A Double Blind Randomized, Placebo Controlled Study Evaluating the Effect of Ondansetron in Reducing Spinal-Induced Hypotension Using Low Dose Bupivacaine in Parturients Undergoing Caesarean Section.

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ABSTRACT

Background: Spinal induced hypotension is the most common intraoperative complication after spinal anesthesia during cesarean delivery. Various adjuvant techniques/drugs had been used in the past to minimize the haemodynamic effects of spinal anaesthesia. Five-hydroxytriptamine (5-HT), a serotonergic receptor, may be an important factor associated with inducing the Bezold Jarish reflex (BJR) that may lead to the bradycardia and hypotension in the setting of decreased blood volume. Some animal and human studies further supported that BJR can be decreased by 5-HT3 antagonists. **Aim:** The present study work is to assess the effects of Inj. Ondansetron (a selective 5-HT3 receptor antagonist) in preventing spinal induced hypotension in patient undergoing elective Caesarean section. **Methods:** Sixty parturients scheduled for elective caesarean section were randomly allocated into two groups. Group O (30 patients): Inj. Ondansetron (4 mg IV) diluted in 10 mL of normal saline, administered 5 minutes before spinal anaesthesia and Group N (30 patients): Normal saline 10 mL given 5 minutes before spinal anaesthesia. We observed the haemodynamic parameters as our primary outcome and neonatal outcome in terms of APGAR scoring as secondary outcome. **Results:** Both the groups were comparable in terms of demographic characteristics. The decrease in mean arterial pressure in Group O was significantly lesser than Group N from 6 min until 30 min. The requirement of vasopressor (Inj. Phenylephrine) was significantly less in Group O than Group N (P = 0.015). Neonatal outcome in terms of APGAR Score and gas analysis were comparable between the groups. **Conclusion:** Inj. Ondansetron (4 mg IV), given intravenously 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section.

Keywords: Ondansetron, Spinal-Induced Hypotension, Low Dose Bupivacaine.

INTRODUCTION

Spinal anaesthesia has become the gold standard anaesthetic technique for elective caesarean section. It is a simple, promptly performed, powerful, and reliable technique. But this most popular form of anaesthesia is frequently associated with hypotension and bradycardia.[1] Maternal hypotension is the most common intraoperative complication after spinal anesthesia during cesarean delivery, with an incidence as high as 50-80%.[2] Maternal hypotension may cause maternal nausea and vomiting as well as detrimental neonatal effects, such as apnea.

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Hypotension results primarily from decreased vascular resistance, while bradycardia is secondary to a relative parasympathetic dominance, increased baroreceptor activity, or induction of the Bezold Jarisch Reflex (BJR). The responsible receptors for the BJR are mechanoreceptors located in the heart walls which participate in systemic responses to hypo and hypervolemia. They also include chemoreceptors sensitive to serotonin (5-HT3 receptors).[3-6] This BJR reflex is elicited by stimulation of peripheral serotonin receptors 5-hydroxytryptamine (5-HT3 type).

Ondansetron is a selective serotonin 5-HT3 receptor antagonist and may prevent spinal induced hypotension in patients undergoing cesarean section. Some animal and human studies also illustrated that BJR can be decreased by 5-HT3 antagonists.[7-10] Ondansetron has been proven as a well-tolerated drug.

The present work is a prospective, randomized study, which attempts to assess if blocking of the serotonin receptors by Ondansetron (a selective 5-HT3 receptor antagonist) can help in preventing spinal induced hypotension in patient undergoing spinal anaesthesia. In this study we will observe the haemodynamic parameters as our primary outcome and neonatal outcome in terms of APGAR scoring and gas analysis as secondary outcome.

MATERIALS AND METHODS

This study was conducted on 60 patients after obtaining institutional Ethical approval and written

informed consent at the Department of Anaesthesia, TMMC & RC, Moradabad, India. Obstetric patients of term pregnancy who was ASA physical status I and II, between 18 and 40 years of age, and undergoing an elective, lower segment caesarean section (CS) were included for the study. Patients with contraindications to subarachnoid block (patient refusal, unstable haemodynamics, coagulation abnormality), pregnancy induced hypertension, multiple gestation, weight > 100 kg, any end organ disease, history of hypersensitivity to Ondansetron or local anaesthetic agents, cardiovascular insufficiency, receiving selective serotonin reuptake inhibitors or migraine medications were excluded.

To detect a 20% difference in the primary outcome among the groups with a standard deviation of 22% estimated from initial pilot observations, with 80% power and 5% alpha error, 20 subjects per group is required. We selected 60 parturient in each group, to compensate an expected dropout rate of 5%, estimated from initial pilot observations. The sample size was calculated using the power and sample size calculator of the department of biostatics, Vanderbilt University, USA.

BLINDING??? The study drug and the placebo were prepared by nurse anaesthetic. She was oriented of the study procedure but neither involved in the study nor in the patient care. Both the patients and anaesthesiologist performing the spinal anesthesia and collecting the post-operative data were blinded as to the study drug. A nurse anaesthetic not involved in the study assisted in maintaining the randomization of sample in a double blinded fashion, using a simple chit and box method.

Patients were randomly allocated into two groups of 30 patients each using a computer generated randomization. Group O received Ondansetron (4 mg IV) diluted in 10 mL of normal saline or Group N in which 10 mL of normal saline (Group N) was administered over 1 min. Both the study solutions were given 5 min before spinal anaesthesia.

In the pre-anaesthesia room, after securing a peripheral 20-gauge IV cannula premedication was done with Inj. Ranitidine (50 mg IV) and Inj. Metoclopramide (10 mg IV). Thereafter, all patients were preloaded with lactated Ringer's solution 20 mL/kg/h over 30 min.

After attaching the standard monitors, combined spinal-epidural anaesthesia was administered in sitting position in all patients by using standard technique. Under full aseptic conditions, a 18 gauze Tuohy needle (Espocan, B. Braun, Germany) was inserted into the L3-4 or L4-5 interspace and epidural space has confirmed using loss of resistance to 2 ml of air. Thereafter, the intrathecal sac was punctured with a 27 gauge Whitacre spinal needle using needle through needle technique. After confirming free flow of cerebrospinal fluid, considered as initiation of spinal anaesthesia, 0.5% hyperbaric bupivacaine 1.1 ml (5.5 mg) with a fixed dose of fentanyl (25ug) diluted to 2.5 ml volume with normal saline through intrathecal route was injected. The spinal needle was then withdrawn and epidural catheter was then inserted 4-5 cm in the epidural space and after securing the catheter, the patients was immediately placed in the supine position with 15 degree left tilt.

All patients were continuously monitored in the operating room, baseline values of pulse oximetry (SpO2), non- invasive BP and electrocardiogram (ECG) were recorded. All patients were continuously monitored for any haemodynamic variations (primary outcome). Heart rate (HR), systolic (SBP), diastolic (DBP) and pulse rate(PR),respiratory rate(RR) and oxygen saturation (SpO2)were recorded at 3min intervals for the first 30 minutes thereafter at 5 minutes intervals, until the completion of surgery. Any episode of hypotension (SBP <90 mmHg or >25% of the baseline) was treated with bolus dose of phenylephrine (25ug IV) and additional rapid infusion of Ringer's Lactate solution. Vasopressors was repeated every 2 min if hypotension persisted or recurred; Bradycardia (HR <50 beats/min) was treated with injection atropine 0.5 mg iv bolus. Nausea and vomiting were treated with bolus dose of Ondansetron (4 mg i.v.). Supplemental oxygen was delivered through a facemask, if SpO2 falls below 94%. A blood sample (1 ml) was collected from the umbilical artery and vein to examine blood gas immediately on a fully automated blood gas analyzer (GEM Premier 3000, Instrumentation Laboratory; Bedford, MA).

Statistical Analyses:

All statistical analyses were performed using SPSS 19.0 statistical software. The continuous variables (demographic characteristics, hemodynamic parameters, fetal blood gas parameters, Apgar score, vasopressor requirement and sensory characteristics) were compared by Mann-Whitney U test. Discrete variables (side effects) were compared using Fisher's exact test/Chi-square test, whichever appropriate. A P value of <0.05 was considered significant.

RESULTS

All the parturients were successfully enrolled in the study. The groups were comparable with regard to demographic profile as there was no statistically significant difference between both the groups with regard to variables like age, weight and height [Table1].

After giving spinal anaesthesia mean arterial pressures were comparable in both the groups from zero minutes to 5 minutes, but it came statistically

significant from 6 minutes to 30 minutes (P=.001) [Table2]. Vasopressor use is greater in Group N and that was significant compared to Group O [Table 2].

There were no significant differences in Apgar scores at 1 and 5 min after neonatal delivery or neonatal birth weight among the groups [P > 0.05, Table 3]. The gas analysis results from umbilical arterial blood and umbilical venous blood showed that there were no significant differences in pH, Pco2, PO2, Hco3-, (P > 0.05, [Table 3].

Bradycardia was observed in 1 patients in Group O, whereas it was more frequent in the Group N i.e. 6 patients with a significant difference (P<0.05). The incidence of nausea in Groups O was significantly lower than that in group N (P < 0.05). No vomiting was observed in Group O, while four women in group N had vomiting [Table 4].

Table 1: Demographic data

Variables	Group N	Group O	P value
Age	25.2 ± 3.27	24.2 ± 3.56	0.26
Weight	69.2 ± 9.96	70.8 ± 8.56	0.50
Height	157.4 ± 4.77	156 ± 4.12	0.22

Table-2: Mean Arterial Blood Pressure of both the groups (Mean ± SD)

Variables	Group N	Group O	P value
At 0 Minutes	89.3 ± 2.65	90.0 ± 3.07	0.35
At 3 Minutes	90.0 ± 2.23	91.3 ± 3.33	0.09
At 6 Minutes	73.3 ± 1.73	86.4 ± 2.46	0.001*
At 9 Minutes	78.7 ± 1.67	83.3 ± 2.13	0.001*
At 12 Minutes	70.7 ± 1.13	80.7 ± 2.07	0.001*
At 15 Minutes	67.3 ± 0.77	83.3 ± 2.23	0.001*
At 18 Minutes	79.3 ± 1.91	90.0 ± 3.05	0.001*
At 21 Minutes	76.0 ± 1.66	90.7 ± 3.07	0.001*
At 24 Minutes	81.3 ± 2.11	86.0 ± 2.40	0.001*
At 27 Minutes	82.7 ± 2.19	92.0 ± 3.20	0.001*
At 30 Minutes	84.6 ± 2.27	88.7 ± 2.57	0.001*
At 33 Minutes	85.3 ± 2.33	86.0 ± 2.40	0.67
Vasopressor use Phenylephrine(ug)	107.14±83.13	37.93±27.69	0.001*

Table. 3: Neonatal Outcome

Apgar Score	Group N	Group O	P value
At 1 min	10(7-10)	10(9-10)	-
At 5 min	10(9-10)	10(9-10)	-
Umbilical artery			
pH	7.285±0.033	7.288±0.036	0.07
Pco2 mmhg	52.89±5.24	54.03±4.26	0.35
Po2 mmhg	10.25±5.26	9.12±4.20	0.36
Hco3- mmol/l	24.14±2.50	24.97±2.39	0.19
Umblical Vein			
pH	7.333±0.038	7.367±0.038	0.06
Pco2 mmhg	46.60±4.98	45.68±4.40	0.45
Po2 mmhg	20.26±7.33	23.30±5.78	0.07
Hco3- mmol/l	25.63±1.42	25.89±1.48	0.38

Table 4: Side effects

Variables	Group N	Group O
Bradycardia	6	1
Nausea	6	1
Vomiting	4	0

DISCUSSION

Maternal hypotension is one of the most common complications during spinal anesthesia as sympathetic blockade from spinal anaest0esia decreases systemic vascular resistance and induces peripheral pooling of blood and leads to hypotension.

Hemodynamic changes are usually benign, however in selected patient they may lead to serious consequences, including cardiac arrest, though it is a consequence of progressive bradycardia rather than progressive hypotension.

In 2014, Maharashi SM et al states that with the use of i.v Ondansetron there is decrease in MAP and HR compared to control saline group that was similar to our study.

Many studies states that decreases in MAP were reduced with the use of IV Ondansetron 4 mg given 5 min before spinal anaesthesia in patients

undergoing elective caesarean section. The use of phenylephrine and the incidence of nausea, vomiting and bradycardia were also significantly reduced with Ondansetron.[11]

Ondansetron by blocking the 5-HT3 receptors on platelets inhibits the binding of Serotonin, thereby alleviating the BJR and thus suppresses the peripheral dilatation of blood vessels.[12-15]

In 2004, Einarson et al investigated the risk of adverse fetal outcome relative to Ondansetron administration during pregnancy and found that appropriate exposure to Ondansetron during pregnancy does not cause adverse fetal outcome. [16]

Wang et al have demonstrated that Ondansetron preloading can effectively prevent maternal hypotension and nausea after spinal anesthesia during cesarean delivery.[17]

Above studies and this study finally demonstrated that intravenous injection of 4 mg Ondansetron, 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section and also saw that there were no significant differences in Apgar scores at 1 and 5 min after neonatal delivery among the groups.

Lee et al concluded that for elective Cesarean sections phenylepinephrine was associated with better fetal acid-base status than ephedrine.[18]

Aragaoa et al demonstrated that ephedrine treated mother had lower pH and base excess in newborns and those treated with metaraminol needed fewer rescue boluses as compared with ephhedrine, but not phenylepirine.

So we choose phenylephrine as a vassopressor agent and saw that the use of phenylephrine and the incidence of nausea, vomiting and bradycardia were also significantly reduced with Ondansetron.

Atif A. El-Morsi Ghazi MD, Ahmed Mostafa MD conducted a study in which he saw that Ondansetron doesnot help in preventing spinal induced hypotension and the amount of vasopressor administered for the treatment of hypotension was similar in both groups.

CONCLUSION

This study concluded that Inj. Ondansetron (4 mg IV), given intravenously 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section.

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