



Original Research Article

A comparative study between intravenous Ondansetron and Granisetron in attenuation of hypotension during spinal anaesthesia in patients undergoing caesarean section

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ABSTRACT

Introduction: Hypotension is most common intraoperative complication after spinal anaesthesia during cesarean delivery. The Bezold-Jarisch reflex is one of the causes for occurrence of hypotension after spinal anaesthesia through serotonin with decreased blood volume. Our aim of this study was to compare the two serotonin receptor antagonists Ondansetron and Granisetron to prevent spinal induced hypotension and bradycardia after spinal anaesthesia in parturients undergoing cesarean sections.

Materials and Methods: 90 patients of ASA class-I and II, aged 20-40years, weight 40-80kilograms were included in this study. Patient with history of PIH, convulsion, any major comorbidity were excluded from study. Patients were assigned into 3 groups group A received 4 mg Ondansetron intravenously, group B received 1 mg Granisetron intravenously and group C received 10 ml of intravenous normal saline 5 min before spinal anaesthesia. The difference in mean was analyzed using post hoc Bonferroni test and ANOVA test. The difference in proportions was analyzed by using chi-square test.

Results: SBP, DBP and MBP were statistically lower in both Granisetron and Saline group as compared to Ondansetron group at most of the times after drug administration. Heart rate and shivering were comparable in the three groups. Nausea and vomiting was statistically more in saline group as compared to other groups. Use of ephedrine was also significantly more in saline group (37%).

Conclusion: 4mg intravenous Ondansetron prior to spinal anaesthesia in LSCS patients reduces the incidence of hypotension, bradycardia and need of vasopressor. Granisetron had no effect on haemodynamic parameters.

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1. Introduction

Anaesthesia is given to reduce pain during and after surgeries.¹ Subarachnoid Block is most common and preferred method of anaesthesia for obstetric and gynaecological procedures. To produce subarachnoid block Bupivacaine is injected into the subarachnoid space.

Subarachnoid block is simple to perform, carries high efficiency, involves less drug doses, economical, rapid onset, intense motor and sensory blockade, reliability, less postoperative pain, low failure rate, reduced episodes of nausea and vomiting and avoids side effects of multiple

drugs used in general anaesthesia, keeping the woman awake to see her baby just after birth.

Complications associated with spinal anaesthesia are hypotension, bradycardia and post-dural puncture headache. Hypotension is the most frequent complication.² Hypotension in caesarean section is triggered by many factors including: the pharmacological sympathectomy leading to reduced peripheral vascular resistance, venous return and cardiac output; aorto-caval compression by pregnant uterus in supine position.

Fluids, physical methods and medications are used to reduce the occurrence of hypotension after spinal anaesthesia. Co-loading is superior to preloading. Crystalloids are preferred over colloids because of the

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lower cost with unclear benefit for colloids. Physical methods includes operating table tilting or flexing, the use of wedges or mechanical displacers, leg wrapping or sequential compression devices, head down positioning.

Phenylephrine is preferred vasopressor for prevention and treatment of post spinal hypotension because of faster onset, less incidence of fetal acidosis, less placental passage, less maternal nausea and vomiting despite the similar incidence of post spinal hypotension. Ephedrine is preferred in case of bradycardia, patients with compromised cardiac function and utero-placental insufficiency.

BJR³ has been activated by decreased venous return, pain, stress or fear. BJR is also activated during regional anaesthesia, hemorrhage or supine inferior vena cava compression in pregnancy by paradoxical activation of various non-cardiac baroreceptors. Activation of BJR receptors causes increases parasympathetic nervous system activity and inhibits sympathetic activity which leads to fall in blood pressure and heart rate associated with apnea.⁴ 5-hydroxytryptamine 3 (5-HT₃) receptors are located on the cardiac vagal afferent fibers and in the chemoreceptor trigger zone.

Our aim of this study was to compare the two serotonin receptor antagonists Ondansetron and Granisetron to prevent spinal induced hypotension and bradycardia after spinal anesthesia in parturients undergoing cesarean sections.

2. Materials and Methods

After attaining Ethical Committee approval (Ref. No.2348 MC/EC/2016) and written informed consent, 90 patients belonging to ASA class-I and II, aged 20-40 years, weight 40-80 kilograms, height \geq 150 centimeters and duration of surgery about 1 hour were included in this study. The study was conducted from December 2015 to December 2017. Patient with history of PIH, convulsion, having any deformity or local sepsis in spinal lumbar region, compromised airway or morbid obesity, any major comorbidity, severe hypovolemia, any bleeding or coagulation abnormalities, history of allergy to any of the study drugs, concurrently being treated for nausea or vomiting and required general anaesthesia for supplementation were excluded from study.

Sample size was calculated at 80% study power and alpha error 0.5 assuming mean alteration 10 and standard deviation 9 of hemodynamic changes among Ondansetron (MAP 84 ± 4) and Granisetron (MAP 74 ± 9) so as per seed article sample size is 17 in each group. It was a hospital based, randomized, comparative, double blind, interventional study. Randomization was done by chit in box method.

Patients were divided into 3 groups group A (n=30) received intravenous 4 mg Ondansetron diluted in normal saline (total volume made 10 ml), group B (n=30) received

intravenous 1 mg Granisetron diluted in normal saline (total volume made 10 ml) and group C (n=30) received 10 ml intravenous normal saline 5 minutes before subarachnoid Block.

An anesthesia resident, who was not aware about the study, administered drug to patients intravenously. Neither patient nor the observer was aware of the type of medications given to patient.

A pre-anesthetic checkup was done. After taking informed written consent and confirming 8 hours nil by mouth patient was taken on the operation table. Baseline parameters such as blood pressure, heart rate, oxygen saturation were recorded. Intravenous cannulation was done with 18G cannula and co-loading started with ringer lactate. Study solution was infused intravenously 5 minutes before spinal anaesthesia. After 5 minutes under all aseptic conditions lumbar puncture was done in lateral decubitus position at L3-L4 or L4-L5 interspace in midline approach via 25G Quincke needle. After free flow of CSF 10mg (2ml) 0.5% hyperbaric bupivacaine was injected intrathecally. Patient turned supine immediately. Table was tilted about 10- 15°. Oxygen at 4.0 L/min was given by ventury mask to the patients. Upper level of block was checked by pinprick method from caudal to rostral direction after 5 minutes and after that every 2 minutes until adequate level of block (T) was achieved. Vitals were recorded every 5 minutes till the completion of the surgery. Hypotension was defined as mean arterial pressure <80 mmHg or fall more than 20% from the baseline value and treated with incremental doses of intravenous 6 mg injection ephedrine. Bradycardia was defined as fall in heart rate < 50 beats per min and treated with incremental doses of intravenous atropine 0.5 mg. Vomiting was treated by injection metoclopramide 10mg intravenous. Shivering was treated by injection tramadol 100mg intravenously. If patient needed more sedation during surgery, 1mg midazolam intravenously was given.

Continuous data was summarized in form of mean and standard deviation. The difference in means was analyzed using ANOVA test and post hoc Bonferroni test. The difference in proportions was analyzed by chi-square test. The level of significance kept 95% for all statistical analysis.

3. Results

In the current study 90 patients were investigated for the effect of prophylactic intravenous Ondansetron, Granisetron and normal saline on fall in SBP, DBP and MBP; effect on the level of sensory height, duration of subarachnoid block to start of surgery, duration of surgery, heart rate, use of ephedrine, incidence of nausea, shivering, pain and bradycardia.

Distribution of cases according to the level of sensory height, onset of adequate sensory block and duration of surgery was not significantly different in both groups.

Table 1: Demographic variables

Variable	Ondansetron Group (n=30)		Granisetron Group (n=30)		Normal saline Group (n=30)		P value	Significance
	Mean	SD	Mean	SD	Mean	SD		
Age (Years)	30.53	6.2	28.9	6.1	28.2	6.2	0.324	Non Significant
Weight (Kgs)	61.2	9.6	63.8	10.7	64.1	11.3	0.498	Non Significant
Duration of Surgery (Minutes)	60.13	6.2	60.07	5.9	60.1	5.6	0.999	Non Significant

As Table 1 shows that the mean age of the patients, body weight of patients and mean duration of surgery in all three groups were statistically comparable ($p > 0.05$).

As Table 2 shows the Baseline Clinical Variables were statistically comparable in all three groups.

Figure 1 shows that the three groups were statistically comparable in relation to baseline systolic blood pressure ($P > 0.05$). SBP was significantly less in Granisetron group as compare to Ondansetron group 5 minutes. SBP was significantly less in both Granisetron and Normal Saline group as compared to Ondansetron group at most of the times after drug administration.

Figure 2 reveals that the Diastolic blood pressure was statistically comparable among the three groups at baseline ($P > 0.05$). The DBP falls in all the three groups, but it was significantly less in Granisetron group as compared to Ondansetron group. The DBP was significantly lower in Granisetron and saline group as compared to Ondansetron group at most of times after respective drug administration.

As Figure 3 shows that the mean blood pressure was statistically comparable among the three groups at baseline as shown by ANOVA test ($P > 0.05$). Mean arterial pressure decreased in all groups after administration of respective drug, but MAP was significantly lower in Granisetron and saline group as compared to Ondansetron group at all times till 60 minutes follow up.

Figure 4 shows that heart rate were statistically comparable among the three groups at baseline as shown by ANOVA test ($P > 0.05$). There was no statistically significant difference in mean heart rate among the three group ($P > 0.05$).

Table 3 shows that shivering was seen in 4 (13%) subjects in Ondansetron and Granisetron group and 8 (27%) subjects in saline group ($P = 0.296$). The three groups also did not differ significantly in view of pain and bradycardia ($P > 0.05$). Nausea and vomiting was significantly more in saline group (43%) as compared to Granisetron (10%) and Ondansetron group (7%), ($P < 0.001$). Ephedrine was required significantly more in saline group (37%) and Granisetron group (23%) as compared to Ondansetron group (3%).

4. Discussion

Maternal hypotension is most common perioperative complication following spinal anaesthesia. This study concentrated on two drugs Ondansetron and Granisetron, which can minimize the incidence of maternal hypotension after spinal anaesthesia. These drugs are selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonists.

Ondansetron significantly reduced the need of vasopressor in Ondansetron patients leading to decreased adverse effects on uterine blood flow.

The patients were divided into three groups. In GROUP A (n=30) patients received intravenous 4 mg Ondansetron, in GROUP B (n=30) patients received intravenous 1 mg Granisetron and in Group C (n=30) patients received intravenous 10 ml normal saline.

Meng Wang et al. in 2014 studied different doses of prophylactic intravenous ondansetron for the prevention of hypotension during cesarean delivery. He found that 4 mg prophylactic ondansetron was the optimal dose during cesarean delivery. Various studies done by Wang Q et al., Sahoo T et al. and Walid Trabelsi et al. showed that prophylactic intravenous Ondansetron 4 mg given before subarachnoid block reduced hypotension and vasopressor requirement in parturients undergoing elective caesarean section. So we used 4mg dose of ondansetron in study group.

In our study the mean age of patients in Group A, Group B and Group C were 30.53 ± 6.2 years, 28.9 ± 6.1 years and 28.2 ± 6.2 years respectively which were comparable between the groups. Weight of patients in the three groups were comparable with mean weight being 61.2 ± 9.6 kg in Group A, 63.8 ± 10.7 in Group Band 64.1 ± 11.3 kg in Group C. Duration of surgery of patents in group A, group B and group C was 60.13 ± 6.2 min, 60.07 ± 5.9 min and 60.1 ± 5.6 min respectively which was comparable between the groups.

Study shows that baseline parameters systolic, diastolic and mean blood pressure were statistically comparable in all three groups ($P > 0.05$). Application of ANOVA test with post hoc Bonferroni test shows that SBP, DBP and MBP was significantly lower in both Granisetron and Saline group as compared to Ondansetron group at most of the times

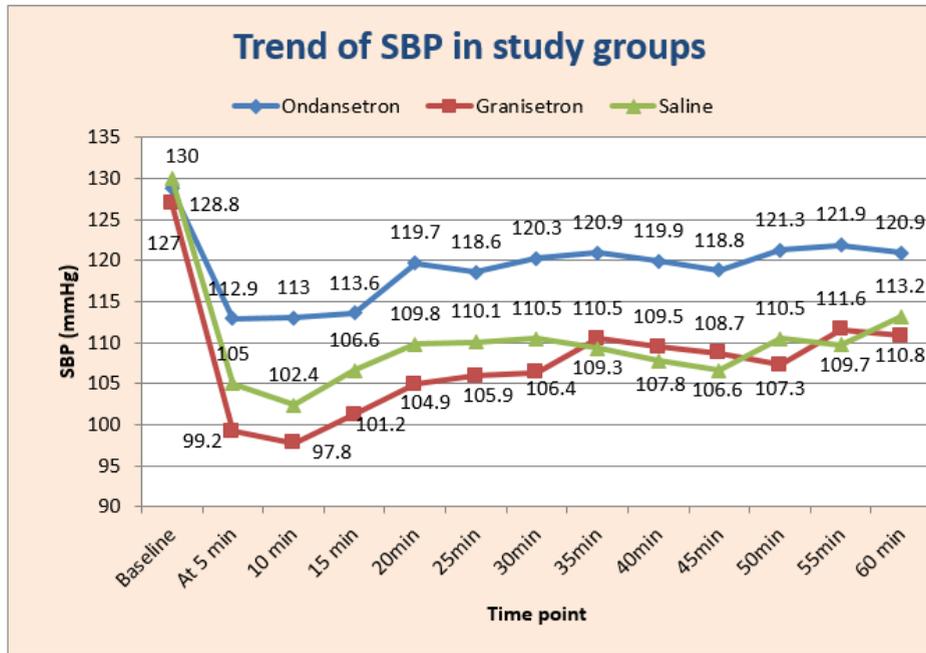


Fig. 1: Trend of Systolic Blood Pressure among the study groups

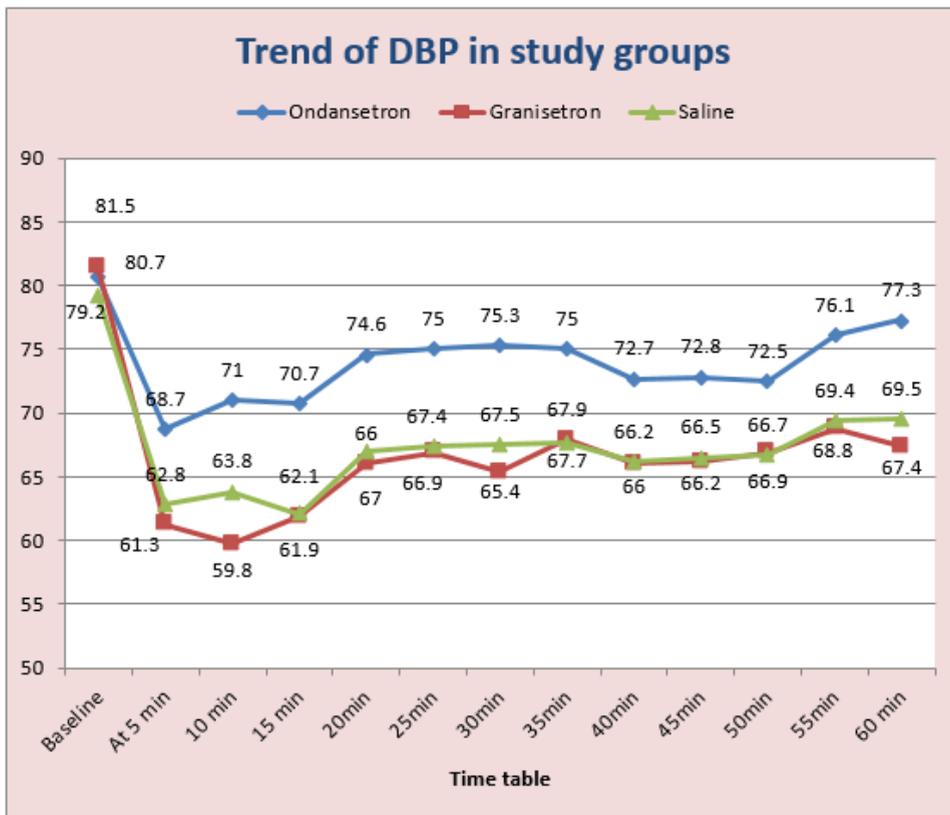


Fig. 2: Trend of Diastolic Blood Pressure among the 3 study groups

Table 2: Baseline Clinical Variables (Mean ± SD)

Variable	Ondansetron Group (n=30)		Granisetron Group (n=30)		Normal saline Group (n=30)		P value
	Mean	SD	Mean	SD	Mean	SD	
Heart Rate	95.1	19.2	99.3	19.5	94.6	15.2	0.549
Systolic BP	128.8	15.5	127	15.2	130	15.2	0.757
Diastolic BP	80.7	13.3	81.5	10.8	79.2	12.4	0.765
MAP	96.8	13.6	96.7	11.8	96.1	12.9	0.979

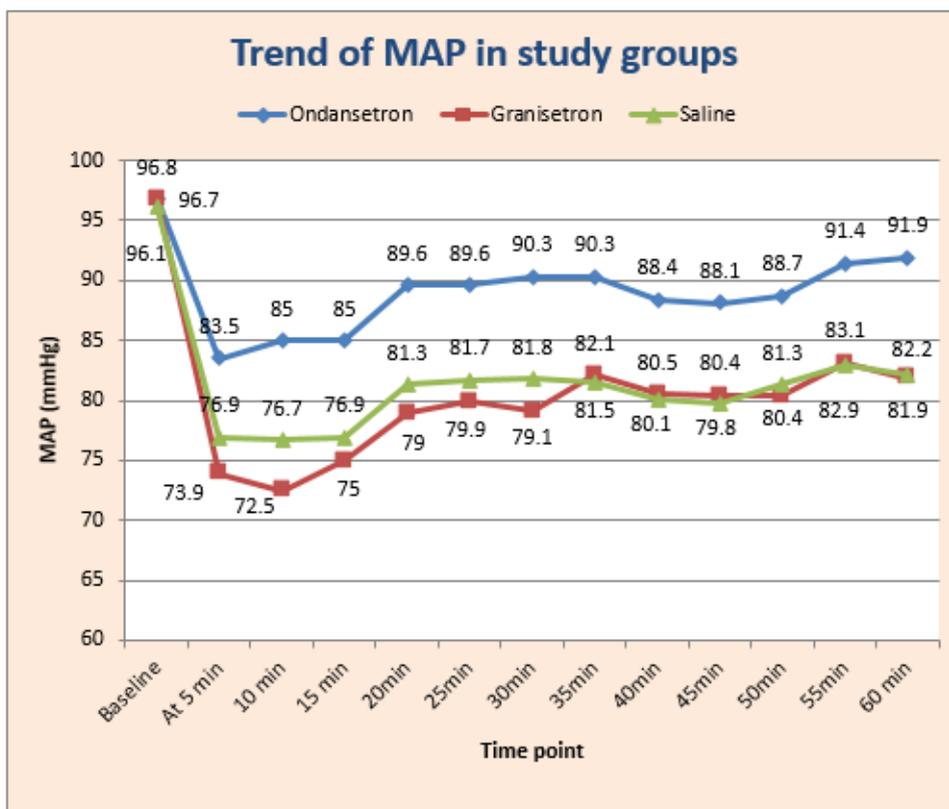


Fig. 3:

Table 3: Comparison of complications in the study groups

Complication	Ondansetron	Granisetron	Saline	P value*
Shivering	4 (13%)	4 (13%)	8 (27%)	0.296
Pain	3(10%)	5(17%)	5(17%)	0.698
Nausea	2(7%)	3(10%)	13(43%)	<0.001
Bradycardia	0	3(10%)	2(7%)	0.227
Ephedrine use	1(3%)	7(23%)	11(37%)	0.006

*P value calculated using Chi square test

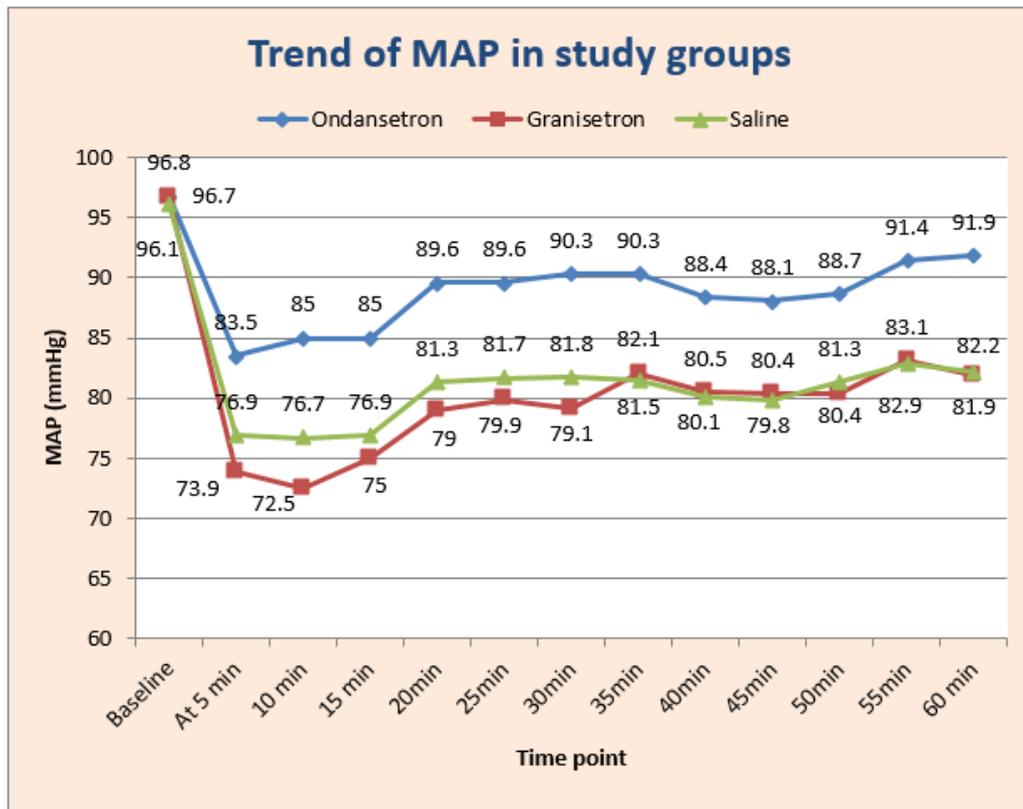


Fig. 4: Trend of MBP among the study groups

after drug administration. Mean arterial pressure decreased in all groups after administration of respective drug. Study revealed that heart rate was comparable among the three groups at baseline as shown by ANOVA test ($P > 0.05$).

In our study shivering was seen in 4 (13%) of subjects in Ondansetron and Granisetron group and 8 (27%) subjects in saline group ($P = 0.296$). The three groups also did not differ significantly in view of pain and bradycardia ($P > 0.05$). Nausea and vomiting was seen in statistically more subjects in saline group (43%) as compared to Granisetron (10%) and Ondansetron group (7%), ($P < 0.001$). Ephedrine use was also required in significantly more subject in saline group (37%) and Granisetron group (23%) as compared to Ondansetron group (3%).

Similar to our study Owczuk R et al, (2008)⁵ Ondansetron 8mg attenuated the decrease in Mean blood pressure but had no effect on Heart Rate compared to control saline group. Meng Wang, Lang Zhuo and Zhi-Ping Wang et al (2014) also concluded that the incidence of maternal hypotension was significantly less in patients who received 4 and 6mg of Ondansetron as compared to group of patients who received normal saline. Sahoo et al. (2012)⁶ concluded that intra venous Ondansetron reduced the hypotensive episodes and vasopressor requirements. Mowafi et al. (2013)⁷ found that Granisetron had no

effect on the hemodynamic variables 2013. Syed Ali Raza Ali Shah, Syeda Sarah Naqvi, Muhammad Ali Abbas (2016)⁸ concluded that intravenous administration of 8 mg of Ondansetron, 5 minutes prior to subarachnoid block, is effective in decreasing incidence of hypotension and bradycardia in elderly patients. Chengmao Zhou, Yu Zhu, Zeqing Bao, Xianxue Wang, Qili Liu (2017)⁹ included 21 RCTs in this study. Meta-analysis showed that the Ondansetron group had decreased incidence of bradycardia and nausea and vomiting than the placebo group during cesarean section under spinal anaesthesia. Meenoti P Potdar, Laxmi L Kamat, Tanya R Jha, et al. (2017)¹⁰ concluded that the incidence of hypotension in patients was statistically less in the Ondansetron group but comparable between different doses of Ondansetron. However in 2015 Arivumani, Arul Anne Rose, Usha Devi et al. (2015) concluded that Intravenous Ondansetron 4mg significantly reduces the spinal induced hypotension. They also found that the episodes of bradycardia and the requirement of vasopressors were less in Ondansetron group. Walid Trabelsi, Chihebeddine Romdhani, Haythem Elaskri et al. (2016)¹¹ showed that prophylactic Ondansetron significantly reduced the incidence of hypotension in healthy parturients undergoing elective caesarean section under spinal anaesthesia. Tito D.

Tubog, Terri D. Kane and Marilyn A. Pugh, (2015)¹² studied effect of intravenous Ondansetron in prevention of hypotension and bradycardia.

Contrary to our study Ahmed A Eldaba, Yasser M. Amr (2015)¹³ studied intravenous Granisetron in the prevention of hypotension and bradycardia during spinal anaesthesia in caesarean delivery. They found that mean blood pressure and heart rate were statistically decreased in normal saline group (P<0.0001). The incidence of hypotension after spinal anaesthesia was 64% in normal saline group and 3% in granisetron group (P <0.00001). The total doses of ephedrine and atropine were significantly reduced in granisetron group versus normal saline.

Alaa El Deen Mahmoud Sayed & Ahmed Shaban, (2017) concluded that prophylactic intravenous administration of Granisetron before spinal anaesthesia will decrease spinal induced hypotension. Terkawi As et al. (2015)¹⁴ demonstrated that there was no statistically significant difference in mean arterial blood pressure between normal saline and ondansetron group (P=0.89). Nivatpumin P et al. (2016)¹⁵ concluded that there were no significant differences in MAP in both groups (Ondansetron and Normal Saline) (P>0.05) which was contrary to our results.

5. Conclusion

Intravenous Ondansetron 4mg administration prior to spinal anaesthesia reduces the episodes of hypotension, bradycardia and vasopressor requirement in LSCS patients. Granisetron had no effect on haemodynamic parameters. There was significantly less incidence of postoperative Nausea and Vomiting in Ondansetron and Granisetron group.

6. Source of Funding

None.

7. Conflict of Interest

None.

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