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INTRAVENOUS ONDANSETRON VERSUS GRANISETRON ON HEMODYNAMIC CHANGES INDUCED BY SPINAL ANESTHESIA IN ELDERLY PATIENTS UNDERGOING LOWER LIMB SURGERIES

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ABSTRACT

Background Although spinal anesthesia avoids the risks of airway management in elderly patients, but hemodynamic instability as hypotension and bradycardia still the major complications of spinal anesthesia. Ondansetron and granisetron are selective serotonin receptor antagonists used mainly as antiemetics and may have a role to decrease the hemodynamic instability.

Methods : Randomized controlled double blind clinical study included 72 Patients of age 65 years or above undergoing lower limb surgeries under spinal anesthesia were randomly allocated into 3 equal groups (24 patients each), group O (ondansetron) received I.V 8mg ondansetron group G (granisetron) received I.V 1mg granisetron, group S (control group) received 10 ml I.V normal saline 5 minutes before induction of spinal anesthesia. Hypotension and bradycardia were recorded.

Results: There were statistically significant decrease in the number of patients developed hypotension (P value 0.011) and bradycardia (P value 0.001) in the O and G groups compared to the control group with no difference between the O and G groups.

Conclusions: In elderly patient undergoing lower limb surgeries under spinal anesthesia, prophylactic intravenous administration of 8mg ondansetron or 1mg granisetron 5 minutes before induction of spinal anesthesia reduces the hemodynamic instability with no significant difference between the two drugs.

Keywords; Ondansetron; Granisetron; Spinal Anesthesia; Lower Limb Surgeries

1. INTRODUCTION

Spinal anesthesia (SA) is considered a safe procedure, but it may have some side effects including hypotension and bradycardia. Sympathetic fiber blockade and vasodilation are the main causes of hypotension [1].

SA is performed more frequent in elderly patients despite the higher risk of hypotension and its consequences. The percentage of hypotension in elderly patients is estimated to be over 70% [2].

The methods that used routinely for prevention of hypotensive side effect (e.g, volume preload or ephedrine) may have risk of hypervolemia or myocardial ischemia in elderly population [2].

Hypotension and bradycardia both of them may arise from Bezold-Jarish reflex (BJR), spinal anesthesia causes decrease in preload that stimulates BJR which may be mediated by peripheral serotonin receptors (5HT-3) (3). These receptors are located peripherally as cardiac chemoreceptors on the cardiac vagal afferent and centrally as chemoreceptor trigger zone [4].

Ondansetron and granisetron are selective 5-hydroxytryptamine 3(5HT-3) receptor antagonists. They act primarily as potent antiemetic and may be useful to decrease the incidence of hypotension and bradycardia caused by spinal blockade [5].

The aim of this study is to compare the prophylactic effects of ondansetron versus granisetron on spinal anesthesia induced hypotension and bradycardia in elderly patients undergoing lower limb surgeries.

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2. PATIENTS & METHODS

After attaining the Institutional Review Board approval (IRB) no 4880/23_9_2018 and written consent were taken from the 72 patients. The study was carried out at zagazig university hospitals. The inclusion criteria were; Age 65 years or above**,** American society of anesthesiologists ASA II**,** Both sex and the body mass index (BMI) between18.5-25. While the Exclusion criteria were; Absolute contraindication to spinal anesthesia (coagulopathy and infection at the site of injection…etc.), Operations need blood transfusion, Patient on selective serotonin reuptake inhibitors or serotonin related migraine medication, uncontrolled hypertensive or diabetic patient and history of cardiac disease. All patients kept fasting for 8 hours. In the operating room, standard monitors connected (pulse oximeter, noninvasive blood pressure and electrocardiogram) and baseline data was recorded.

After insertion of intravenous (I.V) 18-gauge cannula Ringer solution warmed to (37° C) was given at dose of 8 ml/kg as preload and operating room temperature kept at 21-23° C.

Patients randomly divided into 3 equal groups:

Group (O) N=24 patients received I.V 8mg/4ml ondansetron (adwia) completed with normal saline to 10 ml.

Group (G) N=24 patients received I.V 1mg/1ml granisetron (egypharma) completed with normal saline to 10 ml.

Group (S) N=24 patients received 10 ml I.V normal saline.

Syringe contents were given IV 5 minutes before induction of spinal anesthesia over one minute. The anesthetist who collect the data and the patients were blind to the contents of the syringes.

In the sitting position, the skin of the back of the patient was sterilized using Povidone iodine, the spinal space located at L3_L4 or L4_L5 interspace.

After subcutaneous infiltration of local anesthesia, 25-gauge Quincke spinal needle advanced in midline technique (Para-median technique had been used when midline is difficult).

After successful dural puncture which confirmed by free flow of cerebrospinal fluid (CSF), the total volume 2.5ml (12.5mg) of 0.5% hyperbaric bupivacaine and 25 mcg fentanyl was injected in subarachnoid space.

The patients were placed in supine position immediately with elevation of head 15 degrees, and oxygen 3L/min administered by facemask.

Spinal anesthesia is considered successful when sensory block reach T6 by the pin prick technique with inability to move any leg joint (Bromage scale 3) [6]: I Free movement of legs and feet, II Just able to flex knees with free movement of feet, III Unable to flex knees, but with free movement of feet and IV Unable to move legs or feet.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and oxygen saturation were recorded after induction of spinal anesthesia every 5 minutes for 30 minutes then every 10 minutes intraoperative and postoperative for half an hour.

Hypotension defined as SBP below 90 mmHg or decreasing by 20% of the basal readings and treated by I.V 6 mg ephedrine and I.V fluids.

Bradycardia was diagnosed as heart rate below 50 beats per minutes and treated by I.V 0.3_0.5 mg atropine.

Statistical analysis

Data collected, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance. Difference and association of qualitative variable by Chi square test (X2). Multiple quantitative by ANOVA. P value was set at <0.05 for significant results & <0.001 for high significant result.

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3. RESULTS

Seventy-two elderly patients (65 years or above) were included in this study for lower limb surgeries under spinal anesthesia. Patients were divided into 3 groups (O, G &control) each group contains 24 patients. There were no significant differences in the patient age, sex, body weight, height, body mass index and duration of surgery (Table1).

Table1: Demographic characteristics and surgical duration among studied groups

			O Group	G Group	Control	F/X^2	P
Age (year)			**59.21±8.2**	**58.29±8.1**	**58.16±8.7**	**0.110**	**0.896**
Weight (kg)			**86.24±7.9**	**85.42±8.6**	**84.65±7.9**	**0.224**	**0.800**
Height (cm)			**166.58±9.1**	**166.75±9.6**	**169.1±9.4**	**0.530**	**0.591**
BMI (Kg/m^2)			**22.33±2.4**	**21.7±3.1**	**22.1±3.3**	**0.495**	**0.612**
Duration of surgery (min)			**85.33±14.5**	**90.0±12.5**	**85.6±15.5**	**1.254**	**0.112**
Sex	**Male**	**N**	**14**	**12**	**14**		
		%	**58.3%**	**50.0%**	**58.3%**	**0.45**	**0.79**
	Female	**N**	**10**	**12**	**10**		
		%	**41.7%**	**50.0%**	**41.7%**		

Data was expressed by mean ± SD and N (%) F ANOVA X2 Chi square O Ondansetron G Granisetron BMI Body mass index

At the basal SBP there was no difference among the 3 groups but SBP was significantly lower in control group at 5 min and 10 minutes compared to O and G groups (P value was 0.011) with no significant difference between O & G groups and also there was no significant difference among the 3 groups regarding other times (Figure 1).

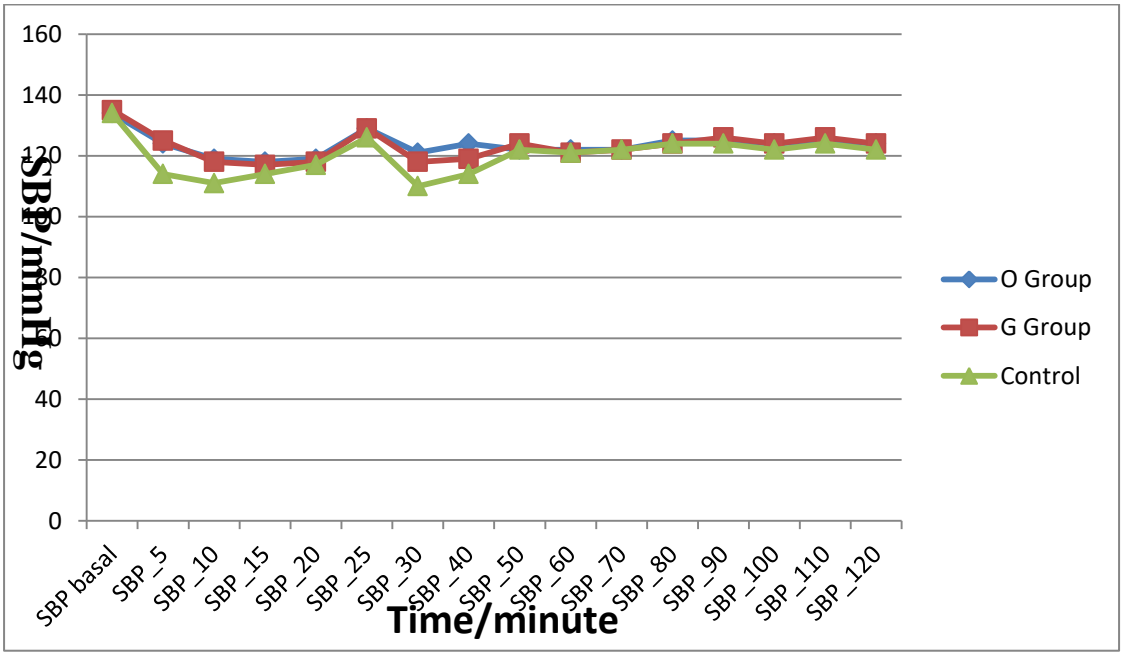

Figure 1: systolic blood pressure "mmHg" among studied groups

Figure 2 reveals that DBP was significantly lower in control group at 5 min and 10 minutes compared to O and G groups (P value was 0.007) with no significant difference between O & G groups and also there was no significant difference among the 3 groups regarding other times.

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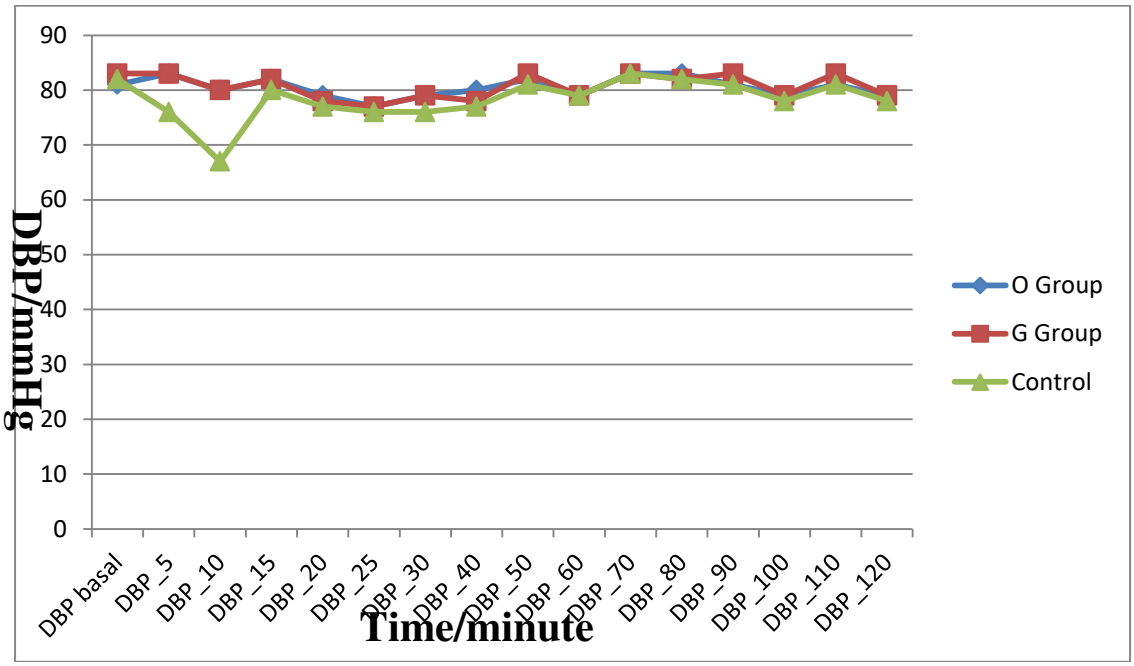

Figure 2: diastolic blood pressure "mmHg" among studied groups

Regarding the heart rate table 2 shows that HR was significantly lower in control group at 5 min and 10 minutes compared to O and G groups with no significant difference between O & G groups and also there was no significant difference among 3 groups regarding other times.

Table 2: Heart rate "beat/min" distribution among studied groups

Beat/min	O Group N=24	G Group N=24	Control N=24	F	P
HR basal	76.2±2.3	76.25±1.7	76.66±2.5	0.304	0.739
HR after 5 min	77.2±2.4	75.87±4.6	71.2±8.07	7.737	0.001**
HR_10 min	76.2±2.4	74.75±4.5	70.2±8.07	7.648	0.001**
HR_15 min	76.2±2.3	75.33±3.8	74.83±6.2	0.584	0.561
HR_20 min	74.2±2.2	74.28±1.88	74.69±2.2	0.304	0.739
HR_25 min	77.2±2.4	76.75±2.7	76.41±4.0	0.388	0.680
HR_30 min	78.37±2.4	77.0±4.6	76.69±8.14	1.229	0.124
HR_40 min	76.2±2.46	74.87±4.59	73.2±8.07	0.817	0.441
HR_50 min	80.2±2.3	79.33±3.8	78.83±6.2	0.584	0.561
HR_60 min	75.33±2.1	75.37±1.7	75.87±2.5	0.468	0.628
HR_70 min	75.37±2.06	74.45±3.43	73.2±2.5	1.814	0.289
HR_80 min	82.37±2.5	81.0±4.69	79.04±3.7	1.758	0.299
HR_90 min	75.45±1.9	75.5±1.6	75.37±3.0	0.019	0.982
HR_100 min	76.54±1.95	76.54±1.66	76.15±3.06	0.003	0.997
HR_110 min	75.66±2.8	75.83±2.4	75.44±3.33	0.021	0.977
HR_120 min	76.54±1.95	76.74±2.31	76.5±3.86	0.002	0.998

Data was expressed by mean ± SD F ANOVA ** highly significant
O Ondansetron G Granisetron HR heart rate N number of patients

There was no significant difference among the three groups regarding oxygen saturation. (table 3).

Table 3: SPO2(%) distribution among studied groups

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SPO2%	O Group N=24	G Group N=24	Control N=24	F	P
SPO2_basal	97.5±1.8	97.8±1.21	97.4±1.64	0.001	0.999
SPO2_5	97.58±1.8	97.41±1.13	97.5±1.53	0.069	0.933
SPO2_10	97.88±1.86	97.75±1.39	97.83±0.7	0.195	0.823
SPO2_15	97.83±1.71	97.08±1.2	96.83±1.76	1.600	0.282
SPO2_20	97.25±1.62	97.16±1.9	96.91±1.3	0.257	0.774
SPO2_25	97.75±1.72	97.41±1.13	97.83±1.8	0.464	0.631
SPO2_30	97.58±1.88	97.66±1.34	96.83±1.43	2.046	0.137
SPO2_40	97.5±1.74	97.58±0.65	97.25±1.6	0.355	0.702
SPO2_50	97.75±1.7	97.41±1.52	97.08±1.69	0.424	0.656
SPO2_60	97.83±1.57	97.25±1.18	97.29±1.23	1.172	0.316
SPO2_70	97.88±1.4	97.69±1.12	97.33±1.11	1.234	0.298
SPO2_80	98.25±1.77	98.15±1.87	98.0±1.1	1.468	0.225
SPO2_90	98.5±1.47	98.0±0.89	97.9±0.78	1.039	0.359
SPO2_100	98.87±0.99	98.7±0.79	98.5±0.88	1.239	0.312
SPO2_110	98.55±1.55	98.5±0.89	98.6±0.98	1.088	0.362
SPO2_120	98.85±0.98	98.6±0.88	98.7±0.78	1.214	0.315

Data was expressed by mean ± SD F ANOVA O Ondansetron G Granisetron SPO2 peripheral oxygen saturation
N number of patients

There was statistically significant increase in the number of patients developed hypotension in the control group compared to O and G groups (p value 0.027). There was no significant difference between O&G group. (table4)

There was statistically significant increase in the number of patients developed bradycardia in the control group compared to O and G groups (p value 0.019).There was no significant difference between O&G group. (table4

Table 4: number of patients developed hypotension and bradycardia

			Group O Group N=24	G Group N=24	Control Group N=24	Total	X^2	P
Hypotension	No	N	22	22	16	60		
		%	91.7%	91.7%	66.7%	83.3%		
	Yes	N	2	2	8	12	7.2	0.027*
		%	8.3%	8.3%	33.3%	16.7%		
Bradycardia	No	N	24	20	17	61		
		%	100.0%	83.3%	70.8%	84.7%		
	Yes	N	0	4	7	11	7.9	0.019*
		%	0.0%	16.7%	29.2%	15.3%		
Total		N	24	24	24	72		
		%	100.0%	100.0%	100.0%	100.0%		

Data was expressed by N (%) X^2 chi square O Ondansetron G Granisetron

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4. DISCUSSION

Hemodynamic changes such as hypotension and bradycardia occur after spinal anesthesia are usually benign and respond to the fluid therapy and vasopressors. However, rarely, it may cause severe bradycardia and cardiac arrest [7].

Hence, measures to prevent or treat the hemodynamic changes caused by spinal anesthesia are required. Various methods of preventing cardiovascular consequences of subarachnoid block include preloading and coloading with i.v. infusion of crystalloids, administration of atropine or sympathomimetic beside patient positioning which facilitating the venous return [8].

Volume preload may cause fluid overload and cardiovascular collapse in labile patients. Prophylactic use of vasopressors has no role in preventing hypotension which in turn may causes hypertension and increase cardiac workload [9].

This study results demonstrated that administration of ondansetron 8 mg and granisetron 1mg effectively decreased spinal anesthesia induced hypotension and bradycardia with no significant difference between the two groups. These results may be attributed to the action of those two 5-HT3 receptor antagonists as they block the BJR.

Two studies done by Sahoo et al. [10] and Trabelsi et al. [11] to evaluate the effect of ondansetron on the hemodynamics following subarachnoid block in patients undergoing elective cesarean section. In their studies, patients divided into two groups: group O received intravenous ondansetron 4 mg and group S received normal saline. Results showed that decreases in mean blood pressure were significantly less in Group O than Group S, patients in Group O required significantly less vasopressors, also decreases in HR was common in group S, and this is in agreement with the findings of the present study.

Our results were consistent with that obtained by Eldaba and Amr [12] on patients scheduled for elective cesarean section showed that administration of 1 mg of granisetron can reduce significantly the incidence of hypotension in these patients. Moreover, they also reported that the dosages of ephedrine and atropine in the granisetron group were significantly lower.

Also the results of the present study matched with that of Megahed et al. [13] that Compared the effect of granisetron 1mg versus ondansetron 4mg on pregnant patients undergoing cesarean section under spinal anesthesia. They concluded that prophylactic administration of intravenous ondansetron or granisetron 5min before induction of spinal anesthesia was significantly reduced the severity of spinal-induced hypotension with no significant difference between the two drugs.

Khalifa. [14] studied patients who received either granisetron 1mg, ondansetron 4mg, ephedrine 10mg or 10ml normal saline. He concluded that in the cesarean section, prophylactic use of i.v. granisetron, ondansetron, or ephedrine reduced the severity of spinal-induced hypotension and vasopressor need. The important finding in this study is that, despite the reduction in mean blood pressure in the two therapeutic groups, it still less than that in group C, with significant difference recorded. These results are consistent with our results.

In the study of Terkawi et al. [15] to compare between ondansetron 8 mg with placebo on patients undergoing elective cesarean delivery, they concluded that ondansetron premedication does not attenuate hemodynamic changes after subarachnoid anesthesia nor reduce the amount of vasopressor use, which was not in agreement with the findings of the present study. The variability in the findings of the present study with that of Terkawi might be explained as they used a different dose of hyperbaric bupivacaine used a mixture of 15 mg of 0.75% bupivacaine, 20 μg of fentanyl, and 100 μg of preservative-free morphine. In the present study we used 12.5mg of 0.5% hyperbaric bupivacaine and only 25 mcg preservative-free fentanyl.

In contrast to our results Mowafi et al. [16] evaluated the effects of intravenous granisetron on the sensory and motor blockade produced by spinal bupivacaine on patients undergoing elective knee arthroscopy, granisetron group and a control group. They concluded that there were no significant differences between the two groups in hemodynamic variables. One patient in each group required 10 mg of ephedrine to treat hypotension. Atropine was never given, and no complications related to spinal anesthesia were observed. The difference was that Mowafi studied adult patients undergoing elective knee arthroscopy, while the

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present work studied geriatric patients undergoing lower limb surgeries. Additionally, is the definition of hypotension and bradycardia. Different to the definition used in the present study for hypotension, Mowafi used a 30% decrease in systolic blood pressure below baseline and treated with 5–10 mg IV ephedrine, bradycardia (HR < 45 bpm) and treated with 0.5 mg IV atropine.

5. CONCLUSION

In elderly patient undergoing lower limb surgeries under spinal anesthesia, prophylactic intravenous administration of 8mg ondansetron or 1mg granisetron 5min before induction of spinal anesthesia will be significantly reduce the severity of spinal-induced hypotension and bradycardia with no significant difference between the two drugs.

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***Data Availability Statement*:** The data presented in this study are available on request from the corresponding author.

***Conflicts of Interest*:** The authors declare no conflict of interest.

REFERENCES

1. **Spencer L and McDonald B.** Current issues in spinal anesthesia. Anesthesiology. 2001; 94(5):888-906.
2. **Messina AN, Frassanito L, Colombo D.** Hemodynamic changes associated with spinal and general anesthesia for hip fracture surgery in severe ASA III elderly population: a pilot trial. Minerva anestesiologica. 2013; 79(9):1021-1029.
3. **Campagna JA and Carter C.** Clinical relevance of the Bezold-Jarisch reflex. Anesthesiology. 2003; 98(5):1250-1260.
4. **Martinek RM.** Witnessed asystole during spinal anesthesia treated with atropine and ondansetron: a case report. Can J Anesth. 2004; 51(3):226-230.
5. **Marashi, Seyed M, Soltani-Omid S.** Comparing two different doses of intravenous ondansetron with placebo on attenuation of spinal-induced hypotension and shivering. Anesthesiology and pain medicine. 2014; 4(2).
6. **Ziyaeifard M, Azarfarin R, Golzari SE**. A review of current analgesic techniques in cardiac surgery. Is epidural worth it? Journal of cardiovascular and thoracic research. 2014; 6(3): 133.
7. **Rashad M and Farmawy M.** Effects of intravenous ondansetron and granisetron on hemodynamic changes and motar and sensory blockade induces by spinal anesthesia in parturients undergoing caesarean section. Egyptian Journal of Anaesthesia. 2013; 29(4):369–374.
8. **Wang B, Xu X, Ren C, Hu J, Greenberg DA, Chen T, et al .** Age-related Impairment of Vascular Structure and Functions. Aging Dis. 2017; 8(5):590-610.
9. **Watts SW and Davis RP.** 5-hydroxtryptamine receptors in systemic hypertension: An arterial focus. Cardiovascular therapeutics. 2011; 29(1):54–67.
10. **Sahoo T, SenDasgupta 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):24-28.
11. **Trabelsi W, Romdhani C, Elaskri H, Sammoud W, Bensalah M, Labbene I.** 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 Pract. 2015.
12. **Eldaba AA and Amr YM.** Intravenous granisetron attenuates hypotension during spinal anesthesia in cesarean delivery: A double-blind, prospective randomized controlled study. Journal of anesthesiology, clinical pharmacology. 2015; 31(3):329-332.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

13. **Megahed M, Mekhaimer A, Sayed A, Mohamed M**. clinical comparative study of the effects of intravenous ondansetron and granisteron on hemodynamic changes, shivering and motor & sensory blockade induced by spinal anesthesia in women undergoing cesearen section. N Y Sci J. 2017; 10(6):7-16.

14. **Khalifa O.** A comparative study of prophylactic intravenous granisetron, ondansetron, and ephedrine in attenuating hypotension and its effect on motor and sensory block in elective cesarean section under spinal anesthesia. Ain-Shams Journal of Anesthesiology. 2015; 8(2):166.

15. **Terkawi AS, Tiouririne M, Mehta SH, Hackworth JM, Tsang S, Durieux ME.** Ondansetron Does Not Attenuate Hemodynamic Changes in Patients Undergoing Elective Cesarean Delivery Using Subarachnoid Anesthesia: A Double-Blind, Placebo-Controlled, Randomized Trial. Reg Anesth Pain Med. 2015; 40(4):344-348.

16. **Mowafi H, Arab S, Ismail S, AlGhamdi A.** The effects of intravenous granisetron on the sensory and motor blockade produced by intrathecal bupivacaine. Anesthesia and Analgesia. 2008; 106(4):1322-1325.