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Original Research Paper

Anaesthesiology

EFFICACY OF PROPHYLACTIC ONDANSETRON ON PREVENTION OF SPINAL ANAESTHESIA INDUCED HYPOTENSION DURING CAESARIAN DELIVERY; A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT **Background:** Ondansetron a 5HT3 receptor blocker known to block BJR, can be beneficial in attenuating the maternal hypotension and bradycardia when injected before SAB. We aimed to study efficacy of prophylactic ondansetron 8mg iv on prevention of spinal anaesthesia induced hypotension during caesarian delivery. **Methods:** Prospective, Randomized, Double-blinded, Controlled study was conducted on 64 parturient with a single foetus posted for Elective caesarean section under spinal anaesthesia who were divided into 2 groups, Group A received IV normal saline, 5 min before SAB and Group B received IV inj. Ondansetron 8 mg, 5 min before SAB. Both groups were co-loaded with 10ml/kg of RL over 20 min. Patient's SBP,DBP,MAP,HR, ECG,SpO2 were monitored every minute for first 10 minutes after intrathecal injection, 2-minute intervals for the next 10 minutes and at 5-minute intervals thereafter need of vasopressors and adverse effects, outcomes in terms of APGAR score at 1minute and 5 minute. Umbilical arterial blood gas values were assessed. **Results:** Intraoperative incidence of hypotension and hence the need for rescue vasopressors was significantly high ($P < 0.001$) in group A (90.63%). The Systolic Blood Pressure (SBP) remained to be lower in the group A compared to the Group B attaining statistical significance from the fourth minute after the administration of spinal anaesthesia till the twelfth minute. Mean DBP and MAP was decreased more in group A at different time intervals. 12(37.5%) and 5(15.6%) of the patients in Group A and B were presented with IONV. 16(50%) and 6(18.8%) were presented with PONV in Group A and Group B respectively with p value of 0.013. There was no difference in foetal outcome between the groups. **Conclusion:** Prophylactic use of 8 mg ondansetron IV is effective in reducing the incidence of spinal anaesthesia-induced hypotension, PONV, requirement of vasopressor in parturient undergoing elective caesarean section under spinal anesthesia.

KEYWORDS : caesarean section; ondansetron; hypotension; bezold-jarisch reflex; ephedrine; phenylephrine.

INTRODUCTION

Central neuraxial blockade is considered as the gold standard technique for obstetric anaesthesia. As the sympathetic block ascends, the action of the parasympathetic nervous system will become increasingly dominant. It is associated with maternal hypotension with the incidence of 50-80% and also will lead to maternal nausea, vomiting and can also be severe enough to cause cardiovascular collapse, foetal acidosis and foetal apnoea.[1,2] The spinal anaesthesia induced reduction in systemic vascular resistance and reduction in venous return due to peripheral vasodilatation in pregnancy are the main causes for hypotension.[3] There may also be parasympathetic dominance, Bezold-Jarisch reflex(BJR) activation and increased baroreceptor sensitivity leading to bradycardia and hypotension.[4] Various methods are used to prevent and treat maternal hypotension which include left uterine tilt, preloading or coloading with crystalloids or colloids and use of vasopressors such as ephedrine, mephentermine and phenylephrine due to their action on adrenergic receptors.[2-5]

Various vasopressor agents have been tried for the prevention as well as the treatment of spinal block induced hypotension but due to their adverse effect on hemodynamic changes have been restricted their uses.[6-8]

As BJR is one of the causes of maternal hypotension after SAB and the receptors responsible are mechanoreceptors located in cardiac chamber as well as the chemoreceptors sensitive to 5-HT3/ serotonin.[9-11]

Ondansetron, a selective 5-HT3 blocker, primarily a drug used as an effective perioperative antiemetic, that can be also be beneficial in attenuating the maternal hypotension and bradycardia when injected before sub arachnoid block (SAB).[12] And many scientific evidences have found that appropriate exposure to ondansetron during pregnancy have not caused spontaneous abortion, stillbirth, any major birth defect, preterm delivery, or infants born with low birth weight or small for their gestational age. So, we undertook this clinical trial to determine the efficacy of prophylactic ondansetron for preventing hypotension induced by spinal anaesthesia in parturient undergoing elective caesarean section and the effect of the same on fetal outcome.

MATERIAL AND METHODS

We had conducted a Randomized, Double-blinded, Controlled study at Vijayanagar Institute of Medical Sciences, Bellari in the department of anaesthesiology by including 64 booked case of Primiparous & multiparous aged between 18 to 35 years, 37 to 42 weeks of gestation, belonged to ASA grade II and multiparous parturient with a single foetus posted for Elective caesarean section, with normal fetal profile according to previous scans. We had excluded the pregnant women who does not follow under the mentioned inclusion criteria as well as those not willing to participate the study.

This study was conducted after institutional ethical committee approval and registration under Clinical Trials Registry of India (CTRI/2021/02/031305). In this randomized prospective, double blinded trial of 64 ASA II physical status parturient posted for elective caesarean section under spinal anaesthesia, Patients were randomly allocated into 2 groups (Group A and Group B) as per computer generated randomization table. Based on the available contemporary evidence Oh et.al [13] the incidence of hypotension in that study, without use of ondansetron, was 53% (no hypotension in 47%). Assuming improvement in this number by 25% (effect size) with use of inj. Ondansetron, we arrived at the number of patients free from to be 58.7% (47% +11.75% ≅59%). www.powerandsamplesize.come, Considering the above assumptions and possible dropouts, the sample size required would be 58+10% of 58 =64 with, 32 patients being allotted to

each group.

The randomization scheme was generated by using https://www.randomizer.org. Allocation concealment was done using sequentially numbered, opaque sealed envelope (SNOSE) technique. Group A: Received normal saline (NS) 10 ml, 5 min before Spinal Injection and Group B: Received inj. Ondansetron 8 mg (4 ml +6ml NS), 5 min before Spinal Injection.

Preoperative evaluation of all the patients were performed with detailed history, systemic and physical examination, evidence of spinal deformity and mental status of the patient. All the patients were kept nil per oral for 6-8 hours. Fetal status was also noted. Two intravenous (IV) access with 18-gauge cannulas were secured. No IV pre-hydration was given (except maintenance flows of RL 4ml/kg/hour). Inj. Ranitidine 50 mg administered intravenously and patient was maintained in left lateral position during shifting and till spinal anaesthesia administration.

On arrival to the operating room all the patients were met by an anaesthesiologist other than the one who is in charge of giving spinal anaesthesia. Spinal anesthesia was administered according to the standard operating procedure. The time of skin incision, uterine incision and the delivery of the baby were noted down. After a delivery of baby, Inj. Oxytocin 2 U administered by slow intravenous injection followed by infusion of 5 U and a section of umbilical cord was double clamped to allow sampling of the umbilical vein and artery for blood gas analysis.

Hypotension was defined as SAP <80% of baseline or <100 mm Hg, Hypotension with heart rate >80/min was managed with rescue bolus of inj. phenylephrine 50 □g iv, hypotension with heart rate <80/min was managed with rescue bolus of inj. ephedrine 5 mg iv. bradycardia was monitored as the heart rate <50/min, managed with inj. atropine 0.3 mg iv. hypotension accompanied with bradycardia was treated with inj Atropine 0.3 mg iv given and monitored. hypertension, when 20% above the basal values, treated with reduced Ringer lactate infusion and monitored. at the end of procedure, parturient were shifted to recovery room after noting all parameters.

Data was collected by using a structure proforma. Data entered in MS excel sheet and analysed by using SPSS 24.0 version IBM USA. Data was analysed using the appropriate test based on its characteristics.

RESULTS

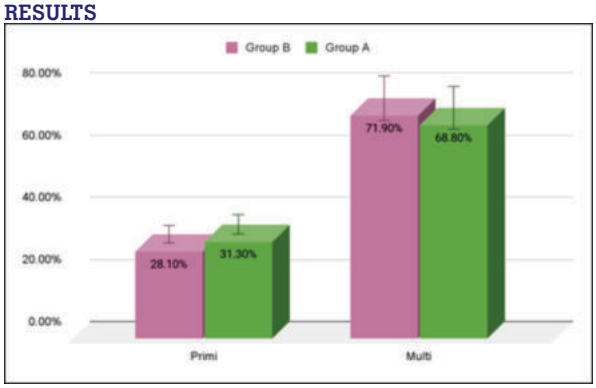

Figure 1: Diagnosis- Frequency distribution in two groups of patients studied

Demographic details of the patients, clinical parameters and the study tools for analysis had entered in the MS Excel and had been updated in the SPSS software for the further analysis. The obtained results are represented as follows; Group B: Patients who were administered with the prophylactic ondansetron. Group A: Patients administered with Normal saline. All the recruited samples in our study belonged to ASA II. The mean age of the recruited participants was 23.64±3.27. Mean age of the patients in Group B was 23.31±2.87 and 23.97±3.64 in group A. There was no statistical significance in the age between two groups. Also, there was no statistical difference in the distribution of number of primi and multiparous women between two groups, which is depicted as bar graph in figure1.

Table 1: Incidence Of Hypotension

	Group A (N=32)	Group B (N=32)	P Value
Incidence of hypotension	29	16	<0.001

<0.001, Significant, student t test.

Table 1 represents the distribution of incidences of hypotension in both groups. In the Group B, the incidence of hypotension was 50% i.e. sixteen out of the thirty-two participants. In the Group A, the incidence of hypotension was 90.63% i.e. twenty nine of the thirty-two.

The Systolic Blood Pressure (SBP) remained to be lower in the group A compared to the Group B attaining statistical significance from the fourth minute after the administration of spinal anaesthesia till the twelfth minute as observed in the below line graph, figure 2.

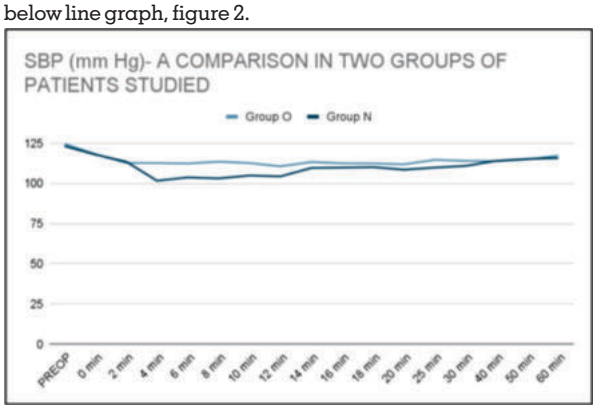

Figure 2: Comparison Of Variation In SBP

Which is similar to routinely observed fall in SBP after spinal anaesthesia. The diastolic Blood Pressure (DBP) remained lower in the group A compared to the Group B throughout the observation period. This difference in the DBP was statistically significant from the fourth minute till the twelfth minute. Beyond this period also, the DBP remained lower in Group A than Group B.

Table 2: MAP (mm Hg)- A Comparison In Two Groups Of Patients Studied

MAP (mm Hg)	Group A	Group B	P value
PREOP	86.06±11.14	89.16±9.18	0.230
0 min	83.41±8.14	84.59±7.89	0.41
2 min	75.72±14.34	80.13±7.79	0.132
4 min	69.78±11.52	77.34±8.25	0.004**
6 min	69.72±12.51	77.94±8.50	0.003**
8 min	71.28±12.20	76.03±9.68	0.089+
10 min	70.88±9.63	76.19±9.19	0.028*
12 min	70.81±15.07	74.09±8.41	0.286
14 min	72.81±12.5	74.16±8.25	0.614
16 min	70.94±9.33	73.94±7.43	0.160
18 min	73.28±9.36	71.81±6.21	0.462
20 min	74.16±9.36	73.59±6.22	0.778
25 min	75.09±10.38	74.06±7.42	0.649
30 min	77.00±9.08	75.28±5.68	0.368
40 min	78.47±7.96	76.94±5.68	0.379

50 min	78.81±6.59	78.66±5.93	0.921
60 min	79.72±6.93	80.34±6.48	0.711

The Mean Arterial Pressure (MAP) remained lower in group A compared to that of Group B which can be observed in table 2. This trend of lower MAP in Group A gained statistical significance from the 4th minute after administration of spinal anaesthesia. It remained statistically significant till the tenth minute. Further the difference decreased and the MAP of the two groups became almost similar by the 50th min.

Similarly, During the initial sixteen minutes after the administration of spinal anaesthesia, the heart rate in the group A was higher than that of group B, attaining statistical significance at twelfth minutes with a p value of 0.031. For the rest of the observation period, the heart rates in the two groups remained similar without any statistically significant difference between the two groups.

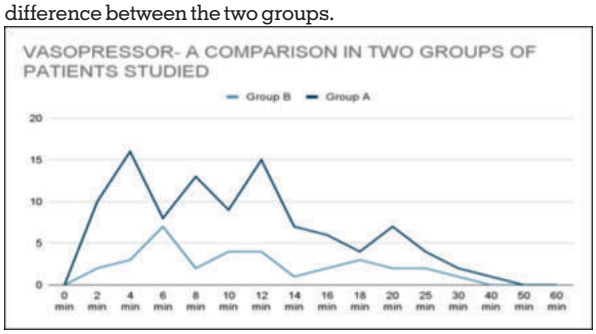

Figure 3: VASOPRESSOR- A Comparison In Two Groups Of Patients Studied

The number of vasopressor boluses required for maintaining the BP was higher in the Group A at all the times (Figure 3). Group B required vasopressors till the 30th minute whereas Group A required vasopressors till the 40th minute.

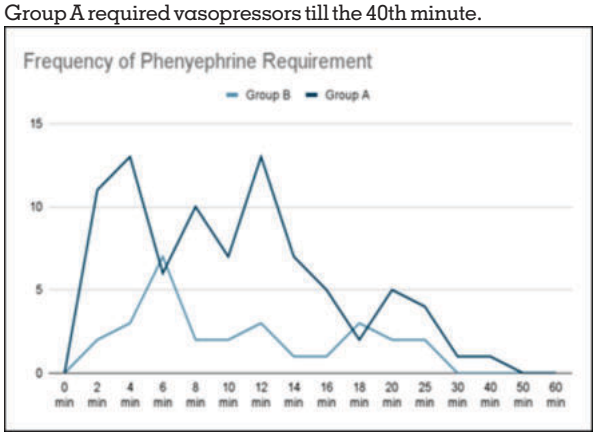

Figure 4: Frequency Of Phenylephrine Requirement.

The frequency of usage of phenylephrine in group B peaked at 6 minutes post administration of spinal anaesthesia and was continued to be required till the 25th minute, this could be observed from the above line graph, figure 4. However, in the group A, the need for phenylephrine peaked at 4minutes and at 12th minute. There was a need for phenylephrine till the 40th minute.

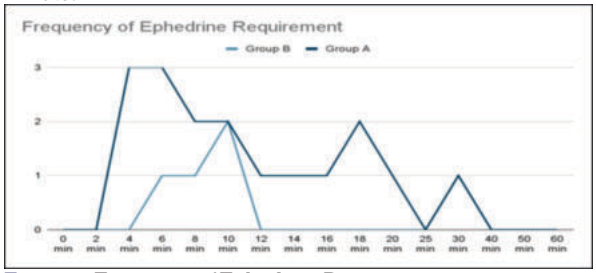

Figure 5: Frequency of Ephedrine Requirements

As we can see in figure 5, the requirement of ephedrine in Group B was minimal from 6th minute to twelfth minute whereas in group A, ephedrine boluses were required from fourth minute till thirtieth minute. This higher requirement of ephedrine was statistically significant with a p value of <0.001.

Table 3: Comparison Of Total Consumption Of Phenylephrine And Ephedrine.

	No. of Phenylephrine Boluses	Total Dose of Phenylephrine (in mcg)	No. of Ephedrine Boluses	Total Dose of Ephedrine (in mg)
Group B	28	1400	5	25
Group A	85	4250	17	85

<0.001, Significant, Student t test

In Group B, twenty eight boluses of phenylephrine and five boluses of ephedrine was required in contrast to that in Group A, in which eighty five boluses of phenylephrine and seventeen boluses of ephedrine was required, the same is explained in table 3.

Table 4: Side Effects- A Comparison In Two Groups Of Patients Studied

	Group A (n=32)	Group B (n=32)	P value
IONV	12(37.5%)	5(15.6%)	0.075+
PONV	16(50%)	6(18.8%)	0.013*

Table 4 represents the comparison of incidences of adverse effect observed among the study population. The most common side effect in the study was PONV, twelve of the patients had it in the Group A and five of them in the Group B had it. IONV was present in five patients in the Group B and twelve ppl in the Group A. Incidence of PONV was comparatively lower in the Group B, with statistically significant p value of 0.013.

The skin incision to delivery time (ID) was 4.22±0.91minutes in the Group B and 3.88±0.75 minutes in the Group A. The uterine incision to Delivery time (UD) was 1.53±0.57minutes in the Group B and 1.53±0.62 in the Group A. This variation in the ID/UD time was not statistically significant.

The average APGAR score at 1 minute in Group B was 6.56±0.5, and that in Group A was 6.41±0.56. The average APGAR score at 5 minutes was 8.75±0.44 in Group B and that in Group A was 8.66±0.55. This variation in the APGAR score was not statistically significant. All neonates in Group A and Group B at 1 min had APGAR score between 5 to 7 and at 5 min all neonates in Group A and Group B had score between 8 to 10.

Table 5: UV BG & UA BG- A And B Comparison In Two Groups Of Patients Studied

UV BG	Group A	Group B	P value	UA BG	Group A	Group B	P value
$_{p}$H	7.41±0.06	7.42±0.08	0.48	$_{p}$H	7.36±0.02	7.35±0.03	0.239
PaCO2	33.25±4.73	34.08±4.76	0.3	PaCO2	38.64±5.28	38.08±5.63	0.682
PaO2	25.86±6.9	27.11±5.18	0.31	PaO2	18.55±4.40	18.69±6.58	0.41
HCO3-	20±2.48	19.03±3.02	0.08	HCO3-	19.64±2.34	20.25±2.16	0.281
Na	137.43±3.70	137.80±6.50	0.781	Na	136.82±3.49	136.73±7.57	0.162
K	4.40±1.43	4.64±1.29	0.477	K	4.40±1.64	4.57±1.35	0.648

Cl-	97.79±7.81	99.85±8	0.19	Cl-	107.32±2.98	106.98±9.73	0.1

As per the above table 5, none of these parameters were statistically significant.

DISCUSSION

Spinal anaesthesia has been the technique of choice for caesarean section. It is frequently accompanied by hypotension. The incidence of hypotension can be as high as 70-80% when pharmacological prophylaxis is not used. [1,2] Many adjuvant drugs have been used in order to avoid the decrease in blood pressure after spinal anaesthesia. Ondansetron, a 5HT3 blocker has proved to reduce the BJ reflex and thereby the reduction in blood pressure has been the recent advances in management of spinal anaesthesia induced hypotension during LSCS. [3] Hence, we conducted a study to analyse the efficacy and safety of ondansetron as a prophylactic drug in the management of spinal anaesthesia induced hypotension. Group A, the Patients administered with Normal saline, the control group and Group B represents the patients who were administered with the prophylactic ondansetron. [8,9]

In our study, all the recruited samples in our study belonged to ASA II, as we had recruited pregnant women and were considered as moderate risk, hence ASA II. Based on ASA classification, pregnancy is considered as ASA II.

There was no statistical significance in the distribution age between two groups. The average age of our patients was less than 29 years. Contrary to this, the average age of the patients recruited in **Trabelsi et al** was 33±4 y[redacted]

Similar to our study, **Trabelsi et al** observed fewer patients in the O group experiencing hypotension as compared to those in the S group with the incidence of 15 (37.5%) and 31 (77.5%) respectively with the *P* value of < 0.001. [12]

Contrary to our study, **Samarah et al** did not find significant changes in the incidence of hypotension between two groups. [14] The SBP and DBP remained to be lower in the Group A compared to the Group B attaining statistical significance from the fourth minute after the administration of spinal anaesthesia till the twelfth minute. Also, in our study, the MAP remained lower in Group A with statistical significance difference from the 4th minute after administration of spinal anaesthesia till the 10 minutes. Further the difference decreased and the MAP of the two groups became almost similar by the 50th min. Similar to our observations, **Sahoo et al,** observed that SAP, DAP, and MAP were higher in Group O than in group S between the 4th and 10th minutes and no difference was found until the 60th minute were comparable to our study. [15] Even **Shabana et al,** observed Systolic blood pressure (SBP) measurements were significantly decreased in group II(control group) when compared with group I(received 4 mg ondansetron). There were no statistically significant differences between the two groups as regards the MBP after 10, 20, 30, 40, 50 min and 1 and 2 h, respectively. However, there was a statistically significant difference between the two groups just after spinal anesthesia. [16] Similar to our study, **Shabana et al,** observed there were statistically significant differences between the two groups as regards the mean pulse rate just after spinal anesthesia (P = 0.02), after 20 min (P = 0.01), and after 50 min (P = 0.02). [16] **Trabelsi W et al.,** reported similar HRs in both groups and bradycardia was observed in 6 patients in Group O (15%), whereas it was more frequent in the S group (15 cases, 37.5%) with a significant difference (*P* = 0.022). [12] **Samarah et al** also found a statistically significant increase in HR at 4, 16, 25, 35 and 40 minutes after the spinal injection in between Group O4 (patients administered with 4mg of ondansetron), Group O6 (administered with 6 mg of ondansetron) and Group C (contol group). HR at minute 1 was significantly more in group C than in group O4, while at minute 40, HR in the group C was significantly higher than HR in group O6. [14]

The frequency of usage of phenylephrine in Group B peaked at 6 minutes post administration of spinal anaesthesia and was continued to be required till the 25th minute. However, in the Group A, the need for phenylephrine peaked at 4 minutes and at 12th minute. There was a need for phenylephrine till the 40th minute.

The requirement of ephedrine in Group B was minimal from 6th minute to twelfth minute whereas in Group A, ephedrine boluses were required from fourth minute till thirtieth minute. This higher requirement of ephedrine was statistically significant (p of <0.001). In our study the difference in need for rescue drug was significantly lesser in ondansetron group (<0.001). Similar to this observation, in **Trabelsi W et al.,** the average consumption of ephedrine intraoperatively was 5.10 ± 7.78 mg in Group O while it was 12.90 ± 9.24mg in group S with a significant difference (<0001). **Sahoo et al** observed Group O patients required significantly less vasopressor with a statistically significant P value of 0.009. **Samarah et al** had used ephedrine only in the management of spinal anaesthesia induced hypotension. Their data showed that patients in control group received significantly higher doses of ephedrine per patient compared with patients in the other two groups; significance (*P* =.004) for Group O4 and (*P* < .001) for Group O6. **Shabana et al,** also reported the need for vasopressor was significantly lower in group I than in group II (30 vs. 70%, respectively); There was a statistically significant difference between the two groups as regards the dose of vasopressor required. [12,14,15]

The most common side effect in the present study was IONV and PONV. 12(37.5%) and 5(15.6%) of the patients in Group A and B were presented with IONV. Patient having mild nausea due to spinal anaesthesia induced hypotension. Whereas 16(50%) and 6(18.8%) were presented with PONV in Group A and in Group B respectively with statistically significant P value. Inj. Ondansetron 4mg iv given to treat this. Similar to our study **Trabelsi W et al. observed** Fewer patients in Group O experienced nausea and vomiting as compared to those in group S: 9 (22.5%) and 25 (62.5%), respectively which was statistically significant (< 0.001). [12] Even **Sahoo et al** also observed that the patients in Group O had significantly lower incidences of nausea and vomiting (P=0.049). Even in **Shabana et al** nine patients in saline group and two patients in ondansetron group complained of vomiting which was statistically significant (*P* 0.03) whereas fifteen patients in saline group and six patients in ondansetron group had nausea which was statistically significant (*P* = 0.03). [13,15] **Badawy AA et al** did not find any significant difference in the incidence of vomiting between two groups but the incidence of nausea was statistically significant higher in group control group with the incidence of 29.7% compared to ondansetron group in (5.2%) with significant p value. [16]

The average APGAR score at 1 minute in Group B was 6.56±0.5, and that in Group A was 6.41±0.56. The average APGAR score at 5 minutes was 8.75±0.44 in Group B and that in Group A was 8.66±0.55. This variation in the APGAR score was not statistically significant. Apgar scores in Group O were higher than those in group S until the fifth minute after birth in **Trabelsi W et al.** Even **Shabana et al** found There was no statistically significant difference between the two groups as regards Apgar score at 1 and 5 min and with respect to neonatal intensive care unit admission. [12,14]

Mean pH of umbilical vein in Group B was 7.42±0.08 and that in Group A was 7.41±0.06. The average PaCO2 was 34.08±4.76 and 33.25±4.73, PaO2 was 27.11±5.18 and 25.86±6.9 in Group B and Group A respectively. The HCO3-

levels in Group B was 19.03±3.02 and that in Group A was 20±2.48. Similarly, the Chloride levels in Group Bwas 99.85±8 and that in Group A was 97.79±7.81, with no significant changes between the two groups. Similar to our study, **Trabelsi W et al,**[12] observed, pH of blood from the umbilical artery was closer to physiologic ranges in Group B than in Group A (7.38 ± 0.045 versus 7.35 ± 0.047, resp.; $P = 0.01$). The average pH of umbilical artery in Group B was 7.35±0.03 and that of Group A was 7.36±0.02. Bicarbonate levels in the uterine artery in Group B was 21.69±6.58 and that in Group A was 19.64±2.34.

Chloride levels in Group B was 112.98±9.73 and that in Group A was 107.92±2.98. None of these parameters were statistically significant. The average PaO2 in Group B was 21.69±6.58 and that of Group A was 16.55±4.40. This variation in the PaO2 values was statistically significant. Limitations and Future scope of this study is we were unable to monitor levels of Lactate and Calcium in umbilical blood gas analysis Inj. Ondansetron with preloading can be considered in future studies. As oral Ondansetron is easy to administer and more cost effective, further studies comparing oral vs iv Ondansetron may be considered. Use of ondansetron to prevent spinal anaesthesia induced hypotension in non-parturient cases may be considered.

CONCLUSION:

With the above findings, we conclude that the prophylactic IV administration of inj. ondansetron at the dose 8mg is an effective alternative medication in reducing the incidence of spinal anaesthesia induced hypotension thereby reducing the requirement of vasopressor dose with the added benefit of reducing the severity of PONV in parturient undergoing elective caesarean section under spinal anaesthesia.

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