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COMPARATIVE EFFICACY STUDY OF TWO DOSES OF ONDANSETRON ON MATERNAL HEMODYNAMICS DURING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANESTHESIA.

Anaesthesiology

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ABSTRACT

Introduction: Spinal anesthesia for cesarean section (CS) is associated with common & serious side effects like hypotension and bradycardia. The Bezold–Jarisch reflex (BJR) is considered to contribute to this and is mediated by serotonin receptors (5-HT3 subtype). Ondansetron, a 5-HT3 receptor antagonist, is assumed to block the effect of serotonin and inhibit BJR. The aim of this study was to evaluate the effect of two different doses of ondansetron on maternal hemodynamics, need for vasopressors, maternal complications & neonatal outcome when given as prophylaxis during spinal anesthesia for caesarean section. **Materials and Methods:** A hospital based single blinded prospective, randomized, placebo-controlled study was done (from June 2021 – May 2022) on 90 antenatal patients divided into three groups (Group 04 -ondansetron 4mg, Group O6-onansetron 6mg, Group N-normal saline 5ml), each containing 30 patients. All the patients were monitored for blood pressure, heart rate, vasopressor requirement, Neonatal outcomes and side effects. Hemodynamic variables and demographic data were compared by analysis of variance (ANOVA) and Chi-square test was used for analyzing adverse effects and P value <0.05 was considered significant. **Results:** Ondansetron (4mg and 6 mg) group had less fall in Systolic blood pressure, diastolic blood pressure & mean arterial pressure with significant P value (<0.05) Also O6 groups had improved SBP, DBP,& MAP profile compared to O4 groups with P value <0.05. Need for vasopressor use was significantly reduced in O6 group compared to O4, and N groups. Neonatal Outcomes measured by APGAR score, found to be comparable with no significant difference among all three groups. **Conclusions:** Intravenous ondansetron given prophylactically attenuate the incidence of hypotension and requirement of vasopressors in patients undergoing CS under spinal anesthesia, with a further decrease in requirement of vasopressor in Group O6.

KEYWORDS

Bezold-Jarisch reflex, caesarean section, ondansetron, spinal induced hypotension, Blood pressure

INTRODUCTION

Neuraxial analgesia techniques are considered the most effective methods to provide pain relief during labor .Spinal anesthesia is now considered the method of choice for urgent or elective Caesarean section. The most common side effects of this method include hemodynamic changes, nausea and vomiting, back pain, and headache, altered consciousness, failed or total block, and sometimes increases the risk of aspiration Specifically Spinal anesthesia induced hypotension and bradycardia is of significant concern as it occurs in approximately 1/3 of non-obstetric patients, compared to 70-80% in obstetric population.

Also, the occurrence of hypotension can be dangerous as it can compromise the uteroplacental circulation.

In the term pregnant woman, baseline HR, stroke volume, and cardiac output are already increased to meet the metabolic demands of the fetus, impairing the ability of the cardiovascular system to compensate hypotension. The supine position causes the gravid uterus to compress the inferior vena cava, reducing venous return and cardiac output.

BJR is an inhibitory parasympathetic reflex originating in cardiac sensory receptors caused by decreased filling of the right atrium. In the setting of decreased blood volume, serotonin sensitive chemoreceptors and mechanoreceptors induces the Bezold Jarisch reflex via 5-HT3 receptors located in intracardiac vagal nerve endings, leading to bradycardia and hypotension.

Ondansetron is a serotonin receptor subtype 3 (5-HT3) antagonist. Aside from its central action in the brain, ondansetron binds to 5-HT3 receptors peripherally, including those within the cardiac ventricles and on the vagus nerve, which help to mediate the BJR Binding these receptors prevents induction of the BJR and decreases parasympathetic dominance, lessening the degree of bradycardia and hypotension brought about by spinal anaesthesia[1]

In multiple studies Ondansetron has been shown to reduce the incidence of spinal anaesthesia induced hypotension and the dose requirement of vasopressor needed to treat or prevent hypotension. However, studies with conflicting outcomes also have a list.

So, in this study we will try to evaluate the efficacy of administering intravenous ondansetron prior to spinal anaesthesia to attenuate hemodynamic compromise in patients of elective Caesarean section. To our knowledge, the optimal dose of ondansetron in this regard not recommended yet.

MATERIALS AND METHOD

This study was a hospital based single blinded prospective, randomized, placebo-controlled study , done for period of 1 year from June 2021 – May 2022. Sample size of 90 antenatal patients was taken and were randomly divided into three groups (GROUP 04 - ondansetron 4mg, GROUP O6-onancetron 6mg, GROUP N-normal saline 5ml), each containing 30 patients. The study population was selected from the patients who were electively posted for LSCS during our study period using inclusion and exclusion criteria of our study.

The study was undertaken after obtaining Institutional Ethical committee clearance and written informed consent from the patients.

The patients included were 19- 39 years pregnant ASA GRADE II women undergoing Elective LSCS at term with singleton baby. Patients excluded were those with H/O Allergy to Ondansetron, Coagulopathies, Infections at spinal injection site, Severely altered spine anatomy, Pre-existing neurological deficits, Hypertensive disorders, Patients on SSRI (Selective serotonin reuptake inhibitors),Patient with ASA Grade III and IV, Multiple parities (twins /triplets),Expected blood loss more than 1000ml, Patients who presented with cardiac history (coronary artery disease, myocardial infraction, congestive heart failure, murmurs, mitral valve prolapse/regurgitation, dysrhythmias, aortic stenosis/regurgitation).

After the arrival of the patient to operating room, an IV line is secured in right forearm with a 18 Gauze cannula and patient was pre-loaded with 500 ml Ringers lactate, patients were monitored for ECG tracing, heart rate, non-invasive arterial blood pressure and SPO^2 via pulse oximeter.

2.2 to 2.4 ml of 0.5% of injection hyperbaric bupivacaine heavy as Spinal Anesthesia. Immediately after injection, patients were laid supine with left lateral uterine displacement, after spinal procedure parameters were observed initially at an interval of 1min after spinal anesthesia, followed by interval of 5min,10min,15min,20min,25min,

30min and 45 mins till the completion of surgery

Surgery was started after establishment of the surgical blockade. Oxygen@5 L per minute was administered by face mask until the end of surgery.

Statistical Analysis

Sample size was calculated using software EpiInfo™ 7 with the assumption of alpha error 5%, that is, confidence level 95%, and beta error to be 20%, that is, power of study to be 80% and odds ratio of 2, a sample size of 30 patients in each group was sufficient to detect a 20% reduction in SBP among the groups. Thus, total of 90 patients were considered for the study. Data were presented as mean, standard deviation, median (range), or percentage, as appropriate. Comparison of numerical variables between study groups was done using unpaired student t- test and Manny Whitney U test for symmetric and asymmetric data respectively. Hemodynamic variables and demographic data were compared by analysis of variance (ANOVA) test while Chi-square test was used for adverse effects. Significance was determined at P value <0.05.

RESULTS

Age distribution, BMI , SPO2, Neonatal Outcomes measured by APGAR score , amounts of fluids given to the patients ,amounts of blood lost ,Duration of surgery across the 3 groups were found to be comparable with no significant difference. Baseline SBP were non-significant across 3 groups. (P value between O4 & N group (0.321), O6 group & N (0.511) were Nonsignificant. From T1 to T25 , O6 group had shown significant difference with Respect to Normal saline group in comparison to O4 group.(fig 1). Baseline DBP were non-significant across 3 groups. (P value between O4 & N group (0.270), O6 group & N Group (0.814) were Nonsignificant. From T1 to T15, then again at T25,T30 ; O6 group had shown significant difference with Respect to Normal saline group in comparison to O4 group, which implied higher dose (6mg) ondansetron had significant effect on the Diastolic BP at respective intervals after SA.

Baseline MAP were non-significant across 3 groups. (P value between O4 & N group (0.146), O6 group & N (0.550) were Nonsignificant. From T1 to T30, O6 group had shown improved MAP with significant difference with Respect to Normal saline group in comparison to O4 group, which implied higher dose (6mg) ondansetron had significant effect on the MAP at respective intervals after SA.

Fig. 1a Multiple Comparison Of Mean Arterial Pressure At Different Timelines Between The Three Groups

Time	(Group)	Group N	Sig. (P value)
T0	O4	NS	0.146
	O6	NS	0.55
T	O4	NS	0.001
	O6	NS	0.998
T1	O4	NS	0.324
	O6	NS	<0.001
T5	O4	NS	0.014
	O6	NS	<0.001
T10	O4	NS	0.219
	O6	NS	<0.001
T15	O4	NS	<0.001
	O6	NS	<0.001
T20	O4	NS	0.957
	O6	NS	0.021
T25	O4	NS	<0.001
	O6	NS	<0.001
T30	O4	NS	0.065
	O6	NS	0.008
T45	O4	NS	<0.001
	O6	NS	0.153

Fig. 1b Multiple Comparison Of Mean Arterial Pressure At Different Timelines Between The Three Groups

	NS	O4 GROUP	O6 GROUP	P Value
MAP(MMHG)_Baseline	93.77± 5.76	90.8± 8.27	94.23± 5.71	0.104
MAP(MMHG)_T 10_MIN AFTER Study Drug	93.4± 3.75	91.6± 3.4	93.44± 4.17	0.098
MAP(MMHG)_T1_1 MIN AFTER Spinal Anaesthesia	91.23± 3.38	87.43± 1.98	92.98± 4.17	<0.001
MAP(MMHG)_T5_5 Min after SA	89± 2.67	85.13± 1.61	92.08± 4.35	<0.001
MAP(MMHG)_T10_10 Min after SA	86.97± 1.82	88.01± 1.61	93.59± 3.67	<0.001
MAP(MMHG)_T15_15 Min After SA	82.43± 2.39	90.7± 2.17	95.17± 3.93	<0.001
MAP(MMHG)_T20_20 Min After SA	92.2± 2.93	92± 2.69	94.3± 3.72	<0.001
MAP(MMHG)_T25_25 Min after SA	89.5± 2.42	94± 2.46	93.03± 3.35	<0.001
MAP(MMHG)_T30_30 Min After SA	90.71± 2.49	92.37± 3	93± 3.44	<0.001
MAP(MMHG)_T45_45 Min SA	90.4± 2.62	93.07± 2.46	91.6± 2.94	<0.001

Need for use of vasopressor medicines in patients with lower MAP < 70 mmhg across the three groups, when compared; found significant differences (P value 0.35) implying O6 group have lower requirement of Vasopressor than compared to O4 group. Both groups had significant lower need than compared to normal saline group.

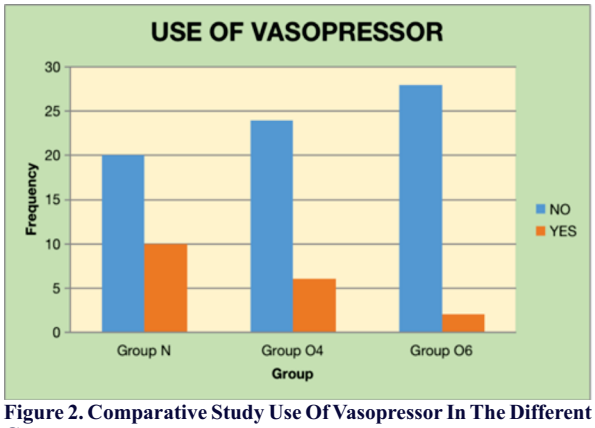

Figure 2. Comparative Study Use Of Vasopressor In The Different Groups

The O6 mg group showed Significantly better effects than Normal saline compared to O4 group in preventing common adverse effects like nausea, vomiting, Shivering etc. (P value (<0.0013)

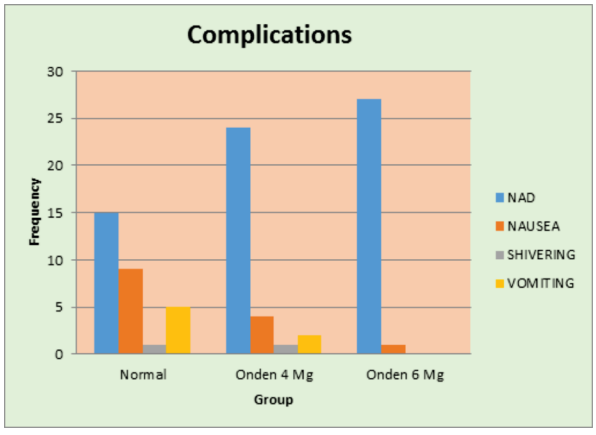

Fig 3. Distributiion Of Different Complications Between The Three Groups

DISCUSSION

The high incidence of post spinal hypotension needs combination of different methods for prevention and management of this problem. Spinal hypotension in LSCS is a common daily situation and a challenge to all anaesthetists. Focusing on simple and rapid protocols that can be easily applied by anaesthetists with moderate and low experience and minimal need to complex devices is necessary. Though Multiple strategies employed to prevent spinal induced hypotension include fluid preloading/coloading, prophylactic vasopressors, Trendelenburg positioning, use of lower dose of

anaesthetic agents, none has come out as front runner as standard management for prevention of hypotension. Furthermore, administration of vasoconstrictors may have adverse effects on uterine blood flow in pregnant women. Therefore it is always righteous to prevent hypotension rather than treating it. In many previous studies Ondansetron has been shown to reduce the incidence of spinal anaesthesia induced hypotension and the dose requirement of vasopressor needed to treat or prevent hypotension. The optimal dose of ondansetron in this regard not recommended yet. In this study 90 antenatal patients were randomly divided into three groups "Ondansetron 4mg(O4)" "Ondansetron 6mg(O6)" & Group N(Normal Saline) 5ml groups, each containing 30 patients. We observed after analysing all the data that Compared to the Normal saline group, Ondansetron (4mg and 6 mg) group had less fall in Systolic blood pressure, diastolic blood pressure & Mean arterial pressure with significant P value (<0.05) Also Group O6 groups had improved SBP, DBP,& MAP profile compared to Group O4 groups with P value <0.05. Baseline hemodynamic parameters, anthropometric measurements, demographic profiles, ASA grading were found to have non-significant differences across the three groups compared. Our study results are similar to Anil Kumar Bhiwal et al [2] who did a prospective randomized double-blinded controlled study in 150 full-term parturient (Divided into 3 groups Normal Saline, Ondansetron 4 mg, or 8 mg). Intraoperative incidence of hypotension was found significantly higher (P < 0.001) in normal saline (58%) as compared to group O8 (16%) and group O4 (31.25%). Total requirement of ephedrine (mg) was also significantly higher in normal saline group when compared to group O8. On comparison of group O8 and O4, the incidence of hypotension was higher in O4 group (31.25%) as compared to O8 (16%) (P = 0.074) while the requirement of total dose of ephedrine was found to be significantly higher (P = 0.034) in O4 as compared to O8. Our study is also in accordance with the study of D Tubog T, S Bramble R. et al [3] which did a systematic review and meta-analysis found, Patients treated with ondansetron have higher mean arterial pressure 15 to 20 minutes after spinal anaesthesia induction and higher systolic arterial pressure 5, 10, 15 and 20 minutes after spinal anaesthesia.

Randomized control trial done in China in 2014 by Wang M, Zhou L, Wang Q et al [4] in 150 patients, gave ondansetron in different doses (Group 2 mg, 4 mg, 6 mg. or 8 mg) and compared with Group Normal Saline(5 ml) .They found that those mothers who received 4mg and 6 mg were statistically significant (p<0.005) but those who had taken 2mg and 8mg was not statistically significant (p>0.005).

Arivumani, Arul Anne Rose, Usha Devi et al, Sahoo T et al, Sharad Narayan Sharma et al [5] studies echoed similar conclusion that ondansetron reduces the spinal induced hypotension; reduced requirement of vasopressors in Ondansetron group compared to placebo group. Most of these studies used 4 mg ondansetron in their studies, on the other hand, we used both 6mg & 4 mg of ondansetron doses, in which we got better results with 6 mg compared to 4 mg group.

Our study findings were in opposing to the some of the studies in certain results. Ortiz-Gomez et al. [6] found the incidence of hypotension in control group and ondansetron group (2, 4, and 8 mg) were comparable but larger doses of ondansetron significantly decreased ephedrine requirement in a dose-dependent fashion. Also, Marciniak A et al [7] did not find any difference in the incidence of hypotension and requirement of vasopressors in the placebo and ondansetron groups; hypotension was observed in 14(39%) in ondansetron group and 15(44%) in Placebo group (p>0.005). The observed difference was due to they have used 8 mg of ondansetron as prophylaxis. There is also study done in United State of America by Terkawi et al [8], that compared 8mg ondansetron with normal saline, they found there is no statistical difference between the groups (p>0.05); however, in our study there was significance difference between the control and study groups.

No major complications / adverse events in any of the groups. The O6 mg group showed Significantly better effects than Normal saline compared to O4 group in preventing common adverse effects like nausea, vomiting, Shivering etc. (P value (<0.0013). Other parameters like amounts of blood lost & quantities of fluids infused during the procedure, duration of the surgery across the three groups were comparable and non-significant. Neonatal Outcomes measured by APGAR score found to be comparable with no significant difference among all three groups. Safety of ondansetron use in terms of neonatal APGAR scores and the pH of the umbilical artery, when used for prevention of hypotension in parturient undergoing caesarean section, have also been demonstrated in the studies by Trabelsi et al [9], Wang Q et al and Wang M et al [4]

A meta-analysis conducted by Gao et al. [10] included 10 randomized controlled trials with 863 patients who underwent surgical procedures under spinal anesthesia. This database review suggested that prophylactic administration of I.V ondansetron reduces the incidence of spinal anesthesia-induced hypotension and vasopressor consumption in both obstetric and non-obstetric patients.

The strength of the study is that we have tried to make comparable study groups in terms of socio demographic distribution, perioperative and clinical factor that affect study outcome so that the difference observed may be due to exposure factors. This study has certain limitations small number of patients and also this study was single blinded study which may have led to biased results.

CONCLUSION

On the basis of our study, we conclude that, compared to the Normal saline group, Ondansetron (4mg and 6 mg) group had less fall in Systolic blood pressure, diastolic blood pressure & Mean arterial pressure. Also, O6 groups had improved SBP, DBP,& MAP profile compared to O4 groups. It can be concluded by our results that 6mg ondansetron prophylaxis given intravenously 10 minutes prior to spinal anesthesia decreases the incidence of spinal induced hypotension and need for vasopressor medications for parturient undergoing elective cesarean section.

Though many studies as mentioned above are supportive of the evidence that ondansetron helps in reducing the incidence of post spinal anesthesia hypotension; Further research for comparative dose study of ondansetron across different population group, with more patient sample should be directed, so that it helps toward finding an optimum dose of ondansetron. The finding of the study supports use 6 mg prophylactic ondansetron 10 minutes prior, to all elective cesarean section undergoing spinal anesthesia to prevent spinal induced hypotension except those who are contraindicated.

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