ISSN 2515-8260 Volume 09, Issue 02, 2022

Hospital based study to know the effectiveness of ondansetron over spinal anesthesia induced hypotension & bradycardia

[1]Dr. Naga Satya Suryanarayana Ruttala, [2]Dr. Padmalatha Seelam, [3]Dr. Nalli Venkata Krishna Mallik, [4]Dr. Vengamamba Thummala

[1]Senior Resident, NRI Institute of Medical Sciences, Vizag, Visakhapatnam, Andhra Pradesh, India
[2]Assistant Professor, NRI Institute of Medical Sciences, Vizag, Visakhapatnam, Andhra Pradesh, India
[3]Associate Professor, Katuri Medical College, Guntur, Andhra Pradesh, India
[4]Professor, Department of Anesthesiology, Katuri Medical College, Guntur, Andhra Pradesh, India

Corresponding Author:
Dr. Padmalatha Seelam (spadma43@yahoo.com)

Abstract

Introduction: Spinal anaesthesia is simple, rapid and most reliable anaesthetic technique. It is the most common regional anaesthesia technique, practiced worldwide. It is an efficient technique, which is easy to perform. However, associated with side effects like hypotension, bradycardia and also post-operative nausea, vomiting and chills. Decrease in vascular resistance caused by sympathetic blockade leads to drop in arterial pressure. Bradycardia is caused due to parasympathetic over activity, increase in baroreceptor activity and Bezold Jarish reflex (BJR). Ondansetron is a well-tolerated drug with 5HT3 antagonising effects which is used most commonly for peri-operative nausea and vomiting with minor side effects. Ondansetron poorly penetrates the blood brain barrier with minimal influence on central serotogenic mechanisms. Hence has less chances of causing cognitive side effects like headache, agitation and confusion. The objectives of this study is to assess the effect of intravenous ondansetron on spinal anaesthesia induced hypotension and bradycardia and the effect of ondansetron on Peri-operative nausea, vomiting and chills.

Materials & Methods: Hospital based randomised comparative controlled study with double blinding. The study was conducted on patients who were posted for elective surgeries under spinal anaesthesia in katuri Medical College and Hospitals during the period from November 2016 to October 2018.Prior approval from the institutional Ethics committee was taken.140 grade I and II patients were enrolled in the study. The protocol was explained in a detailed manner to all patients in their own understandable language and informed consent was taken.

Inclusion criteria

1. Age between 20-60 years.
2. American Society of Anaesthesiologists (ASA) grade I-II.

Exclusion criteria

1. Patients in whom spinal anaesthesia is contraindicated.
2. Patients having known allergy to ondansetron.
3. Patients having hypertension and coronary artery disease.

ISSN 2515-8260 Volume 09, Issue 02, 2022

Statistical analysis was carried out using Student t test, Chi-square/Fisher Exact used wherever necessary using SPSS 20.0.

Results: In this study a decrease in >20% of basal MAP as hypotension for use of ephedrine at every 3 minute time interval in the span of 30 mins. In Group A 17 (24.3%) patients required one dose of ephedrine, 1(1.4%) patient required two doses, 1(1.4%) patient required 3 doses in group A. In group B 23(32.9%) patient's required one dose of ephedrine, 7(10%) patient's required two doses, 3(4.3%) patient's required 3 doses. A total of 19(27.1%) and 33(47.1%) patients required ephedrine in Group A and Group B respectively with a significant P value of 0.029. In group A, not a single patient had nausea, one (1.4%) patient in group B which is statistically not significant with P value 0.496. None of the patients in both the groups have incidence of vomiting. 12 (17%) patients in group B had chills and none of the patients in group A had chills. It was statistically significant with P value of 0.0001.

Conclusion: This study indicates prophylactic use of intravenous ondansetron 4mg reduces the requirement of ephedrine in patients undergoing surgeries. Ondansetron showed no significant effect on bradycardia in this study. But Ondansetron significantly decreases the incidence of chills after spinal anaesthesia.

Keywords: Ondansetron, chills/shivering, spinal anaesthesia, bradycardia, hypotension

Introduction

Spinal anaesthesia is simple, fast and reliable anaesthetic technique. It is the most common regional anaesthesia technique, practiced worldwide [1, 2]. It is an efficient technique, which is easy to perform. But, spinal anaesthesia is associated with side effects like hypotension, bradycardia and also post-operative nausea, vomiting and chills [3, 4]. Decrease in vascular resistance caused by sympathetic blockade leads to drop in arterial pressure [5]. Bradycardia is caused due to parasympathetic over activity, increase in baroreceptor activity and Bezold Jarish reflex (BJR) [6]. Bezold Jarish reflex is triggered by chemoreceptors and mechanoreceptors which are sensitive to serotonin [2]. Serotonin is an additive trigger for BJR in hypovolemic patients [9].

Ondansetron is a well-tolerated drug with 5HT3 antagonising effects which is used most commonly for peri-operative nausea and vomiting with minor side effects [10, 11]. Ondansetron poorly penetrates the blood brain barrier with minimal influence on central serotogenic mechanisms. Hence has less chances of causing cognitive side effects like headache, agitation and confusion [12, 13, 14]. Spinal anaesthesia impairs thermoregulatory control of body with increased incidence of shivering by 56.7% [15]. Serotonin is a thermoregulatory neurotransmitter which decreases the core temperature and trigger chills. Chills has deleterious effects like increase in Co2 production and increased cardiac work [16]. The primary objective of this study is to assess the effectiveness of intravenous ondansetron on spinal anaesthesia induced hypotension and bradycardia. The secondary objective is to know the effectiveness of ondensetron in peri-operative nausea, vomiting's and chills.

Materials & Methods

Hospital based randomised comparative controlled study with double blinding. The study was conducted on patients who were posted for elective urological, orthopaedic, gynaecological, general surgical procedures under spinal anaesthesia in katuri Medical College and Hospitals from November 2016 to October 2018. Prior approval from the institutional Ethics committee was taken. 140 grade I and II patients were enrolled in the study. The protocol was explained in a detailed manner to all patients in their own understandable language and informed consent was taken.

ISSN 2515-8260 Volume 09, Issue 02, 2022

Inclusion criteria

1. Age between 20-60 years.
2. American Society of Anaesthesiologists (ASA) grade I-II.

Exclusion criteria

1. Patients in whom spinal anaesthesia is contraindicated.
2. Patients having known allergy to ondansetron.
3. Patients having hypertension and coronary artery disease.

One hundred forty (140) patients planned for elective infra umbilical surgeries were selected in this study. The randomization process of allocating into the two groups was done using computer generated random numbers.
Group A: Received intravenous ondansetron 4mg (2ml).
Group B: Received normal saline of 2ml.

Grouping was done in such a way that both patient and the monitoring anaesthesiologist were blinded to the study. The patients clinical evaluation is done in the operative room with standard monitor connected to all patients which include, pulse-oximeter (spo2), electrocardiography (ECG), and non-invasive arterial blood pressure (NIBP). Supplemental Oxygen was given by face mask at rate of 5 litres per minute. After securing Intravenous (IV) cannula (18 G/20 G) in upper limb, IV fluids were given at a volume of 5ml per kilogram during the study period. An unlabelled 2ml syringe was given to monitoring anaesthesiologist and he/she injected that 2ml of drug 5minutes before performing spinal anaesthesia. The person performing spinal anaesthesia and monitoring were blinded to the study. All patients were given spinal anaesthesia in sitting position.
Results on continuous variables are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The data attained was spread over Microsoft word and Excel for analysis and generation of graphs, tables. Statistical analysis was done using the Student t test, Chi-square/Fisher Exact used wherever necessary and also using SPSS 20.0 software.

Results

In this study, 140 patients were randomly assigned to two groups. Group A received ondansetron 4mg (2ml) and Group B received normal saline (2ml) 5min before spinal anaesthesia.

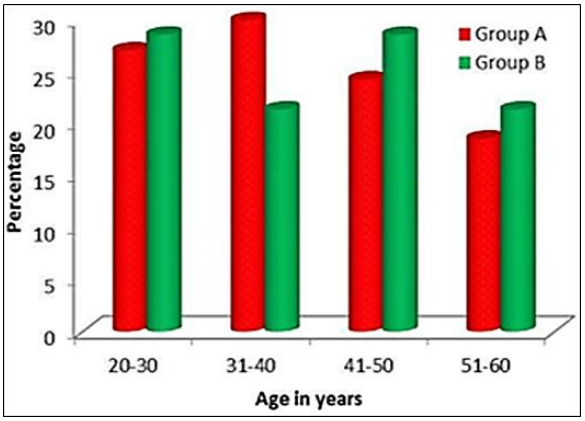

Fig 1: Age distribution among the study participants (Group A & Group B)

ISSN 2515-8260 Volume 09, Issue 02, 2022

The mean age of in group A and B are 39.39+/-11.62 and 40.19+/-11.66 respectively. Samples in each group are age matched with P value of 0.685

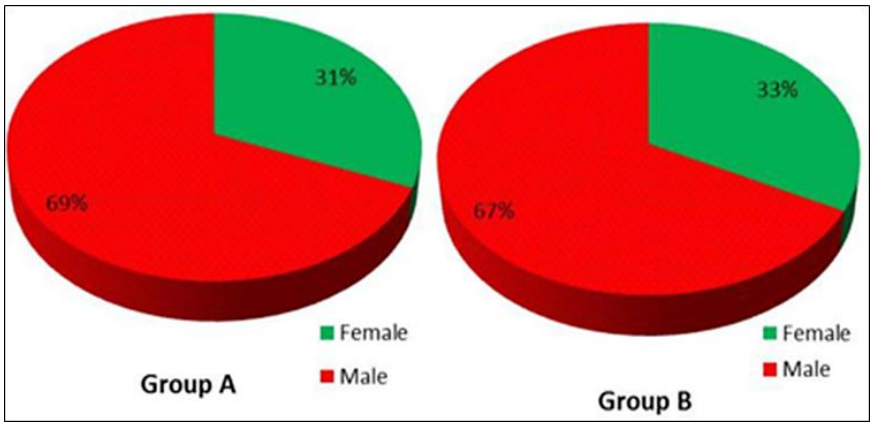

Fig 2: Gender distribution among the study participants

Group A and Group B are gender matched with Pvalue-0.856

Table 1: Distribution of Height, Weight, BMI among the two groups (A&B)

Variables	Group A	Group B	Total	P value
Weight (kg)	63.67±13.23	62.44±13.51	63.06±13.33	0.587
Height (cm)	163.11±8.50	163.23±9.25	163.17±8.85	0.939
BMI (kg/m^2)	23.82±4.01	23.34±4.36	23.58±4.18	0.498

There is no statistically significant difference in weight, height and BMI between two groups. The mean weight group A and B are 63.67+/-13.2 and 62.4+/-13.5 respectively with a P value of 0.587.The mean height of group A and B are 163.11+/-8.50 and 163.2+/-9.25 respectively with P value of 0.939.The mean BMI of group A and B are 23.82+/-4.01 and 23.34+/- 4.36 respectively with P value of 0.498.

Table 2: Bromage scale distribution among the two groups of participants (A&B)

Bromage Scale	Group A(n=70)	Group B (n=70)	Total (n=140)	P value
0 min				
0	68(97.1%)	67(95.7%)	135(96.4%)	1.000
1	2(2.9%)	3(4.3%)	5(3.6%)	
5 min				
1	21(30%)	28(40%)	49(35%)	
2	28(40%)	23(32.9%)	51(36.4%)	0.452
3	21(30%)	19(27.1%)	40(28.6%)	
10 min				
1	2(2.9%)	1(1.4%)	3(2.1%)	
2	10(14.3%)	20(28.6%)	30(21.4%)	0.100
3	58(82.9%)	49(70%)	107(76.4%)	
15 min				
1	0(0%)	0(0%)	0(0%)	
2	5(7.1%)	4(5.7%)	9(6.4%)	1.000
3	65(92.9%)	66(94.3%)	131(93.6%)	
20 min				
1	0(0%)	0(0%)	0(0%)	
2	1(1.4%)	0(0%)	1(0.7%)	1.000
3	69(98.6%)	70(100%)	139(99.3%)	

ISSN 2515-8260 Volume 09, Issue 02, 2022

There is no statistically significant difference in the Bromage scale grade at 5th, 10th, 15th and 20th min with P values of 0.452, 0.100,1.000 and 1.000 respectively

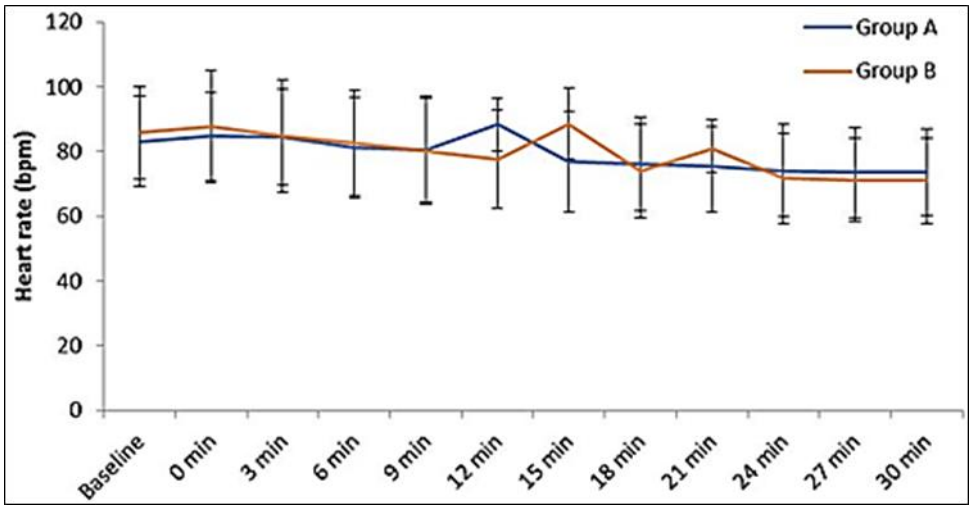

Fig 3: Comparison of Mean Heart rate (bpm) distribution in two groups of patients There is no significant difference in heart rate between both Group A and B at any point of 3 minutes interval in span of 30min. P values > 0.05 at all-time interval in the span of 30 mins

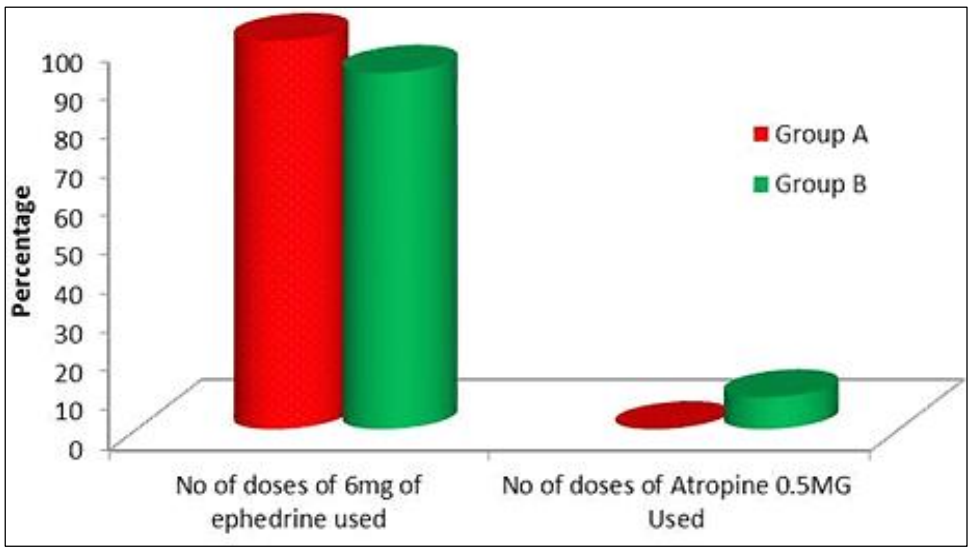

Fig 4: Atropine and Ephedrine usage among the two groups (A&B)

Decrease in >20% of basal MAP as hypotension for use of ephedrine at every 3 minute time interval in the span of 30 mins. In Group A 17 (24.3%) patients required one dose of ephedrine, 1(1.4%) patient required two doses, 1(1.4%) patient required 3 doses in group A. In group B 23(32.9%) patient's required one dose of ephedrine, 7(10%) patient's required two doses, 3(4.3%) patient's required 3 doses. A total of 19(27.1%) and 33(47.1%) patients required ephedrine in Group A and Group B respectively with a significant P value of 0.029.

Table 3: Frequency of Nausea, Vomiting, Chills distribution in two groups of patients

	Group A (n=70)	Group B (n=70)	Total (n=140)	P value
Nausea	0(0%)	1(1.4%)	1(0.7%)	0.496
Vomiting	0(0%)	0(0%)	0(0%)	-
Chills	0(0%)	12(17.1%)	12(8.6%)	0.0001*

ISSN 2515-8260 Volume 09, Issue 02, 2022

In group A none of the patients had nausea, One (1.4%) patient in group B which is statistically not significant with P value 0.496. None of the patients in both the groups have incidence of vomiting. 12 (17%) patients in group B had shivering and none of the patients in group A had shivering. It was statistically significant with P value of 0.0001.

Discussion

Spinal anaesthesia is a safe anaesthetic technique practiced commonly worldwide. Hemodynamic changes like hypotension and bradycardia occur after spinal anaesthesia are usually mild and they respond by the fluid therapy and vasopressors. But rarely may cause severe bradycardia and cardiac arrest [3, 4, 5 17]. Sympathetic blockade causes decrease in SVR and lead to blood redistribution finally results in decrease preload which in turn cause hypotension [18, 19]. The decrease in preload stimulates chemoreceptors and mechanoreceptors in ventricular wall which are also serotonin sensitive and stimulates BJR [2]. Bradycardia is due to parasympathetic over activity, increased baroreceptor activity and BJR. Serotonin is an additive trigger to activate BJR in a hypovolemic patient [1]. So measures to prevent or treat the hemodynamic changes caused by spinal anaesthesia are required.

Various methods of preventing cardiovascular consequences of sub arachnoid block include preloading and coloading with intravenous infusion, administration of sympathomimetic, administration of atropine and patient positioning facilitating venous return [2, 20, 21]. Volume preload may cause fluid overload and cardiovascular collapse in labile patients [22].

Matzen *et al*. Performed HUTT and discovered that ondansetron abolished the Adrenomedullary response to hypotension [23]. In a study conducted by Blaw *et al*. They observed that administration of serotonin to radial artery cause vasodilatation in healthy volunteers and its response is supressed by Tropisetron which is a 5HT3 blocker [24]. In 2004 Martinek successfully revived a patient of circulatory arrest caused by post sub arachnoid block by atropine and ondansetron [25]. In this study there is no statistically significant difference between ondansetron and control groups in SBP, DBP and MAP. However, we found that 19(27.1%) patients in ondansetron group and 33(47%) patients in saline group required ephedrine with statistically significant P value of 0.029. As we have considered a decrease in >20% basal MAP as hypotension for use of ephedrine at any of the 3 minute time interval in the span of 30 mins, possibly our results showed significant difference in vasopressor usage. In Group B 4(5.7%) patients and no patients in Group A had episode of bradycardia (HR <45 bpm or fall >20% of basal HR) and required atropine which is not statistically significant with P value of 0.12.

In a similar study conducted by Syed Mojtaba they compared two different dose of ondansetron 6mg, 12mg with placebo group (210 patients). 12% of patients in control group had hypotension and required vasopressors. 45% had shivering, 14% had bradycardia [1]. When compared with this study similar results regarding vasopressor consumption were observed but no difference in results with regard to bradycardia. In another similar study conducted by Walid Trabelsi *et al*, in 80 patients posted for elective LSCS they found vasopressor consumption is significantly more in saline group as compared with the ondansetron group (P<0.0001). In another study conducted by T. Sahoo in 52 patients posted for elective caesarean surgery found hypotension and vasopressor consumption is significantly reduced in ondansetron group. (P value-0.009) [26]. In a study conducted by Rashad *et al*. (2013) in 60 parturient females undergoing elective caesarean section, they concluded that patients who received intravenous ondansetron 4mg before subarachnoid block significantly decreased both the hypotension and the doses of vasopressors consumption (P value 0.005) [18]. In the study conducted by R. Owczuk *et al*., they premedicated 71 patients who were undergoing surgeries under sub arachnoid block with intravenous ondansetron 8mg and found that there was a significant difference between MAP

and SBP between study and control group but there was no significant difference in heart rate [2]. In a Meta-analysis conducted by L. Gao and colleagues (2015) included 10 randomized controlled trials with 863 patients who underwent surgical procedures under spinal anaesthesia. This database review is suggesting that prophylactic administration of intravenous ondansetron reduces the incidence of spinal anaesthesia induced hypotension and vasopressor consumption in both obstetric and non-obstetric patients [27]. However in this study we have not observed any significant difference in sensory level attained between ondansetron group and control group. But we have not monitored the regression of spinal anaesthesia. There was no difference seen in Bromage scale grade in both the groups [19].

Chills is a response to hypothermia caused by spinal anaesthesia. Deleterious effects of shivering include increased metabolic activity and oxygen consumption consequently may cause lactic acidosis and arterial hypoxemia [1, 16]. Spinal anaesthesia causes internal redistribution of blood from core to peripheral compartment. Loss of vasoconstriction capacity post sub arachnoid block causes increased heat loss from patient body surface mainly from lower extremities. Serotonin is a thermoregulatory neurotransmitter which decreases the core temperature and trigger shivering. Ondansetron is inhibitor of 5HT3 system which attenuates the serotonin induced effects on thermoregulation. Ondansetron inhibits the Serotogenic actions at the level of hypothalamus where bulk of thermoregulatory centres occurs [1]. Chills are more deleterious in older patients with low cardiopulmonary reserve, so it is very important and preventing perioperative shivering plays a significant role in patient's outcome.

In this study we observed 12(17%) patients had chills in control group whereas none in ondansetron group had shivering (P value0.0001). In a study conducted by Syed Mojtaba Marashi in 210 patients divided into 3 groups they compared 6mg and 12mg of ondansetron with a control group. They have not found any significant difference in incidence of chills between two ondansetron groups but 32 (45%) patients had incidence of shivering in control group [1]. The present study results are similar to that of this study.

In a study by Kalkasha *et al.*, in 75 patients undergoing spinal anaesthesia they compared incidence of chills in patients who received intravenous ondansetron 8mg and ephedrine 0.4 mg/kg immediately before spinal anaesthesia. They concluded that ondansetron has similar effects like ephedrine so Nausea and vomiting commonly occur during spinal anaesthesia with incidence of 18% and 7% respectively. Unopposed vagal activity occurs by sympathetic blockade and cerebral hypoxia caused by spinal anaesthesia induced hypotension are some of the mechanisms involved in spinal anaesthesia induced nausea and vomiting [4, 11, 28]. 5-HT type serotonin receptors are present peripherally on vagal nerve terminals and centrally on the chemoreceptor trigger zone of the area postrema, which is known to be associated with nausea and vomiting.

In a study conducted by Nabih I. El Khouly and Ashraf M. Meligy in 100 patients for elective caesarean section concluded that prophylactic administration of ondansetron decreases incidence of nausea and vomiting [31] (P value 0.020 and 0.031 respectively). In a study conducted by Rashad MM, Farmawy MS in 60 patients they concluded that intravenous ondansetron prevents spinal anaesthesia induced nausea as compared with saline group P value-0.008 [18].

Where as in this study no patients in ondansetron group and only one patient (1.4%) in control group had nausea with a P value of 0.452. None of the patients in either groups had incidence of vomiting. There is no significant difference in incidence of nausea and vomiting between ondansetron group and saline group. Our results are similar to the results of Terkawi AS *et al*. who conducted study on 68 patients and concluded that premedicating patients with ondansetron 8mg before spinal anaesthesia have no role in preventing nausea and vomiting [32].

ISSN 2515-8260 Volume 09, Issue 02, 2022

Conclusion

This study indicates that prophylactic use of intravenous ondansetron 4mg reduces the requirement of ephedrine in patients undergoing surgeries under sub arachnoid block. Ondansetron showed no significant effect on bradycardia in our study. This study revealed Ondansetron significantly decreases the incidence of chills after spinal anaesthesia. Further studies with larger samples and randomised controlled studies are required to understand the significance of ondansetron effect hypotension and bradycardia in patients undergoing surgeries under sub arachnoid block.

Conflict of interest: None to be Declared.

Funding: Nil.

References

1. Seyed Mojtaba Marashi, Saeid Soltani-Omid, Sussan Soltani Mohammadi, Yasaman Aghajani, Ali Movafegh. Comparing Two Different Doses of Intravenous Ondansetron with Placebo on Attenuation of Spinal-induced Hypotension and Shivering. Anesth Pain Med., 2014. Article ID12055, Available from: Doi: 10.5812/aapm.12055.
2. Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszulowicz R, Dylczyk-Sommer A, *et al*. Ondansetron Given Intravenously Attenuates Arterial Blood Pressure drop due to Spinal Anesthesia: A double-blind, placebo controlled study. Reg. Anesth. Pain Med. 2008;33:332-339.
3. Mayumi Yamano, Hiroyuki Ito, Takeshi Kamato, Keiji Miyata. Characteristics of Inhibitory Effects of Serotonin (5-HT)3-Receptor Antagonists, YM060 and YM 114 (KAE-393), on the von Bezold-Jarisch Reflex Induced by 2-Methyl-5-HT, Veratridine and Electrical Stimulation of Vagus Nerves in Anesthetized Rats. Jpn J Pharmacol. 1995;69:351-356.
4. Randall Carpenter, Robert A Caplan, David L Brown, Carol Stephenson. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology. 1992;76:908-916.
5. Kinsella SM, Tuckey JP. Perioperative bradycardia and a systole-relation to vasovagal syncope and Bezold Jarish reflex. British journal of anesthesia. 2001;86(6):859-68.
6. Walid Trabelsi, Chihebeddine Romdhani, Haythem Elaskri, Walid Sammond, Mohamed Bensalah, Iheb Labbene, *et al*. Effect of Ondansetron on the Occurrence of Hypotension and on Neonatal Parameters during Spinal Anesthesia for Elective Caesarean Section: A Prospective, Randomized, Controlled, Double-Blind Study. Anesthesiol Res and Pract. 2015, 7. Article ID 158061. Available from: Doi: 10.1155/2015/158061.
7. Srinivasa Rao Nallam, Sudheer Dara. Effect of intravenous ondansetron on reducing the incidence of hypotension and bradycardia events during shoulder arthroscopy in sitting position under interscalene brachial plexus block: A prospective randomised trial. Indian J Anaesth. 2015;59(6):353-358.
8. Mayumi Yamano, Hiroyuki Ito, Takeshi Kamato, Keiji Miyata. Characteristics of Inhibitory Effects of Serotonin (5-HT)3-Receptor Antagonists, YM060 and YM 114 (KAE-393), on the von Bezold-Jarisch Reflex Induced by 2-Methyl-5-HT, Veratridine and Electrical Stimulation of Vagus Nerves in Anesthetized Rats. Jpn J Pharmacol. 1995;69:351-356.
9. Jason A. Campagna and Christopher Carter. Clinical Relevance of the Bezold-Jarisch Reflex. Anesthesiology. 2003;98:1250-60.
10. Meng Wang, *et al***.** Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension during cesarean delivery: a dose-dependent study. Int. J Clin. Exp. Med. 2014;7(12):5210-5216.

11. Dengxin Zhang, Zhiyun Shen, Jie You, Xiaolian Zhu, Qi-Feng Tang. Effect of ondansetron in preventing postoperative nausea and vomiting under different conditions of general anesthesia: a preliminary, randomized, controlled study. Upsala Journal of medical sciences. 2013;118:87-90.
12. Kenneth R. McQuaid. Drugs Used in the Treatment of Gastrointestinal Diseases. In: Bertram G Katzung, Susan B Masters, Antony J Trevor, editors. Basic and Clinical Pharmacology. 12th ed. New York: McGraw Hill, 2012, 1097-99.
13. Elaine Sanders-Bush, Steven E Mayer. 5HT (Serotoinin) receptor agonists and Antagonists In: The Pharmacological Basis of Therapeutics, Goodman and Gillman's. 11th ed. Laurance L Bruton, John S Lazo, 297-315.
14. Carlos M Villalon, David Centurion. Cardiovascular responses produced by 5-hydroxytriptamine a pharmacological update on the receptors/mechanisms involved and therapeutic implications. Naunyn-Schmiedeberg's Arch Pharmacol. 2007;376:45-63.
15. Golparvar M, Saghaei M, Saadati MA, Farsaei S. Effect of ondansetron on prevention of post-induction hypotension in elderly patients undergoing general anesthesia: A randomized, double-blind placebo-controlled clinical trial. Saudi J Anaesth. 2015;9:365-9.
16. Safavi M, Honarmand A, Mohammadsadeqie S. Prophylactic use of intravenous ondansetron versus ketamine-midazolam combination for prevention of shivering during spinal anesthesia: A randomized double-blind placebo-controlled trial. Adv Biomed Res 2015;4:207.
17. Juliana Arruda Godoy Limongi Rossana Sant Anna de Melo Lins. Cardiopulmonary Arrest in Spinal Anesthesia. Rev Bras Anestesiol. 2011;61(1):110-120.
18. Rashad MM, Farmawy MS. Effects of intravenous ondansetron and granisetron on hemodynamic changes and motar and sensory blockade induces by spinal anesthesia in parturients undergoing caesarean section. Egypt J Anaesth. 2013;29(4):369-74.
19. Fassoulaki A, Melemeni A, Zotou M, Sarantopoulos C. Systemic ondansetron antagonizes the sensory block produced by intrathecal lidocaine. Anesth Analg. 2005;100(6):1817-21.
20. Wang Q, Zhuo L, Shen MK, Yu YY, Yu JJ, Wang M. Ondansetron preloading with crystalloid infusion reduces maternal hypotension during cesarean delivery. Am J Perinatol. 2014;31:913-22.
21. Somboonviboon W, Kyokong O, Charuluxananan S, Narasethakamol A. Incidence and risk factorsn of hypotension and bradycardia after spinal anesthesia for caesarean section. Med J Med Assoc. Thail. 2008;91(2):181.
22. Morgan P. The role of vasopressors in the management of hypotension induced by spinal and epidural ansesthesia. Can J Anaesth. 1994;41:404-13.
23. Matzen S, Secher NH, Knigge U, Pawelczyk J, Perko G, Iversen H, *et al*. Effect of serotonin receptor blockade on endocrine and cardiovascular responses to head-up tilt in humans. Acta Physiol. Scand. 1993;149:163-176.
24. Blauw GJ, Van Brummelen P, Chang PC, Vermeji P, Van Zwieten PA. 5HT3 receptor mediated vasodilation in human forearm. J Hypertens Suppl. 1988;6:S33-S35.
25. Robert M Martinek. Witnessed asystole during spinal anesthesia treated with atropine and ondansetron: a case report. Can. J Anesth. 2004;51(3):226-230.
26. Sahoo T, Sen Dasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: a double-blind randomised, placebo-controlled study. Int J Obstet Anesth. 2012;21(1):24-8.
27. Gao L, Zheng G, Han J, Wang Y, Zheng J. Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: a meta-analysis. International Journal of Obstetric Anesthesia. 2015;24:335-343.
28. Jabalameli M, Honarmand A, Safavi M, Chitsaz M. Treatment of postoperative nausea

and vomiting after spinal anesthesia for cesarean delivery: A randomized, double-blinded comparison of midazolam, ondansetron, and a combination. Advanced Biomedical Research. 2012;1:2. Doi: 10.4103/2277-9175.94424.

29. Saeeda Islam, Jain N. Post-operative nausea and vomiting (ponv): A review article. Indian J Anaesth. 2004;48(4):253-258.
30. Mahmoud Eidi, Khosro Kolahdouzan, Hamzeh Hosseinzadeh, Razieh Tabaqi. A Comparison of Preoperative Ondansetron and Dexamethasone in the Prevention of Post-Tympanoplasty Nausea and Vomiting. Iran J Med Sci. 2012;37(3):166-72.
31. Nabih I El Khouly, Ashraf M Meligy. Randomized controlled trail comparing ondansetron and placebo for the reduction of spinal anesthesia- induced hypotension during caesarean delivery in Egypt. International journal of Gynecology and Obstetrics. 2016;135:205-209.
32. Terkawi AS, Tiouririne M, Mehta SH, Hackworth JM, Tsang S, Durieux ME. Ondansetron does not attenuate hemodynamic changes in patients undergoing elective caesarean delivery using subarachnoid anesthesia. Reg. Anesth. Pain Med. 2015;40(4):344-348.