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PROPHYLACTIC EFFECT OF ONDANSETRON IN COMPARISON WITH KETAMINE ON SPINAL ANESTHESIA-INDUCED HYPOTENSION IN CESAREAN SECTION

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ABSTRACT

Background and Objective: spinal anesthesia is one of the most common local anesthesia especially in parturient but hypotension and bradycardia due to sympathetic blockade are its major complications which can effect maternal and neonatal health. The aim of present study was to compare the prophylactic effect of Ondansetron and Ketamine on spinal anesthesia-induced hypotension in pregnant women undergoing elective cesarean section.

Material & Methods: Ninety-three parturients scheduled for elective caesarian section were randomly selected and divided into three equal groups (n=31). After induction of spinal anesthesia group O received Ondansetron 4mg; group K received Ketamine 25mg; group S received normal saline intravenously. Blood pressure, heart rate, mean arterial blood pressure

(MAP) every 5 minutes to 30 minutes after induction of spinal anesthesia were compared between groups.

Results: Mean, systolic, and diastolic arterial pressure as well as in heart rate were decreased significantly in three groups compared with baseline values (p=0.000) but there was no significant difference between O and K groups in any of hemodynamic parameters.

Conclusion: According to the result of present study intravenous injection of Ondansetron and Ketamine compared to saline can significantly reduce the hypotension induced by spinal anesthesia. These two medications had no superiority over each other in ameliorating hypotension.

Keywords: Caesarean section, drug-induced hypotension, Ketamine, Ondansetron, Spinal anesthesia

INTRODUCTION

In recent years, regional analgesia especially spinal anesthesia has emerged as the method of choice for elective caesarean delivery because of the ease of performing, reliable nerve block, using minimal doses of local anesthetics which avoids risks involved in airway management of the parturient and has the added significant benefit of mother being awake for the birth of her child. At the same time, spinal anesthesia is associated with some important maternal and neonatal consequences (1).

Most common side effects of spinal anesthesia are hypotension and bradycardia which occurring in 50-60% of patients (2, 3).It is well-known that maternal hypotension may lead to sever nausea and vomiting which can pose serious risks to the mother and the baby (4) and unfavorable outcome of pregnancy due to low uterine perfusion (5, 6).

Spinal anesthesia-induced hypotension in pregnant women is due to combination of decreased systemic vascular resistance because of sympathetic blockade and aortocaval compression by the gravid uterus (4). Spinal-induced bradycardia is particularly due to the Bezold-Jarisch Reflex (BJR) which is mediated by serotonin receptors within the wall of the ventricle in response to systemic hypotension (7).

Many studies have been conducted on prevention and treatment of spinal anesthesia-induced hypotension (9) but there is no established strategy to prevent or treatment of theses sequences.

Ondansetron, a widely used anti-emetic and serotonin antagonist, has been safely used to blunt the BJR, resulting in less bradycardia

and hypotension first in animals and later in humans undergoing spinal anesthesia (7, 8).Sahoo et al. observed that Ondansetron 4 mg, given intravenously 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section (10).

Ketamine is classified as an NMDA receptor antagonist, but it also acts at numerous other sites (including opioid receptors and monoamine transporters). Ketamine is frequently used in severely injured people and appears to be safe in this group (11). A 2011 clinical practice guideline supports the use of ketamine as a dissociative sedative in emergency medicine (12). It is the drug of choice for people in traumatic shock who are at risk of hypotension. Low blood pressure is harmful in people with severe head injury (13) and ketamine is least likely to cause low blood pressure, often even able to prevent it (14).

The effect of ketamine on the respiratory and circulatory systems is different from that of other anesthetics. When used at anesthetic doses, it will usually stimulate rather than depress the circulatory system and can prevent systemic hypotension (14).

The aim of present study was to compare the prophylactic effect of Ondansetron and Ketamine on spinal anesthesia-induced hypotension and bradycardia.

PATIENTS AND METHODS

Before recruitment of first subject, Study protocol was approved by local ethics committee of University and registered in official database for registry of clinical trials. The study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and was guided by Consolidated Standards of Reporting Trials (CONSORT) checklist.

All patients signed the informed consent forms prior to recruitment in the study.

93 Parturients with15-45 years old and functional class I, II scheduled for elective cesarean section surgery with spinal anesthesia were enrolled in this randomized and triple-blinded clinical trial. Exclusion criteria included any contraindication for spinal anesthesia, systemic blood hypertension, known cardiovascular or liver disease, body mass index (BMI) more than 35 kg/m^2, history of migraine headache and epilepsy, consumption of any medication that affect blood pressure of heart rate, allergy to the study medications and need to additional medications or failure of spinal anesthesia.

All patients were received75mg of lidocaine 0.5%for spinal anesthesia induction. All of

them were monitored with a non-invasive blood pressure and pulse oximetry.

Random allocation was performed, group O (n=31) received Ondansetron 4mg (2 ml); group K (n=31) received Ketamine 25mg (diluted in sterile water for injection up to 2ml); group S (n=31) received normal saline IV slow injection. Systolic and diastolic blood pressure, heart rate, mean arterial blood pressure (MAP) and vasopressor requirements were assessed every 5 minute to 30 minute after induction of spinal anesthesia, sedation level of patients before and 30 minute after induction of spinal anesthesia were assessed using Ramsay Sedation Scale.

All of the medication containing syringes have same volume (2ml) and labeled as 1, 2, and 3. Anesthesiologist who was responsible for injection of medication and recording the variables and who was responsible for analyzing our data were blinded to patient group assignment.

All statistical analyses were performed with SPSS software21 (using chi-square test and repeated measure ANOVA) and Statistical significance was considered at $P \leq 0.05$.

RESULTS

The mean age of participants in Ondansetron, Ketamine and Normal saline groups were 30.68±4.24, 30.31±4.42 and 29.56±6.21 respectively. There was no significant difference between groups in age, weight and baseline clinical evaluation ($p>0.05$).

Systolic and diastolic blood pressure, mean arterial blood pressure and heart rate of all patients were shown in Tables 1 to 4.

Before induction of anesthesia the systolic blood pressure in O, K, and S groups were 127.34±10.71, 122.18±11.24, and 122.43±10.57 mmHg respectively. There was no statistical differences between three groups at the beginning of the study using one-way ANOVA test (p=0.427).

There was significant reduction in systolic blood pressure in all three groups using Wilk's Lambda test (F= 18.18, p=0.000) which was significant between groups (F=1.84, p=0.036) but the difference between O and K group was not statistically significant (F=2.002, p=0.071) (Table1).

At the beginning of the study the diastolic blood pressure in O, K, and S groups were 79.9±10.7, 74.7±9.8, and 78.2±11.8 mmHg respectively. There was no statistical differences between three groups using one-way ANOVA test (p=0.157).

Wilk's Lambda test was performed to compare diastolic blood pressure between groups too. There was significant reduction in diastolic blood pressure in all three groups using (F= 19.1, p=0.000). The difference

between groups was not statistically significant (F=1.65, p=0.70) (Table2).

Mean arterial blood pressure (MAP) prior to induction of anesthesia were calculated and in O, K, and S groups were 95.0±10.8, 90.1±10.1, and 92.3±10.8 mmHg respectively. There was no statistical differences between three groups using one-way ANOVA test (p=0.231).

There was significant reduction in MAP in all three groups using Wilk's Lambda test (F= 17.73, p=0.000) which was significant between groups (F=2.13, p=0.012) but the difference between O and K group was not statistically significant (F=2.002, p=0.071) (Table3).

The heart rate of patients in O, K, and S groups were 101.8±14.3, 93.9±11.4, and 98.6±15.6beat/minute respectively prior to induction of spinal anesthesia. There was no statistical differences between three groups at the beginning of the study using one-way ANOVA test (p=0.09).

Heart rate has significant reduction in all three groups using Wilk's Lambda test (F= 4.8, p=0.000) which was not significant between groups (F=1.65, p=0.07) (Table 4).

Table1: The mean of systolic blood pressure (mmHg) of patients every 5 minutes to 30 minutes after induction based on intervention group (±SD)

variables	Minute0	Minute5	Minute10	Minute15	Minute20	Minute25	Minute30
Ondansetron	117.1±13.8	110.4±16.9	113.2±11.9	115.2±10.8	113.9±10.4	113.5±11.3	117.1±8.0
Ketamine	118.6±14.1	109.1±17.5	110.8±15/0	112.5±10.8	115/0±10.0	115.0±8.9	117.2±7.0
Normal saline	105.5±14.8	95.1±16.1	106.4±16.2	110.1±11.4	110.5±11.9	111.4±10.3	115.3±7.4

Table2: The mean of diastolic blood pressure of patients every 5 minutes to 30 minutes after induction based on intervention group (±SD)

variables	Minute0	Minute5	Minute10	Minute15	Minute20	Minute25	Minute30
Ondansetron	70.2±12.9	64.1±15.2	63.8±10.6	63.5±11.5	62.8±9.6	65.3±11.9	66.3±9.5
Ketamine	69.6±14.7	63.6±16.7	64.2±11/2	62.9±12.4	64/0±10.3	65.9±9.7	67.3±10.0
Normal saline	63.2±15.0	53.4±12.4	60.1±14.1	62.4±10.9	60.7±9.1	61.4±11.1	64.6±9.1

Table3: The mean of MAP (mmHg) of patients every 5 minutes to 30 minutes after induction based on intervention group (±SD)

variables	Minute0	Minute5	Minute10	Minute15	Minute20	Minute25	Minute30
Ondansetron	84.8±11.9	78.1±15.8	79.6±10.0	78.5±10.2	79.5±9.2	79.7±11.1	82.3±9.1
Ketamine	85.9±13.8	78.7±16.6	80.1±13/4	78.8±12.6	81/0±9.1	82.3±9.1	83.2±9.2
Normal saline	75.6±14.0	66.5±13.0	74.9±14.8	76.8±10.9	77.2±10.1	76.7±10.6	79.9±8.9

Table 4: The mean of heart rate (beat/minute) of patients every 5 minutes to 30 minutes after induction based on intervention group (±SD)

variables	Minute0	Minute5	Minute10	Minute15	Minute20	Minute25	Minute30
Ondansetron	96.9±16.8	90.7±18.2	92.0±14.4	92.6±13.7	92.4±11.3	91.4±8.7	90.2±9.0
Ketamine	96.1±15.5	91.7±14.5	97.4±13/7	96.7±11.7	96/7±11.5	95.8±11.0	94.2±10.2
Normal saline	90.5±21.3	86.4±21.1	88.6±16.8	93.2±15.4	94.1±11.5	94.8±11.9	92.2±9.5

DISCUSSION

This study demonstrated that administration of intravenous Ondansetron 4mg and ketamine 25mg attenuates spinal anesthesia-induced hypotension compared to normal saline group. There were no significant

differences between Ondansetron and Ketamine groups and these two medications has no superiority over each other.

Hypotension is a common side effect of spinal anesthesia (2). Different strategies such as prehydration or administration of vasoactive agents have been attempted to prevent this side effect (15). Vasodilation, hypotension, and bradycardia caused by spinal anesthesia are due to sympathetic blockade, the BJR, and stimulation of 5-HT3 receptors in vagal nerve endings (16).

Ondansetron, a widely used anti-emetic and serotonin antagonist, has been safely used to blunt the BJR, resulting in less bradycardia and hypotension first in animals and later in humans undergoing spinal anesthesia (7, 8). Sahoo et al. observed that Ondansetron 4 mg, given intravenously 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section (10) which is similar to our result.

Marashi et al. investigate the effect of intravenous administration of ondansetron ketamine on hemodynamic stability of 210 patients who scheduled for spinal anesthesia and showed that 6 and 12 mg intravenous Ondansetron may attenuate hypotension and bradycardia induced by spinal anesthesia (17).El SayedGoda et al. in her clinical trial with 60 parturients sample size concluded that 8 mg intravenous Ondansetron is effective in preventing of post-spinal hypotension, bradycardia, nausea, vomiting, and shivering in caesarean section (18). In our study ondansetron attenuates systolic and diastolic hypotension but its effect on MAP and heart rate was not significantly better than normal saline which it can be because of lower dose of Ondansetron in our study.

Ketamine is an NMDA receptor antagonist which can induces activation of the sympathetic nervous system (19) and it is frequently used in severely injured people who are at risk of hypotension (11) and ketamine is able to prevent it (14).

Hemmingsen et al. compared the hemodynamic effect of 1.5 mg/kg BW intravenous fentanyl and 0.7 mg/kg BW intravenous ketamine before spinal anesthesia (n=30) and showed that in both groups the spinal anesthesia caused a reduction in MAP which was lower in the fentanyl group than in the ketamine group at all times. Hemodynamically unstable condition was observed in six and one subjects in the fentanyl and ketamine group respectively ($P < 0.05$) without any significant change in heart rate in either group. He concluded that during spinal anesthesia patients can in part be kept

hemodynamically stable by intravenous administration of ketamine (14).

Shakya et al. in his study evaluated the prophylactic effect of low dose ketamine and ondansetron on shivering of 120 patients with spinal anesthesia and reported hypotension in 9, 4 and 8 cases in Ondansetron, ketamine and saline groups respectively which in ketamine group was lower than other groups but there was no significant difference between groups. He concluded that Prophylactic low dose ketamine (0.25mg kg-1) and Ondansetron (4mg) significantly decreased shivering in patients undergoing spinal anesthesia without significant side effects (19). Ketamine has sympathetic stimulation and vasoconstructive effect which can explain the less incidence of hypotension in Shakya's study. In our study the mean blood pressure of patients in Ketamine group reduced significantly but less than control group. It can be because of dose of ketamine used in our study.

In our study similar to Shakya's study results (19), Ondansetron and ketamine has no superiority over each other in attenuating of hemodynamic parameters.

Hypotension and bradycardia are Side effects of spinal anesthesia. Administration of intravenous 4 mg ondansetron and 25mg ketamine significantly attenuates spinal induced hypotension and may control bradycardia. This finding could be crucially useful for high risk population like elderly patients with cardiovascular decomposition or pregnant women in whom the administration of vasoconstrictors can have adverse effects on uterine blood flow during spinal anesthesia.

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