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Research Article

COMPARISION OF GRANISETRON AND ONDANSETRON FOR ATTENUATION OF SUBARACHNOID BLOCK INDUCED HYPOTENSION IN PARTURIENTS UNDERGOING ELECTIVE CAESAREAN SECTION: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

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A B S T R A C T

Background: Maternal hypotension after subarachnoid block (SAB) for cesarean section can jeopardize the fetus and the mother. Bezold Jarisch Reflex (BJR), mediated through serotonin or 5-hydroxytryptamine (5-HT), has been implicated as a cause. Antagonism of serotonin, therefore, alleviates BJR, inhibits peripheral vasodilatation, increases venous return to the heart, thereby alleviating hypotension

Aims: Aims of our study were to compare the effects of two selective 5-HT3 receptor antagonists Ondansetron and Granisetron on SAB induced hypotension, regression of sensory and motor blockade and the incidence of nausea and vomiting in parturients undergoing elective LSCS.

Methods: We had randomized 120 pregnant women, aged 20-40 years with uncomplicated pregnancies, ASA grade 1 and 2, scheduled for elective LSCS to one of the three groups with 40 patients each. Study drugs were administered intravenously 5min prior to SAB; Group A: Inj Ondansetron 4 mg (in 10 ml NS); Group B: Inj Granisetron 1 mg (in 10 ml); Group C: NS 10 ml. Patient's systolic, diastolic and mean arterial pressure and heart rate were recorded at pre-assigned regular intervals till the end of surgery. Time to maximum sensory and motor block as well as regression of blocks and any nausea/vomiting or shivering were also recorded. The statistical analysis was done using Statistical Package for Social Sciences Version 15.0. ANOVA was used to compare the intergroup differences and change within groups was compared using paired't' test. Proportional differences were analysed using Chi-square test. p value < 0.05 was considered to be significant.

Results: We observed significant differences in MAP between all three groups ($p < 0.001$) at most time intervals. In Group A, there was no steep decline in MAP as compared to other two groups. Consequently, requirement of vasopressor was significantly lesser in Group A ($p<0.001$). No significant changes in HR was noted between the groups. The sensory regression ($p<0.001$), maximum motor block ($p=0.02$) and time to motor recovery by one level ($p=0.018$) were significantly earlier in Group B. Nausea/vomiting was experienced in a significantly lesser ($p <0.001$) number of cases in Group B (7.5%) as compared to Group A (22.5%) and Group C (47.5%)

Conclusions: Both ondansetron and granisetron significantly decreased the degree of hypotension and hence the requirement of vasopressor, however ondansetron was more effective and prevented maternal hypotension for a longer time period, thus providing better haemodynamic stability. Granisetron induced faster motor blockade as well as sensory recovery compared to both ondansetron and placebo. Both the drugs significantly reduced the incidence of nausea and vomiting, granisetron being more effective.

INTRODUCTION

Spinal anesthesia or Sub Arachnoid Block (SAB) has been the most popular choice for elective caesarean section (LSCS) since it offers various advantages like avoiding risks of general anaesthesia, effective postoperative pain relief and offering the new mother an instant first glimpse of her baby.[1] It is generally preferred over epidural anaesthesia because of the simplicity of technique, a rapid onset dense surgical block, low drug dose and thereafter decreased systemic toxic effects.[2,3] Hypotension and bradycardia are the most frequent complications encountered after SAB, their incidence in obstetric patients being as high as 50-80%.[4] Hypotension is

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hazardous for the mother and the baby as it can cause loss of consciousness, aspiration and even cardiac arrest for the mother and uteroplacental hypoperfusion leading to foetal bradycardia and neurobehavioral changes in the newborn.[5,6,7]

In this study, we used Ondansetron and Granisetron to minimize the occurrence of maternal hypotension after SAB. These two drugs are selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonists and are safe to use during pregnancy.[8,9] The rationale behind use of these drugs was the recent implication of Bezold Jarisch Reflex (BJR) in the phenomenon of hypotension following SAB in numerous studies.[10,11] BJR explains the occurrence of hypotension after SAB through serotonin or 5-HT.[12] Stimulation of cardiac chemoreceptors in the heart by decreased venous return increases the parasympathetic activity and decreases the sympathetic activity resulting in vasodilatation and bradycardia.[13] Antagonism of serotonin, therefore, alleviates BJR, inhibits peripheral vasodilatation, increases venous return to the heart, thereby alleviating hypotension.[12]

Aims and Objectives:

The primary aim of our study was to compare the effects of ondansetron and granisetron on the SAB induced hypotension after intrathecal hyperbaric bupivacaine and the secondary objectives were to study their effects on regression of sensory and motor blockade and the incidence of nausea and vomiting in parturients undergoing elective LSCS.

MATERIALS AND METHODS

This randomised prospective placebo-controlled double-blind study was undertaken in the department of Obstetrics and Gynaecology of our institute over a period of one year (Sept 2013 - Aug 2014) after obtaining clearance from Institutional ethical committee and informed consent from all the patients. A total of 120 pregnant women, aged 20-40 years, at term, with uncomplicated pregnancies, ASA grade 1 and 2, scheduled for elective LSCS were included in this study and were randomly allocated to one of the three groups with 40 patients each, using computer generated random number generation method. Blinding was done by the use of labeling and encoding method.

Exclusion criteria were: (a) Patient's refusal (b) Unstable haemodynamics, cardiovascular insufficiency or fixed cardiac output states (c) Hypertensive disorders of pregnancy, Diabetes mellitus or other causes of peripheral neuropathy and autonomic dysfunction (d) Known history of allergy to local anaesthetics or study drugs (e) Patients taking ant-migraine or receiving selective serotonin reuptake inhibitors. (f) Patients with coagulation abnormalities, or on anticoagulants (g) Features of soft tissue infection at the site of spinal block.

A detailed pre-anaesthesia evaluation was conducted on the evening before surgery assessing general condition of the patient with complete antenatal history, nutritional status and weight of the patient, other associated diseases, detailed systemic examination and review of relevant investigations. Patients were explained about the study and informed consent was obtained. All patients were instructed to keep fasting for 8 hours preoperatively.

On arrival of patient in the operating room, a 16-gauge/18-gauge cannula was inserted for peripheral intravenous (IV) access. All patients were preloaded with ringer's lactate @20 ml/kg/hr over 30 min and infusion was continued at 15 ml/kg/hr till the end of surgery. All patients received Inj ranitidine 1mg/kg IV and Inj metoclopramide 0.4 mg/kg IV. Study drugs were administered IV after preloading and approximately 5 minutes prior to performance of SAB as per the following groups:

Group A: Inj Ondansetron 4 mg diluted in 10 ml of normal saline
Group B: Inj Granisetron 1 mg diluted in 10 ml of normal saline
Group C: Normal saline 10 ml (without any drug)

Standard anaesthesia monitors were attached and baseline noninvasive blood pressure (NIBP), heart rate (HR) and oxygen saturation (SpO_2) were recorded and cardiac rate and rhythm were also monitored from a continuous visual display of electrocardiogram from lead II. Approximately 5 min after administration of study drugs, SAB was performed with patients in sitting position using the midline approach at levels L_3-L_4 or L_4-L_5 intervertebral space with a 25 or 27 gauge Quincke-tip spinal needle after taking strict aseptic precautions. Once a free flow of cerebrospinal fluid was obtained, 2 ml of 0.5% hyperbaric bupivacaine with 25µg fentanyl was administered intrathecally over 15 seconds. Left uterine displacement was maintained till the end of surgery.

A resident anesthesiologist blinded to the study drug solution recorded the HR, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) every 3 min for first 20 min and then at 5 min interval till the end of surgery which was approximately 60 min in all patients. The resident also recorded the occurrence of any side effects like nausea/vomiting, shivering or inadequate analgesia. The upper sensory level was assessed by bilateral loss of pinprick at the mid-clavicular line every 2 min till the fixation of sensory level (same at two consecutive times), and this was recorded as the maximum sensory level; then, the patients were evaluated every 15 min till sensory level regression to S_1. Motor block was assessed every 2 min till the complete motor block, then every 15 min till complete motor recovery on a previously described Modified Bromage scale (0: able to move hip, knee, ankle, and toes; 1: unable to move hip, able to move knee, ankle, and toes; 2: unable to move hip and knee, able to move ankle and toes; 3: unable to move hip, knee and ankle, able to move toes; 4: unable to move hip, knee, ankle and toes).[14] From the recorded variables, the following time intervals were assessed, defined as time elapsed from spinal injection to:

1. Maximum Sensory block(TUSB)
2. Regression of sensory level by two dermatomes(TTSR)
3. Regression of sensory level to T_{10} (TSR T_{10})
4. Regression of sensory level to T_{12} (TSR T_{12})
5. Regression of sensory level to S_1 (TSR S_1)
6. Maximum motor block (modified Bromage scale 4)(TMB4)
7. Motor recovery by one level (modified Bromage scale 3)(TMB3)
8. Complete motor recovery (modified Bromage scale 0)(TMB0)

If the MAP fell below 60 mmHg, Inj phenylepherine 50µg IV bolus was administered. If the HR dropped below 50 beats/min, Inj atropine 0.4mg IV was administered. In these cases, measurements prior to pharmacological intervention were recorded and considered for analysis. Rigors and pain were treated with Inj Tramadol 25 mg IV and Inj Fentanyl 50 µg IV (only to be given after delivery of baby), respectively. Nausea/vomiting was treated with Inj promethazine 12.5 mg IV. Pain that persisted after a single dose of fentanyl was considered a failed spinal anaesthesia, was converted to general anaesthesia, and the patient excluded from the study.

Statistical analysis: The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 Statistical Analysis Software. The values were represented as Number (%) and Mean±SD. ANOVA was used to compare the intergroup differences and change within groups was compared using paired't' test. Proportional differences were analysed using Chi-square test. p value < 0.05 was considered to be significant.

Sample size calculation*:* The sample size calculation was based on a 7 mmHg difference observed by Owczuk *et al*. in non-pregnant patients[15]. In order to detect a 6 mmHg difference in MAP between groups with 80% power and 5% probability of type I error, a sample size of 23 subjects per group was required. However, considering for dropouts and to keep the sample size within reasonable limits for quantitative assessment, we kept a sample size of 40 in each group.

RESULTS

In the present study, the groups were comparable with respect to age (p=0.968) [Table 1] and previous obstetric history including parity, gravid status and history of previous LSCS [Table 2].

Table 1 Intergroup Comparison of Age of Study Population

	Group A (n=40)	Group B (n=40)	Group C (n=40)	Total (n=120)	F	p
Mean age ± SD (years)	25.50±3.07	25.65±3.04	25.65±3.04	25.60±3.02	0.032	0.968

Table 2 Intergroup Comparison of Previous Obstetric History of Study Population

Variables	Group A (n=40)	Group B (n=40)	Group C (n=40)	Total (n=120)
	No.(%)	No.(%)	No.(%)	No.(%)
	Gravida			
1	29(72.50)	21(52.50)	20(50.00)	70(58.33)
2	7(17.50)	14(35.00)	13(32.50)	34(28.33)
3	4(10.00)	5(12.50)	7(17.50)	16(13.33)
	χ^2=5.490(df=4); p=0.241(NS)			
	Parity			
1	29(72.50)	21(52.50)	20(50.00)	70(58.33)
2	7(17.50)	14(35.00)	13(32.50)	34(28.33)
3	4(10.00)	5(12.50)	7(17.50)	16(13.33)
	χ^2=5.490(df=4); p=0.241(NS)			
Previous LSCS	11(27.50)	9(22.50)	7(17.50)	27(22.50)
	χ^2=1.147 (df=2); p=0.564 (NS)			

There were no significant differences between the three groups regarding gestational age, fetal lie, presentation and the incidences of contracted pelvis and cephalopelvic disproportion during the current pregnancy [Table 3]. Also, the baseline haemodynamic variables including the MAP, HR and SpO2 were comparable in all three groups.

Table 3 Intergroup Comparison of Present Obstetric History of Study Population

Variables	Group A (n=40)	Group B (n=40)	Group C (n=40)	Total (n=120)
	No.(%)	No.(%)	No.(%)	No.(%)
	Gestational Age (Weeks)			
36-37	8(20.00)	12(30.00)	14(35.00)	34(28.34)
38-39	16(40.00)	13(32.50)	13(32.50)	42(35.00)
40-42	16(40.00)	15(37.50)	13(32.50)	44(36.67)
	χ^2=3.991 (df=10); p=0.998 (NS)			
Cephalopelvic Disproportion	13(32.50)	14(35.00)	10(25.00)	37(30.83)
	χ^2=1.016 (df=2); p=0.602 (NS)			
Contractedpelvis	9(22.50)	7(17.50)	12(30.00)	28(23.33)
	χ^2=1.770(df=2); p=0.413(NS)			
Transverse Lie	5(12.50)	12(30.00)	10(25.00)	27(22.50)
	χ^2=3.728 (df=2); p=0.155 (NS)			
	Presentation			
Breech	8(20.00)	14(35.00)	12(30.00)	34(28.33)
Head	28(70.00)	23(57.50)	24(60.00)	75(62.50)
Shoulder	4(10.00)	3(7.50)	4(10.00)	11(9.17)
	χ^2=2.389(df=4); p=0.665 (NS)			

It was observed that the HR of Group A was more than Group B which in turn, was more than Group C at all time intervals till the end of operation [Table 4]. However this difference was statistically insignificant except at 3 min (p=0.022), 21 min (p=0.006) and 30 min (p=0.024). Moreover, the changes in HR from baseline in all the groups were too small to be of any clinical importance [Figure 1]. In fact, the mean HR was never below 75 beats/min in any of the study groups.

Table 4 Intergroup Comparison of Heart Rate at different time intervals

Variables	Group A	Group B	Group C	Statistical Significance	
	Mean±SD	Mean±SD	Mean±SD	F	'p'
Baseline	79.23±4.68	78.00±4.78	77.08±4.17	2.248	0.110
At 3 min	82.28±5.49	80.35±4.42	79.43±3.83	3.947	**0.022**
At 6 min	81.93±6.12	81.38±4.26	81.88±4.55	0.146	0.865
At 9 min	83.10±5.40	82.30±4.06	83.10±4.68	0.379	0.686
At 12 min	83.48±5.11	82.23±3.87	82.13±5.12	1.010	0.367
At 15 min	83.40±4.22	83.20±3.32	82.16±5.21	0.829	0.439
At 18 min	83.88±3.41	84.34±3.85	82.00±4.50	2.469	0.090
At 21 min	84.18±3.19	83.47±3.12	81.16±3.89	5.429	**0.006**
At 25 min	84.38±3.66	82.91±8.14	82.05±5.94	1.083	0.343
At 30 min	84.68±4.18	83.26±2.59	81.68±4.93	3.887	**0.024**
At 35 min	83.29±3.32	81.87±2.62	81.05±5.31	2.609	0.080
At 40 min	83.47±2.96	82.65±2.70	81.84±5.97	1.181	0.312
At 45 min	82.06±2.87	82.84±1.13	81.26±5.55	1.402	0.252
At 50 min	81.71±4.35	82.94±3.00	80.58±5.38	1.939	0.150
At 55 min	82.79±4.18	83.58±2.51	81.79±4.58	1.346	0.266
At 60 min	81.53±6.08	83.77±0.76	81.21±5.40	2.529	0.086

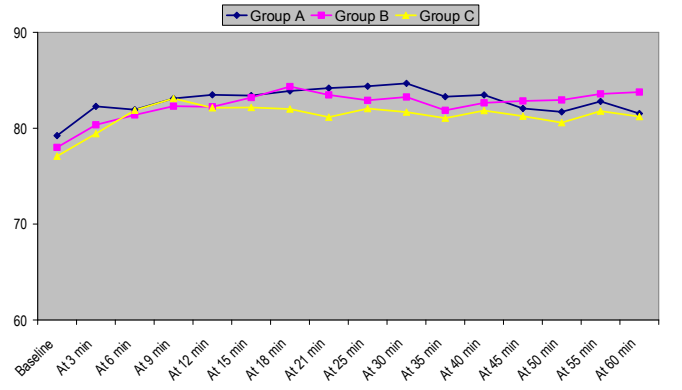

Figure 1 Intergroup Comparison of Change in Heart Rate from Baseline (Paired 't' test)

We observed significant differences in MAP between all three groups (p <0.001) at all time intervals upto 30 min (except at 21 min) and there was no significant difference thereafter [Table 5].

Table 5 Intergroup Comparison of Mean Arterial Pressure at different time intervals

Variables	Group A	Group B	Group C	Statistical Significance	
	Mean±SD	Mean±SD	Mean±SD	F	'p'
Baseline	101.80±3.31	102.05±3.20	102.45±3.24	0.407	0.667
At 3 min	99.50±3.88	97.33±2.99	89.73±5.22	61.675	<0.001
At 6 min	95.95±4.41	91.55±4.28	82.33±5.35	87.414	<0.001
At 9 min	92.98±4.55	87.43±6.32	74.60±7.14	95.595	<0.001
At 12 min	91.58±5.42	84.13±8.26	68.10±6.39	124.716	<0.001
At 15 min	89.05±6.32	81.65±8.75	69.55±8.77	52.291	<0.001
At 18 min	85.35±5.81	84.13±8.66	77.89±2.35	8.395	<0.001
At 21 min	83.20±7.45	85.39±12.74	84.37±2.69	0.533	0.589
At 25 min	81.05±7.69	91.94±11.32	89.42±5.11	15.094	<0.001
At 30 min	84.58±9.72	93.19±4.49	91.47±4.59	13.321	<0.001
At 35 min	94.40±6.16	94.42±1.34	92.68±5.20	0.985	0.378
At 40 min	95.47±2.65	96.39±1.28	94.58±5.61	1.889	0.158
At 45 min	96.24±3.81	97.23±1.98	95.05±6.74	1.609	0.206
At 50 min	97.74±4.11	96.32±2.29	96.16±7.49	1.042	0.357
At 55 min	95.38±4.08	97.45±2.75	96.68±5.89	2.051	0.135
At 60 min	96.15±4.38	97.39±1.82	99.00±7.10	2.473	0.091

It is noteworthy that amongst the three groups, the mean value of MAP of Group C fell most steeply and reached its minimum value (68.10±6.39 mm Hg) at 12 min [Figure 2].

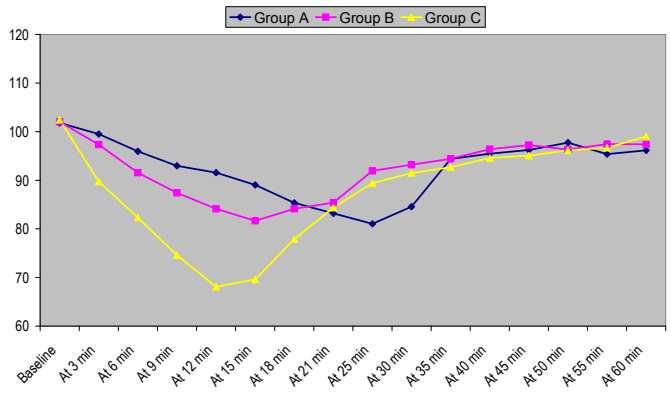

Figure 2 Intragroup Comparison of Change in Mean Arterial Pressure from Baseline (Paired 't' test)

Comparatively, the fall in mean value of MAP was less steep in Group B and reached a nadir of 81.65±8.75 mm Hg at 15min. However, in Group A, there was no steep decline of the mean value of MAP as compared to the other two groups B and C and it fell gradually to a minimum value of 81.05±7.69 min at 25 min. In all the three groups fluctuations were observed for about 10 min and the MAP was restored to baseline with or without vasopressor support.

Vasopressor support was required during the procedure in higher proportion of subjects in Group C (52.50%) as compared to Group A (15.00%) and Group B (25.00%); this difference was found to be statistically significant (p<0.001) [Table 6].

Table 6 Intergroup Comparison of Requirement of Vasopressor in Study Population

	Group A (n=40)	Group B (n=40)	Group C (n=40)	Statistical Significance	
	No. (%)	No. (%)	No. (%)	χ2	'p'
Requirement of Vasopressor	6 (15.00)	10 (25.00)	21 (52.50)	14.145	**<0.001**

Phenylephrine was required at an early stage in Group C and Group B as compared to Group A and this difference was found to be statistically significant (p<0.001) [Table 7].

Table 7 Intergroup Comparison of time of requirement of Vasopressor (from start of procedure)

	Group A (n=40)	Group B (n=40)	Group C (n=40)	Total (n=120)
Number of subjects	6	10	21	37
Minimum duration (min)	25	15	12	12
Maximum duration (min)	35	25	15	35
Median	30	20	15	15
Mean±S.D.	29.17±3.76	20.50±3.69	13.71±1.52	18.05±6.32
Statistical significance	F=84.871; p<0.001			

There were no statistically significant difference in incidence of shivering, pain or bradycardia. Nausea/vomiting was experienced in a significantly lesser (p <0.001) number of cases in Group B (7.5%) as compared to Group A (22.5%) and Group C (47.5%) thus proving that granisetron was more efficacious in preventing nausea/vomiting after SAB [Table 8]. No patients underwent conversion to general anaesthesia or were excluded due to inadequate SAB.

Table 8 Intergroup Comparison of Complications/Side Effects in Study Population

Variables	Group A (n=40)	Group B (n=40)	Group C (n=40)	Statistical Significance	
	No. (%)	No. (%)	No. (%)	χ2	'p'
Nausea and vomiting	9 (22.50)	3 (7.50)	19 (47.50)	17.050	<0.001
Shivering	4 (10.00)	5 (12.50)	9 (22.50)	2.745	0.253
Pain	2 (5.00)	3 (7.50)	5 (12.50)	1.458	0.482

We didn't observe any significant difference in the time of fixation of sensory level (TUSB) among the three groups [Table 9].

Table 9 Intergroup Comparison of time of onset and duration of sensory and motor block

Variables (min)	Group A (n=40)	Group B (n=40)	Group C (n=40)	Statistical Significance	
	Mean±SD	Mean±SD	Mean±SD	F	'p'
TUSB (Time to upper sensory level block)	11.33±1.56	10.68±1.53	11.48±1.54	3.049	0.051
TTSR (Time to two segment regression)	78.95±6.58	71.43±6.54	88.73±4.52	84.739	<0.001
TSRT10(Time to sensory regression to T10	110.95±9.63	107.00±5.79	125.20±4.63	74.488	<0.001
TSRT12(Time to sensory regression to T12)	128.08±3.58	116.90±6.25	127.40±8.31	38.998	<0.001
TSR S1 (Time to sensory regression to S1)	191.73±10.06	182.65±18.86	167.93±30.15	1.144	0.322
TMB4 (Time to modefiedBromage scale = 4)	10.75±0.78	10.20±1.62	10.08±0.76	4.059	0.020
TMB3 (Time to modefiedBromage scale = 3)	118.63±5.84	115.28±17.61	124.75±17.95	4.156	0.018
TMB0 (Time to modefiedBromage scale = 0)	169.23±5.26	241.68±26.42	188.98±85.03	2.152	0.121

However, the mean time for two segments regression (TTSR) and regression to T_{10} and T_{12} in group B was significantly faster (p<0.001) than groups A and C. Time to attain maximum motor block (TMB4) and time to motor recovery by one level (TMB3) was found to be earlier with granisetron and the differences were statistically significant (p=0.02 and 0.018 respectively). Simultaneously, we observed that IV

ondansetron had no significant effect on onset and duration of sensory or motor block of intrathecal bupivacaine.

DISCUSSION

Spinal anesthesia for cesarean section may be associated with hypotension due to greater level of sympathetic blockade, aortocaval compression by the gravid uterus and a decreased systemic vascular resistance in pregnancy.[2] This can jeopardize the fetus and the mother.[16] So, for better maternal and fetal outcomes, it is important to prevent maternal hypotension during spinal anaesthesia.[17]

Numerous studies have highlighted the role of BJR mediated through serotonin or 5-HT in the phenomenon of hypotension following SAB [12]. Antagonism of serotonin, therefore, alleviates BJR, inhibits peripheral vasodilatation, increases venous return to the heart, thereby alleviating hypotension. [12,18]

The present study was aimed to compare the efficacy of two serotonin receptor antagonists, ondansetron and granisetron, for the prevention of SAB induced hypotension and bradycardia after intrathecal hyperbaric bupivacaine in parturients undergoing elective LSCS.

The 5-HT3 receptors are present also in the spine and have anti-nociceptive effect, which can be antagonized by selective 5-HT3 receptor antagonists. [19,20] Some previous studies had found that the level of serotonin increased significantly in cerebrospinal fluid after intrathecal bupivacaine, and the sensory block of intrathecal lidocaine was antagonized by ondansetron.[21,22,23] So, the effects of both these drugs on onset and regression of sensory and motor blockade were also studied.

In present study, administration of both the 5HT3 receptor blockers ondansetron and granisetron, 5 min before SAB, prevented maternal hypotension, however ondansetron prevented the fall in MAP for a longer time period (25 min) as compared to granisetron (15 min), providing the operating surgeon with a more haemodynamically stable patient and probably better maternal and neonatal outcome.

Several previous studies have also shown ondansetron to be efficacious in blunting the BJR and reducing the incidence of hypotension. Abbas *et al*. (2014) [24] had found ondansetron 4mg IV administered 5min before SAB to be effective in decreasing frequency of hypotension. Jarineshin *et al*. (2016) [25] also found less reduction of DBP and MAP after using ondansetron showing the preventive effect of ondansetron on serotonin-induced BJR. Arivumani *et al*.(2016) [26] reported lesser incidence of hypotension, bradycardia and vasopressor use after using 4 mg of ondansetron and Trabelsi *et al*. (2015) [27] reported similar findings using prophylactic ondansetron with bupivacaine and sufentanil in SAB. However, in contrast to our study, the study by Ortiz-Gómez *et al*. (2014)[28] showed that prophylactic ondansetron at 2, 4, or 8 mg IV had little effect on the incidence of hypotension in healthy parturients undergoing spinal anaesthesia with bupivacaine and fentanyl for elective cesarean delivery.

Granisetron was studied independently by Eldaba *et al*. (2015) [29] who showed that administration of 1 mg of granisetron 5 minutes before SAB can significantly reduce the incidence of hypotension in these patients in comparison with placebo (normal saline). They also reported a significantly lesser requirement of ephedrine and atropine in the granisetron group as compared to placebo group. However, contrary to our study, Saberi *et al*. (2016) [30] showed that IV administration of 3 mg of granisetron immediately before spinal anesthesia in parturients (ASA Class I) undergoing non-emergency cesarean surgery had no effect on spinal anesthesia-induced hypotension compared with placebo, but he conceded that further studies are required before a definite statement can be made. Mowafi *et al*. (2008)[19] also found that IVgranisetron administration had no effect on haemodynamic variables. Shrestha *et al*. (2015) [31] concluded that granisetron given intravenously does not decrease the incidence of hypotension and bradycardia following subarachnoid block in patients undergoing lower abdominal surgery. However, it attenuates the fall of diastolic and mean arterial pressure in spinal anesthesia.

Although significant differences in HR were observed between the groups on three occasions in our study, atropine was not required in any of these patient as there was no episode of bradycardia (HR<50bpm). Sahoo *et al.* (2012) [32] also reported similar findings in their study. Arivumani *et al*. (2016) [26] in their study, observed that episodes of bradycardia were low in ondansetron group but it was not found to be statistically significant.

Our study revealed that IV granisetron facilitated a significantly faster recovery of sensory block after bupivacaine SAB ($p < 0.001$) and also had significant effects on motor block. The time to attain maximum motor block (TMB4) and the time to motor recovery by one level (TMB3) were found to be significantly faster ($p=0.02$ and $p=0.018$ respectively). Our findings regarding sensory regression are in concordance with those of Rashad *et al*. (2013), [33] Mowafi *et al*. (2008),[19] Khalifa OSM (2015) [34] and Sayed *et al*. (2017) [35] who also concluded that IV granisetron facilitated a faster recovery of sensory block after bupivacaine subarachnoid anesthesia ($p=0.05$). However they reported no significant differences between the three groups with regard to regression of motor blockade. Simultaneously, we observed that IV ondansetron did not affect sensory or motor block of intrathecal bupivacaine similar to results of studies by Samra *et al.* (2011) [36] and Rashad *et al*. (2013) [33] but against the results of Fassoulaki *et al.* (2005) [21] who found that systemic ondansetron enhanced the sensory block regression after intrathecal lidocaine ($p= 0.019$).

The clinical implications in patients receiving granisetron is that an otherwise successful SAB may prove to be insufficient or of short duration. Secondly, patients with malignancies who experience intractable pain and receive these drugs as antiemetics, may exhibit resistance to analgesic techniques.

In our study, both granisetron and ondansetron were efficacious in preventing nausea/vomiting after SAB ($p<0.001$), granisetron being better than ondansetron. Babu *et al*. (2015) [37] also concluded that granisetron 1 mg I.V is much more effective than ondansetron 4 mg I.V. in minimising severe nausea/vomiting. Rashad *et al*. (2013) [33] and Sayed *et al*. (2017) [35] have also reported a significant reduction in incidences of nausea/vomiting with both ondansetron and granisetron, but they didn't find any significant differences between the two drugs.

A recent meta analysis conducted by Zhou *et al*. (2017)[38] corroborates that ondansetron effectively reduces the

incidences of nausea/vomiting and bradycardia under SAB during cesarean section. On the contrary, metaanalysis conducted by Terwaki *et al*. (2017) [39] fail to confirm evidence that ondansetron reduces the incidence of hypotension and bradycardia after SAB.

The differences between the effects of ondansetron and granisetron may be due to the action of ondansetron on mixed receptors and the high selectivity of granisetron for 5-HT3 receptors but minimal affinity for other 5-HT receptors, adrenergic, histaminic, dopaminergic, or opioid receptors. Also granisetron is not metabolized by the cytochrome P450 (CYP) 2D6 pathway and, therefore, is associated with less variation in patient response due to factors such as pharmacogenomic differences. The reason behind faster sensory regression and faster motor blockade of granisetron on bupivacaine SAB may be that granisetron has a longer elimination half-life (8-9 hrs) compared with ondansetron (3 hours).[16,40]

Limitations of this study included not comparing different doses of both medications and not comparing ondansetron with commonly used vasopressors. In addition, we cannot comment on the effect of ondansetron and granisetron on the incidence of bradycardia, as no patient experienced this complication in our study. Also further studies need to be conducted to determine the dose of intrathecal bupivacaine when granisetron is administered prior to subarachnoid block to avoid reversal of perioperative analgesia.

Notwithstanding these limitations, we could effectively conclude that in parturient females undergoing elective LSCS, ondansetron 4mg IV before SAB significantly decreased maternal hypotension as compared to granisetron, while granisetron 1mg IV prior to subarachnoid block induced faster sensory recovery and motor blockade compared to both the ondansetron and normal saline groups.

CONCLUSIONS

In healthy, non labouring parturients undergoing elective cesarean section, both ondansetron 4mg and granisetron 1mg given 5min before subarachnoid block significantly decreased the degree of hypotension and hence the requirement of vasopressor, however ondansetron was more effective and prevented maternal hypotension for a longer time period, thus providing better haemodynamic stability. Granisetron induced faster motor blockade as well as sensory recovery compared to both ondansetron and placebo. Both the drugs significantly reduced the incidence of nausea and vomiting, granisetron being more effective.

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