S R et al.11 found that 4 mg IV ondansetron to be effective in preventing hypotension and bradycardia under neuraxial blockade. In the study conducted by Marashiet al.1 they compared two different doses of ondansetron 6 mg, 12 mg with the placebo group. 12% of patients in the control group had hypotension and required vasopressors. 45% had to shiver, 14% had bradycardia.

In line with our results, Sahoo et al.[12] concluded that IV ondansetron at 4 mg given prophylactically could attenuate decreased blood pressure following spinal anesthesia. Owczuket al.[13] reported that 8 mg IV ondansetron attenuates the fall of systolic and mean blood pressure but does not influence diastolic BP or HR. A study conducted by Rashad14 and Farmawy on 60 parturient females undergoing elective cesarean section concluded that patients who received IV ondansetron 4 mg before SAB significantly decreased both the hypotension and the dose of vasopressors consumption ($p= 0.005$).

Most studies have quoted that shivering incidence varies 30%–40%15and 40–60%16 following regional anesthesia. During the perioperative period, core body temperature was maintained between 36.5°C–37.5°C because shivering occurs as a response to hypothermia. Under regional anesthesia, shivering may occur in normothermic patients.[17] Several factors, including age, level of sensory block, type and volume of infusion solution, and operating room temperature, are risk factors for developing hypothermia in regional anesthesia.[18] Our study demonstrates a statistically significant incidence of shivering in Group K compared to Group O ($p = 0.001$) after 25 min of SAB.

In this study, shivering is graded using a scale that was validated by Tsai and Chu.[19] Our results were similar to the findings of Shakya et al.[8] who suggested that the prophylactic administration of low dose ketamine (0.25 mg/kg) and ondansetron (4 mg) produces the significant anti-shivering effect in comparison with placebo.They also opine that ketamine (0.25 mg/kg) is significantly more effective than ondansetron (4 mg). Kelsaka et al. study said that 8mg of IV ondansetron effectively prevents the postspinal shivering compared to the control group, which was very similar to our results. Sagiret al. concluded that prophylactic use of ketamine and granisetron separately and in combination, effectively prevented shivering developed during regional anesthesia.

The results of the study were consistent with the study of Mushtaq Waniet al.[20] they evaluated the role of prophylactic low dose ketamine and ondansetron for the prevention of shivering during spinal anesthesia. Rama wasonet al.[21] also found ketamine 0.5 mg/kg IV to be effective in controlling shivering under neuraxial blockade.

In our study, the very low dose of ketamine (0.25mg/kg) was used to minimize the side effects. We found that it was significantly effective, and only grade 1 shivering was observed after 25 min initial dose in 42 patients out of 60 (70%). Sayed ADM[22]showed significant results with ketamine 25 mg IV to prevent shivering under SAB. Dal et al[5] showed that ketamine 0.5mg/kg effectively prevented post anaesthetic shivering in patients receiving general anaesthsia. In our study, 0.25mg/

kg of ketamine was as effective as 0.5mg/kg of ketamine. Sharma. S P et al[23] and Botros. JM et al[24] concluded that 8 mg ondansetron effectively prevented SAB induced shivering. A study conducted by Trabelsiet al,[25] on 80 parturients posted for elective cesarean section found that vasopressor consumption is significantly more in the saline group as compared with the ondansetron group ($p< 0.0001$).

In our study, the primary outcome is low dose IV ketamine effectively prevents the SAB induced hypotension compared with ondansetron andondansetron more efficacious than ketamine in preventing SAB induced shivering, the secondary outcome is the usage of these drugs at the said doses free of adverse effects.

One limitation of our study was that we used a fixed dose of ondansetron 4 mg in all patients irrespective of patients' weight. Another limitation was that we monitored NIBP; probably, invasive blood pressure monitoring would have been more reliable. Effects of low dose ketamine on other anaesthetic parameters such as pain and recovery time was also not studied. The use of sympathomimeticsuch as mephenteramine for hypotension treatmentwhich tends to increase both BP and HR, would have masked the incidence of bradycardia. Hence, this could be one reason for not getting significant values in the incidence of bradycardia.

Conclusion

Based on the present comparative study between ondansetron and low dose ketamine we conclude that IV ketamine 0.25mg/kg resulted in better prophylaxis against hypotension. A single-dose of Ondansetron 4mg intravenous bolus resulted in better prophylaxis against shivering. No significant side effects were observed for both groups during the study.

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