WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 19, 1124-1134. Research Article ISSN 2277–7105

EFFECT OF PROPHYLACTIC INTRAVENOUS ONDANSETRON ON SPINAL ANESTHESIA INDUCED HYPOTENSION AND BRADYCARDIA IN TERTIARY CARE CENTRE - A RANDOMISED CONTROLLED TRIAL

Rakshith N.[1], Hema N. G.[2]* and Shalini A.[3]

[1]Postgraduate, Department of Pharmacology, MMCRI.

[2]*Professor and Head of Department, Department of Pharmacology, MMCRI.

[3]Assistant Professor, Department of Anesthesia, MMCRI.

Article Received on
17 September 2023,

Revised on 06 Oct. 2023,
Accepted on 27 Oct. 2023

DOI: 10.20959/wjpr202319-30146

***Corresponding Author**
Hema N. G.
Professor and Head of Department, Department of Pharmacology, MMCRI.

ABSTRACT

Background: Spinal anaesthesia is a safe anesthetic technique commonly practiced. Hypotension and bradycardia are the common side effects seen after spinal anesthesia, which are induced by hypovolemia, sympathetic blockade, bejold-jarisch reflex through intra cardiac serotonin receptors and vagus nerve. Multiple strategies are tested to prevent the post spinal anesthesia induced hypotension, Recently, ondansetron, a 5HT3 antagonist commonly used as an antiemetic, found to be effective in preventing spinal anesthesia induced hypotension. **Aim:** To assess and compare haemodynamic parameters between study and control group. To study the effect of prophylactic intravenous administration of ondansetron on hypotension and bradycardia. **Methodology:** This is a prospective randomized placebo controlled trial done in tertiary care teaching hospital. Ondansetron, Hypotension, Bradycardia, Spinal Anesthesia, Bezold-Jarish reflex. Of 120 patients, 60 were in Group A and 60 were in Group B. Patients in Group A (ondansetron group) were given 4mg ondansetron diluted in 5ml normal saline, patients in Group B (control group) received 5ml normal saline 5mins prior to spinal anesthesia which is 15mg of 0.5% hyperbaric bupivacaine, injected intrathecally. Mean arterial pressure and heart rate were recorded every minute upto first 5 mins, every 3mins in next 15 minutes and every 5 mins till the end of the procedure. If SBP dropped<90mmhg or decreased more than 20% from the baseline it will be considered as hypotension and treated with injection Ephedrine 6mg and repeated if necessary. Significant bradycardia(HR<50bpm) treated with 0.6mg of

intravenous atropine. Statistical tests used were ANOVA test for quantitative data and Chi-square test for qualitative data. **Results:** One patient in Group A and three patients in Group B had incidence of bradycardia and treated with atropine (pvalue=0.208). 4 patients in Group A and 12 patients in Group B had incidence of hypotension (pvalue=0.786). Dose requirement of ephedrine was more in control group (pvalue=0.337). Mean arterial pressure(MAP) was higher in Group A compare to Group B (pvalue=0.0029).

KEYWORDS: Ondansetron, Hypotension, Bradycardia, Spinal Anesthesia, Bezold-Jarish reflex.

INTRODUCTION

Spinal anesthesia remains a popular method of anesthesia for a wide range of surgeries due to its efficacy, simplicity and safety.[1,3] Spinal anesthesia is a safe and effective choice, but it has its own array of unwanted side effects most commonly hypotension and bradycardia.[1,2,3] Spinal anesthesia induced hypotension is very common with an incidence of 25% to 80%.[3] The mechanism involved in the occurrence of hypotension is decrease in vascular resistance caused by sympathetic blockade which in turn causes vasodilatation and finally leads to drop in arterial pressure. Parasympathetic overactivity, activation of Bezold–Jarisch reflex (BJR), and increased baroreceptor activity may lead to hypotension and bradycardia. BJR is triggered by chemoreceptors and mechanoreceptors which are serotonin sensitive. Animal and human studies have proved that $5HT_3$ antagonists prevent serotonin‑induced BJR.[3-7] Multiple modalities have been tested in preventing and managing hypotension which includes positioning, lower leg compression, preloading and co-loading of fluids and use of vasopressors. Ondansetron is 5-HT_3 receptors antagonist, which is basically used as an antiemetic drug and is thought to counteract bradycardia and hypotension induced by spinal block.[5-7] In the literature, ondansetron was used 5 minutes before performing spinal block to prevent hypotension and bradycardia with moderate reduction in hypotension.[5]

Our primary aim is to assess haemodynamic parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and Heart Rate (HR) after prophylactic administration of ondansetron in patients undergoing elective infraumbilical surgeries under spinal anesthesia and compare the respective parameters with the control group.

METHODS

After obtaining clearance from the Institutional Ethical Committee the study was conducted, all patients were assessed preoperatively counselled, and informed consent was obtained. The present study was carried out in the Department of Anesthesia, K R hospital by Department of Pharmacology, Mysore Medical College and Research Institute. It is a Prospective Randomised Placebo Controlled trial in patients undergoing elective infraumbilical surgeries under spinal Anesthesia, under the age group of 18-50 years, with ASA grade 1 or 2 and height 150-170cms, and willing to give consent. Patients with contraindications for spinal anesthesia, suffering with DM, HTN or other comorbities and history of coagulopathies, thrombocytopenia, allergic to ondansetron, infection at lumbosacral region, history of taking selective serotonin reuptake inhibitors and pregnant and lactating mothers were excluded from the study. 120 patients were randomly divided into two groups, 60 patients in Group A(Ondonsetron) and 60 patients in Group B(Placebo). Preoperative fasting of 6-8 hrs was advised. On arrival to the operating room, standard monitor was applied to all patients, including pulse oximeter, electrocardiogram and non-invasive arterial blood pressure. An 18-gauge intravenous cannula was placed on the dorsum of the hand and patients received 10ml/kg lactated Ringer solution over 15 minutes before spinal Anesthesia. Then patients in Group A was given 4 mg Ondansetron (Inj Ondem 2mg/ml by Alkem Laboratories) diluted to 5ml in normal saline and given IV over 1min. The patients in the Group B received 5ml normal saline IV over 1min. All solutions were prepared by a resident of Anesthesiology. Baseline parameters (including heart rate, MAP) were recorded 5 minutes prior to induction of spinal anesthesia. Subarachnoid block was performed in the lateral position with a 25-gauge Quincke Babcock needle inserted by midline approach into the L3-L4, L4-L5 interspace. After ensuring free flow of CSF, 15 mg of 0.5% hyperbaric bupivacaine (InjAnawin 0.5% Heavy by Neon Laboratories Ltd) injected. Patients were immediately placed in the supine position after spinal block. The upper level of sensory blockade evaluated by pinprick test from caudal to rostral direction at 5-min intervals up to 20 minutes. At the same time, motor blockade assessed by Bromage scale. Bromage scale: 0 - no paralysis, 1- inability to lift the thigh, 2- inability to flex the knee, 3 – inability to move any joint in the leg(effect). MAP and HR are recorded every minute up to first 5 minutes, every 3min in next 15 minutes and every 5min till the end of the procedure. If SBP dropped <90 mm Hg or decreased more than 20% from baseline, this was considered as hypotension and treated with intravenous injection Ephedrine 6mg, and repeated if necessary. Significant bradycardia (heart rate < 50 beats/min) accompanied by hypotension was treated with 0.6 mg

of intravenous Atropine. Number of doses of ephedrine and atropine needed and timings were recorded. Intraoperative nausea, vomiting and shivering was recorded.

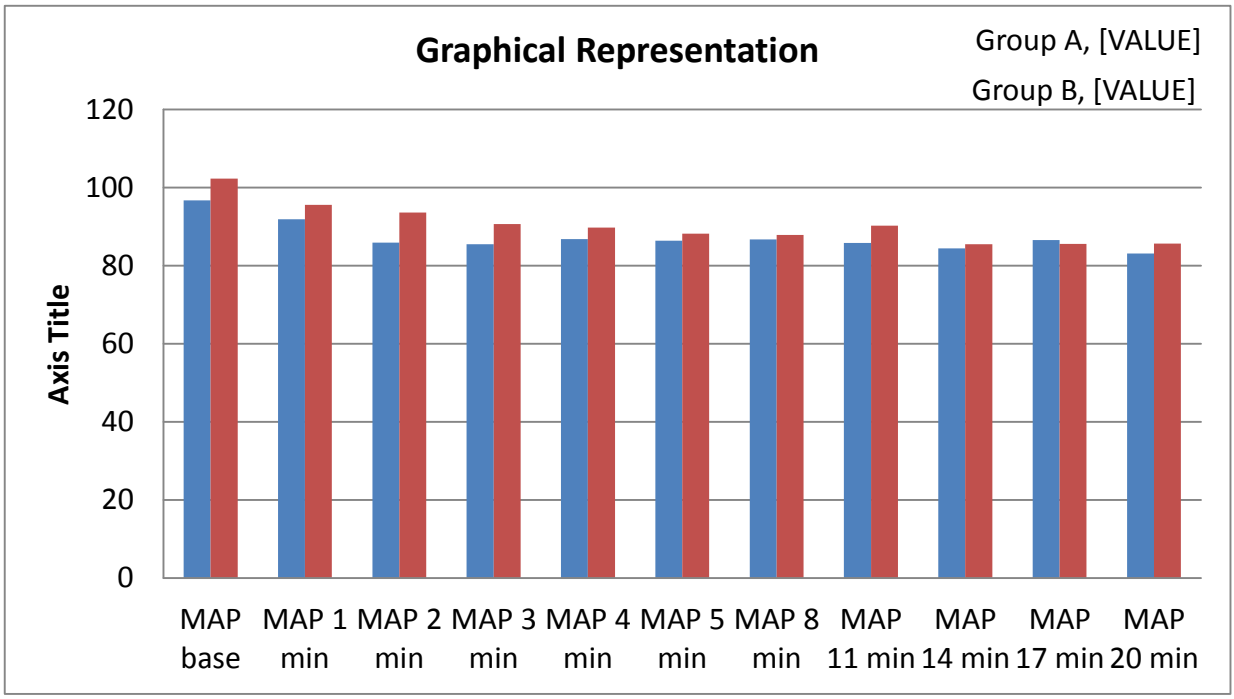
RESULTS

In our study, 120 patients were randomly assigned to two groups. Demographically, both Group A(Ondansetron) and Group B(Placebo) were age and gender matched. There is no statistically significant difference in weight, height, body mass index, and ASA class between the two groups.

4 (6.66%) patients in Group A and 7(11.6%) patients in Group B required Atropine. In Group A 6(10.3%) patients required one dose of ephedrine, 2(3.3%) patients required two doses and none required three doses of ephedrine. In Group B 8(13.3%) required one dose of ephedrine, 5(9.5%) required two doses of ephedrine, 2(3.3%) required more than three doses of ephedrine. Total 8 patients in Group A and 15 in Group B required ephedrine. There was a significant difference in SBP, DBP and MAP between both Group A and Group B at 2nd and 3rd min and after 30 min. Hypotension occurred in 19 patients in our study. Hypotension occurred in 4(6.6%) patients in Group A and 15(25%) in Group B with p value of 0.005. Frequency of hypotension was significantly lower in ondansetron group as compared to placebo group. Bradycardia occurred in 10 patients in our study group. Bradycardia occurred in 2 patients in ondansetron group and 8 patients in placebo group with a p value of 0.047. In Group A none of the patients and in Group B 4 patients experienced shivering.

Table 1: Comparison of Mean Arterial Pressure in Ondonsetron group and Placebo group with graphical representation.

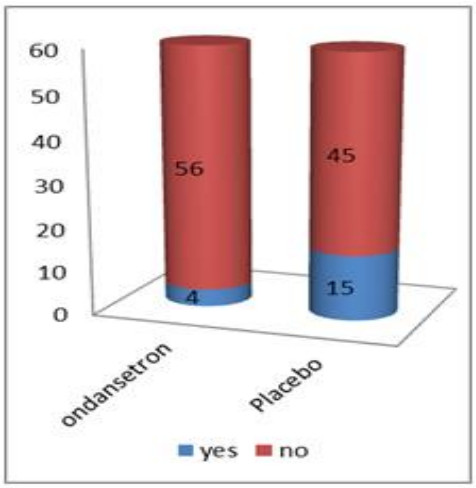
Variables	Ondansetron Group (n=60) Mean±SD	PlaceboGroup (n=60) Mean±SD	P-value(<0.05)
MAP at Baseline	96.7 ± 13.4	102.3 ± 9.8	0.018
MAP after 1min	91.9 ± 13.4	95.6 ± 11.1	0.106
MAP after 2 min	85.9 ± 10.6	93.6 ± 10.2	0.0001
MAP after 3 min	85.5 ± 10.6	90.7 ± 10.3	0.0081
MAP after 4 min	86.8 ± 10.6	89.8 ± 9.6	0.086
MAP after 5min	86.4 ± 9.8	88.2 ± 9.2	0.326
MAP after 8 min	86.7 ± 9.9	87.9 ± 12.0	0.546
MAP after 11min	85.8 ± 10.1	90.3 ± 13.8	0.043
MAP after 14min	84.4 ± 10.4	85.5 ± 9.8	0.536
MAP after 17min	86.6 ± 10.6	85.6 ± 10.1	0.641
MAP after 20min	83.1 ± 19.1	85.7 ± 17.7	0.436



Graph 1: Graphical representation of Mean Arterial Pressure in both the groups.

Table 2: Frequency of hypotension between Group A and Group B.

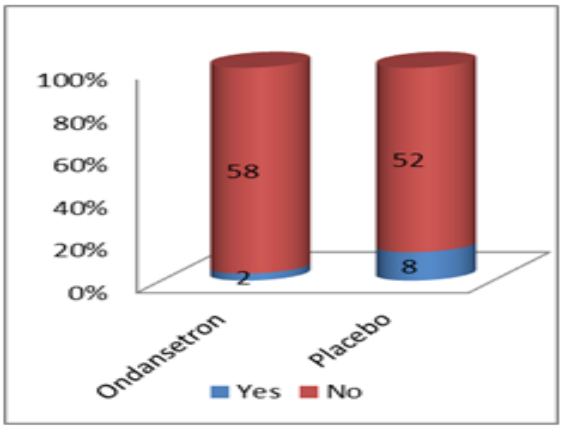
Groups	HYPOTENSION		
	YES	NO	P-value
ONDANSETRON	4	56	0.005
PLACEBO	15	45	



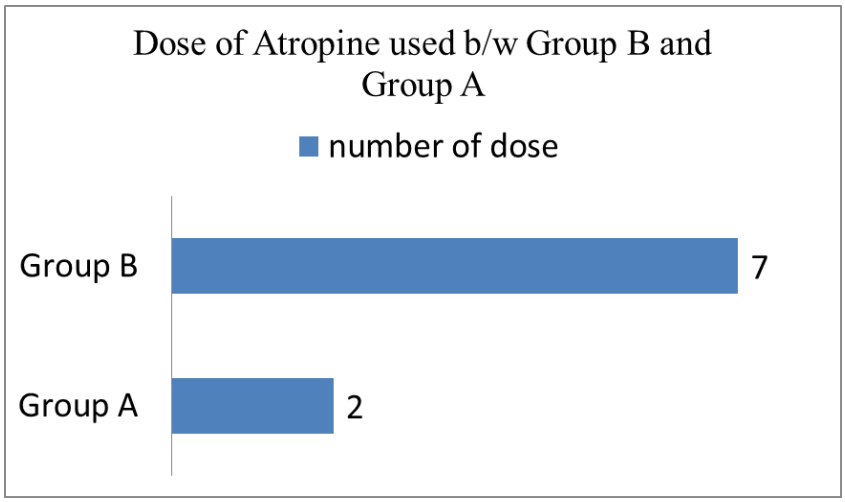
Graph 2: Graphical representation between Group A and Group B.

Table 3: Frequency of Bradycardia between Group A and Group B.

Groups	BRADYCARDIA		
	YES	NO	P-value
ONDANSETRON	2	58	0.04
PLACEBO	8	52	



Graph 3: Graphical Representation of Frequency of Bradycardia between Group A and B.



Graph 4: Doses of Atropine and ephedrine used between Group A and B.

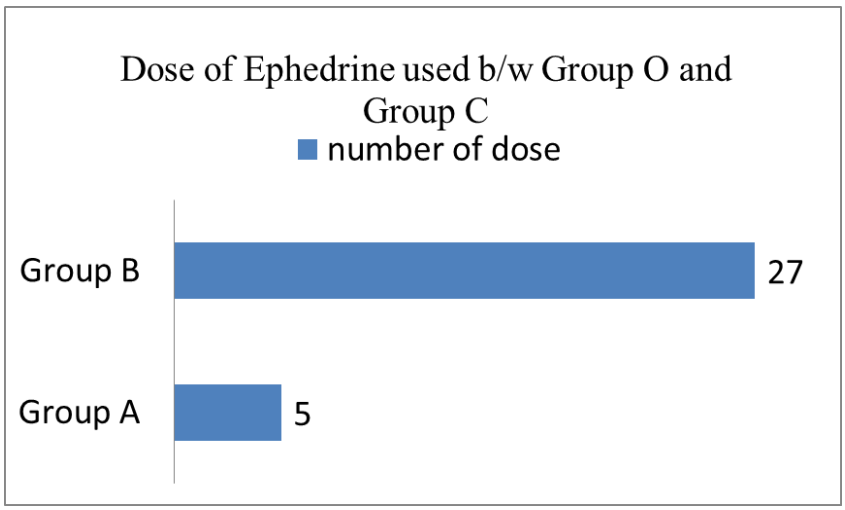


Table 4: Frequency of Shivering between Ondansetron and Placebo Groups.

Groups	SHIVERING	
	YES	NO
ONDANSETRON	0	60
PLACEBO	4	56

DISCUSSION

Post Spinal Hypotension(PSH) is caused most probably due to reducing vascular tone and these results in decreased venous return and systemic vascular resistance. Thus, measures used for prevention of PSH are directed to increase vascular tone and venous return which can be done by using vasoconstrictors, fluid administration, and positioning regimens.[9]

In recent years, studies have been conducted on different treatments for hypotension following spinal anaesthesia, such as fluid therapy and vasopressors. However, the activation of the Bezold–Jarisch reflex is one of the important mechanisms of hypotension after spinal anaesthesia. Numerous studies have focused on preventing hypotension by attenuating the Bezold–Jarisch reflex with 5-HT3 receptor antagonists. Ondansetron was demonstrated to be effective in preventing hypotension in many meta-analyses.[10]

Choosing the right vasopressor agent in spinal anesthesia induced hypotension (SAIH) has been the subject of controversy and debate. In addition to its potent antiemetic properties, recent studies suggested that ondansetron may also reduce the incidence of SAIH and vasopressor requirement in elective patients undergoing surgery. Numerous studies have demonstrated the efficacy of prophylactic ondansetron in the prevention of hypotension after spinal anesthesia.[6]

Rabia Baig et.al conducted a Randomised control study on Use of Ondansetron for Prevention of Spinal Induced Hypotension, with 106 patients concluded that Hypotension occurred in 7.5% cases in Ondansetron group compared to 28.3% in normal saline group (p=0.005), which co relates to our study which showed hypotension occurred in 6.6% in ondonsetron group and 25% in placebo group with p=0.005[1].

Raghu et.al in his study on Effect of Ondansetron in the Prevention of Spinal Anesthesia-induced Hypotension with 110 patients from either gender aged 50-70 years, 55 patients received 8mg ondansetron IV and 55 patients received 4ml saline IV 10 min before spinal anesthesia. Hypotension was seen in 56 patients, of whom 34 were in control group (60.7%)

and 22 were in ondansetron group (39.3%) and the use of ephedrine was greater in control group than Ondansetron group(mean 4.61 ± 1.80 vs. 3.45 ± 1.09, P = 0.0107), and conclude that prophylactic administration of ondansetron is effective in reducing the incidence of spinal anesthesia‐induced hypotension. In our study we used 4mg of ondonsetron 10 min prior to spinal anesthesia, 8 patients in ondonsetron group and 15 patients from placebo group required ephedrine but the total doses were more in placebo group (24) compared to ondonsetron(8) group which concludes that our study in line with Raghu et.al study reduces the use of ephedrine and incidence of hypotension in ondonsetron group.[3]

Our study showed decreased utilization of ephedrine and decreased incidence of shivering in ondansetron group which correlates to Chandra Mouli Tatikonda et.al, in his study on Effect of Intravenous Ondansetron on Spinal Anesthesia‐Induced Hypotension and Bradycardia: A Randomized Controlled Double‐Blinded Study, with 140 patients stated that patients whom ondansetron was given has reduced requirement of ephedrine and reduced shivering compared to the group received placebo. Also in this study they didn't find any statistical difference in bradycardia but our study concludes there is less incidence of bradycardia in ondansetron group.[4]

Sherif Abdallah Mohamed et al conducted study titled Ondansetron is an effective alternative to decrease the incidence of postspinal hypotension in healthy subjects undergoing infra-umbilical surgeries compared to combined volume loading and vasoconstrictors: randomized controlled trial on 90 patients with 45 patients in each group. Group I patients (ondansetron group) received 4 mg ondansetron in 5 ml normal saline (IV) 15 minutes before induction of spinal anaesthesia. Group II patients (combination group) received preloading with 7.5 ml/kg/min of Ringer's lactate over 10 minute period preceding the spinal block followed by intravenous bolus of 2.5 mg ephedrine in the first and second minute and 2.5 mg ephedrine every 5 minutes for the next 20 minutes after the injection of spinal anesthetic drug, concludes preemptive use of ondansetron alone versus combined vasoconstrictors with fluid preload significantly reduces the incidence of post-spinal hypotension (PSH).[9] In our study we used 4mg of ondonsetron 5mins prior to the induction compared with placebo (10ml/kg lactated Ringer solution over 15 minutes). Resulted in decresed incidence of hypotension in ondonsetron group.

Walid K Samarah et.al conducted a study on The effect of ondansetron administration 20 minutes prior to spinal anaesthesia on haemodynamic status in patients undergoing elective caesarean section: A comparison between two different doses, with 101 patients concluded the consumption of ephedrine in the control group is higher than both of the ondansetron groups (P > 0.001) but Prophylactic 4 and 6 mg ondansetron given 20 minutes before spinal anesthesia in caesarean section does not reduce the incidence of hypotension.[5] Similarly Teerawat Poojinya, Preecha Jongstapongpun, Nuttanun Meekaew conducted a study comparing Ondansetron and Placebo for Reduction of Spinal Anesthesia-Induced Hypotension: a Double-Blind Randomized Control Trial on 133 patients and concluded Intravenous ondansetron administered 5 min prior to spinal anesthesia does not significantly prevent spinal anaesthesia-induced hypotension.[11] In our study patients were administered 4mg of ondansetron 5 mins prior to the spinal anesthesia in patients undergoing infraumbilical surgeries excluding C-section and concludes ondansetron effectively reduces the incidence of spinal anaesthesia induced hypotension.

Raghu Shishir Kumar et al, conducted randomised control trial with 110 patients using 8mg of ondansetron before spinal anesthesia and concluded the prophylactic use of 8mg ondansetron is effective in reducing spinal induced hypotension, bradycardia and vomiting in contrast to this our study with 4mg ondansetron given 5min prior to spinal anesthesia reduces both hypotension and bradycardia.[3]

Many studies.[2,3,12,13] compared different doses of ondonsetron and found that, 8mg of ondonsetron given 5 to 10 min prior to spinal anaesthesia reduces the incidence of hypotension and bradycardia more compared with 4 mg of ondonsetron but Potdar et al in his study concludes, increasing the dose of ondonsetron from 4 to 8 mg does not benefit and decrease the incidence of hypotension.[6]

STRENGTH AND WEAKNESS

The strength of the study is the study design as the double-blinded, randomized controlled trial, sufficient sample size for statistical significance and nature of the participants. However, there were some limitations in the study. First, we could not monitor and record the dermatome level of anesthesia, which can affect the degree of hypotension, blood/fluid loss during the procedure. Second, more invasive hemodynamic monitoring like Swan-Glanz catheter, can be helpful to properly assess decrease in venous return and cardiac filling

pressures. Third, we used fixed dose of ondansetron 4 mg in all patients irrespective of weight of patients.

CONCLUSION

Our study concludes that prophylactic intravenous administration of ondansetron significantly reduces dose of Ephedrine and dose of atropine. Administration of 4mg of intravenous ondansetron 5mins prior to spinal anesthesia significantly reduces the spinal anesthesia-induced hypotension when compared with placebo.

REFERENCES

1. Baig R, Shah AA, Khurshid T, Abid L, Tariq Z. Use of Ondansetron for Prevention of Spinal Induced Hypotension. JIMDC, 2017; 6(4).
2. Ahmed A. Badawy & Ali M. Mokhtar. The role of ondansetron in prevention of post-spinal shivering (PSS) in obstetric patients: A double-blind randomized controlled trial, Egyptian Journal of Anaesthesia, 2017; 33: 1, 29-33.
3. K Raghu, Shishir kumar, G Rajaram, N Nikhil, P Damodar. Effect of Ondensetron in the Prevention of Spinal Anesthesia-induced Hypotension. Journal of the Scientific Society, 2108; Volume 45 Issue 3.
4. Tatikonda CM, Rajappa GC, Rath P, Abbas M, Madhapura VS, Gopal NV. Effect of intravenous ondansetron on spinal anesthesia‐induced hypotension and bradycardia: A randomized controlled double‐blinded study. Anesth Essays Res, 2019; 13: 340-6.
5. Samarah WK, Alghanem SM, Bsisu IK, Rahman ZA, Guzu HA, Abufares BN. The effect of ondansetron administration 20 minutes prior to spinal anaesthesia on haemodynamic status in patients undergoing elective caesarean section: A comparison between two different doses. Indian J Anaesth, 2020; 64: 954-9.
6. Feride Karacaer, Ebru Biricik, İlker Ünal, Selim Büyükkurt, Hakkı Ünlügenç Does Prophylactic Ondansetron reduce norepinephrine consumption in patients undergoing cesarean section with spinal anesthesia? Japanese Society of Anesthesiologists, 2017.
7. Ayman A. Shabana, Nabih I. Elkholy, Ashraf M. Mohamed, Mai I. Abdel Hamid. Effect of ondansetron on hypotension and bradycardia associated with spinal anesthesia during cesarean section. Menoufia Medical Journal, 2018; 31: 1.
8. F.T. Mendonc¸a, L.C. Crepaldi Junior, R.C. Gersanti et al. Effect of ondansetron on spinal anesthesia-induced hypotension in non-obstetric surgeries: a randomised, double-

blind and placebo-controlled trial Brazilian Journal of Anesthesiology, 2021; 71(3): 233-240.

9. Mohamed et al. Ondansetron Is an Effective Alternative to Decrease the Incidence of Postspinal Hypotension in Healthy Subjects Undergoing Infra-Umbilical Surgeries Compared To Combined Volume Loading and Vasoconstrictors: Randomized Controlled Trial. Open Access Maced J Med Sci, 2018 Dec 20; 6(12): 2363-2368.
10. Hou, X.-M.; Chen, Y.-J.; Lai, L.; Liu, K.; Shen, Q.-H. Ondansetron Reduces the Incidence of Hypotension after Spinal Anaesthesia: A Systematic Review and Meta-Analysis. Pharmaceuticals, 2022; 15: 1588.
11. Teerawat Poojinya, Preecha Jongstapongpun, Nuttanun Meekaew. Comparing Ondansetron and Placebo for Reduction of Spinal Anesthesia-Induced Hypotension: a Double-Blind Randomized Control Trial. Thai J Anesthesiol, 2023; 49(5).
12. Potdar MP, Kamat LL, Jha TR, Talnikar AS, Mahevi ZM, Save MP. Effect of ondansetron in attenuation of post-spinal hypotension in caesarean section: A comparison of two different doses with placebo. J Obstet Anaesth Crit Care, 2017; 7: 69-74.
13. Bhiwal AK, Chauhan K, Choudhary S, Bhatt HA, Gupta S. Intravenous ondansetron to prevent hypotension during cesarean section under spinal anaesthesia. J Obstet Anaesth Crit Care, 2021; 11: 15-9.