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Cardiovascular Effects Associated with Use of Prophylactic Intravenous Ondansetron in Patients undergoing Orthopedic Surgeries under Spinal Anesthesia

SlemanIfhimaSleman[1],Mohamed Anwar Refki[2], Kamelia Ahmed Gamal Eldin Abaza[3], Mohamed Ibrahim Elsayed[4]

[1] M.B.B.CH - Faculty of Medicine Sirt University - Libya.

[2]Professor of Anesthesia & Surgical Intensive care, Faculty of MedicineZagazigUniversity.

[3]Professor of Anesthesia & Surgical Intensive care,Faculty of Medicine Zagazig University.

[4]Lecturer of Anesthesia & Surgical Intensive care, Faculty of Medicine Zagazig University.

Correspondingauthor: SlemanIfhimaSleman

Email: Sulimanefhema@gamil.com

Abstract

Background:Spinal anesthesia is a common choice for patients undergoing orthopedic surgeries.ondansetron was found to attenuate the incidence of SIH and bradycardia during spinal anesthesia.

Aim of the study:This work was done to compare between the effects of prophylactic intravenous of two different doses of ondansetron (4 mg) and (8 mg) in attenuating hypotension in patients undergoing orthopedic surgeries under spinal anesthesia.

Patients and methods:This study wasa prospective comparative randomized controlled clinical trial that have been carried out in Zagazig University Hospitals and included 66 patients, their ages ranged from 21 to 60 years old patients for only unilateral orthopedic surgeries under spinal anesthesia, duration of surgery less than 2 hours in the study.Patients were randomly divided into three equal groups, 22 patients for each group, Group "O1" received IV ondansetron (4mg) diluted in 10 ml saline, group "O2" received IV ondansetron (8mg) diluted in 10 ml saline, and group C (control) received only 10 ml IV saline alone. Medications were administrated 5 min before starting the subarachnoid block by an anesthesiologist blinded to them, they were assessed for their cardiovascular effects including blood pressure, heart rate (HR) before, throughout and after operation.

Results:There was difference between the prophylactic intra venous of the two different doses of ondansetron in attenuating hypotension in patients undergoing orthopedic surgeries, under spinal anesthesia compared with the control group. Mean Blood Pressure (MBP) and HR were significantly, lower among the control group from 5 min tell the 10 minutes compared to (O1) and (O2) groups.

Conclusion:

In patient undergoing orthopedic surgeries under spinal anesthesia, prophylactic intravenous administration of 4mg ondansetron or 8mg ondansetron 5min before induction of spinal anesthesia to reduce the severity of spinal-induced hypotension and bradycardia well significantly.

Keywords:Spinal Anesthesia, Orthopedic Surgeries, ondansetron.

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1. Introduction:

Spinal anesthesia is a common choice for patients undergoing orthopedic surgeries,as it has the advantages of better postoperative pain relief, less incidence of nausea and vomiting, better postoperative recovery ,less incidence of drug-induced anaphylaxis comparable with general anesthesia and being less cost-effective **(1),**However Hypotension and bradcardia are considered the most common complications of spinal anesthesia **(1).**

The mechanism of hypotension is owing to both venous and arterial vasodilation caused by sympathetic blockade, As arterial vasodilatation leads to decreased vascular tone and resistance, thus resultant vasodilation leads to venous blood, pooling and decreased venous return **(2).** Furthermore, the absence of a compensatory response as reflex tachycardia and vagal over activity are assisting factors to the development of spinal-induced hypotension (SIH) **(3).**

The causes of bradycardia can be attributed to increased parasympathetic tone blocking of the cardio stimulatory nerve fibers and diminishing baroreceptor activity, Moreover, Bezold-Jarisch reflex (BJR) has been considered the eminent cause of bradycardia after spinal anesthesia; it is a cardio inhibitory reflex that causes bradycardia hypotension, and cardiovascular collapse via the non-myelinated type C fibers while turning on peripheral serotonin receptors 5-hydroxytryptamine (5-HT3) and initiation of BJR **(4).**

The purpose of treatment of SIH is to recover preload, increase peripheral vascular resistance, and increase cardiac output, this incorporates proper of the positioning lower leg compression preloading, or better co loading of crystalloids and colloids, and lastly giving vasopressors **(5).**

Finaly recent evidence-based practice employed the prophylactic administration of α-adrenergic and β-adrenergic agonists, which have been shown to prevent and treat SIH **(6).**
We aimed in this work to compare between the effects of prophylactic intravenous of two different doses of ondansetron (4 mg) and (8 mg) in attenuating hypotension in patients undergoing orthopedic surgeries under spinal anesthesia.

2. Patients and Methods:

This study was a prospective comparative randomized controlled clinical trial that have been carried out in Zagazig University Hospitals and included 66 patients, their ages ranged from 21 to 60 years old patients for only unilateral orthopedic surgeries under spinal anesthesia, duration of surgery less than 2 hours in the study.

Patients with history of allergic reaction to local anesthetic, bleeding disorders, aspirin ingestion in the preceding week, mental diseases, preexisting neurological or spinal diseases, infection at the site of injection, hypotensive patients, allergy to any of the used drugs, patients autonomic neuropathy, patients with advanced cardiac or liver or renal diseases , patients taken selective serotonin reuptake inhibitor, and history of nausea and/or vomiting during the 24 h before induction of anesthesia have been excluded from the study.

Ethical approval: Approval have been obtained from the Institutional Review Board (IRB) Zagazig University. Written informed consents were obtained from all patients participating in the

study.

- Patients were divided randomly using closed envelops into three groups:

➢ **Group (O1)** (ondansetron (4 mg) n=22).patients received 4 mg ondansetrone intravenous in to 10 ml of normal saline five minutes before the spinal block.

➢ **Group (O2)** (ondansetron (8 mg) n=22). patients received 8 mg ondansetrone intravenous in to 10 ml of normal saline five minutes before the spinal block.

➢ **Group (C)** (control group n=22). patients received 10 ml of normal saline five minutes before the spinal block.

For each patient an 18-G peripheral venous catheter have been be inserted and 500 ml of Ringer's lactate have been infused before and during the blockade at a rate of 10 ml/kg/h. After preoperative fluid infusion standard monitoring (ECG, sphygmomanometer cuff for blood pressure measurement and pulse oximeter) were applied with basal reading obtained for (HR, MBAP and SPO2) Patients in group O1 & O2 had been respectively received 4 & 8 mg ondansetron (Zofran) intravenously before the intra thecal block.

The block was performed in the sitting position at the L3-L4 level, midline approach using 25-G Quincke needle.

A volume of 3-ml hyperbaric bupivacaine 0.5% with 25-µg fentanyl (total 3.5 ml) will be injected intrathecally.

Patients were positioned supine. An oxygen mask was placed with a flow rate of 5 l/min

The Sensory level had been determined by pinprick after the block and every minute until the level will be fixed for five consecutive minutes.

The motor blockade was evaluated using modified Bromage's criteria.

Scale 0 =full flexion of foot, knee and hip, i.e no motor block.Scale 1= full flexion of the foot and knee, unable to hip flexion.Scale 2= full flexion of foot, unable to flex the knee or hip the flexion.
Scale 3=total motor block, unable to flex the foot, knee or hip the flexion.

If the patient complains of inadequate analgesia after 20 minute of spinal anesthesia general anesthesia was given and the patient have been excluded.

The study Mean arterial blood pressure and heart rate were measured and recorded preoperatively (base line), after block then every 5 min till the end of surgery, The highest sensory level, duration of surgery.

Hypotension (mean arterial blood pressure decrease >20% of basal readings) have been managed by intermittent doses of ephedrine 0.1 mg/kg intravenously with increments and the total amount of ephedrine given will be recored

Bradycardia (heart rate <20 of basal reading)was treated by intravenous atropine 0.01 mg/kg (number of patients take atropine was recorded and amount of atropine given was recorded). Any other complications also have been recorded.

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 have been represented as number and percentage, quantitative continues group well be represented 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.

Data were collected and submitted to statistical analysis. The following statistical tests and parameters were used.

3. Results

There was no significant difference among groups regarding the patient characteristics **(Table 1).**

Groups SBP was significantly lower among the control group from (10 min tell the 20) minutes compared to (O1) or (O2) groups, with no significant difference between group (O1) or(O2) groups and also no significant difference among in three regarding other times.DBP was significantly lower among the control group from (10 min tell 20 minutes) compared to group (O1) or (O2) groups however there was no significant difference between (O1) or (O2) groups was also no significant difference among the three groups regarding other times**(Table 2).**

MBP was significantly lower among the control group from (10 min tell the 20 minutes) compared to (O1) and (O2) groups with no significant difference between (O1) or(O2) groups and finally also no significant difference among the three groups regarding other times**(Table 3, Figure 1).**

HR was significantly lower among the control group from (10 min tell the 40 minutes) compared to (O1) or(O2) with no significant difference between (O1) or(O2) groups and there was no significant difference among three groups regarding other times**(Figure 2).**There was no significant difference among groups regarding the spo2 in different periods**(Figure 3).**

Control group was significantly associated with bradicardia, hypotension and need of ephedrine more than other groups, howver Group (O2) was the lowest followed by Group (O1)**(Table 4).**

Table 1. Demographic and clinical characteristics distribution among studied groups:

			Group O1 N=22	Group O2 N=22	Group C N=22	F/X^2	P
Age (years)			**51.22±6.84**	**50.95±7.79**	**50.54±6.80**	**0.050**	**0.951**
Weight (kg)			**85.13±8.29**	**82.59±6.89**	**82.27±5.20**	**0.224**	**0.800**
Height (cm)			**165.36±10.31**	**164.45±7.78**	**164.90±9.49**	**0.530**	**0.591**
BMI ($Kg/m^{2)}$			**30.13±4.23**	**29.97±3.12**	**30.04±3.60**	**0.369**	**0.693**
Sex	**Male**	**N**	**12**	**14**	**13**	**0.37**	**0.82**
		%	**54.5%**	**63.6%**	**59.1%**		
	Female	**N**	**10**	**8**	**9**		
		%	**45.5%**	**36.4%**	**40.9%**		
Smoking	**No**	**N**	**15**	**16**	**15**	**0.14**	**0.93**
		%	**68.2%**	**72.7%**	**68.2%**		
	Smoker	**N**	**7**	**6**	**7**		
		%	**31.8%**	**27.3%**	**31.8%**		
ASA	**I**	**N**	**11**	**16**	**17**	**4.22**	**0.121**
		%	**50.0%**	**72.7%**	**77.3%**		
	II	**N**	**11**	**6**	**5**		
		%	**50.0%**	**27.3%**	**22.7%**		
Total		**N**	**22**	**22**	**22**		
		%	**100.0%**	**100.0%**	**100.0%**		

Table 2. Systolic and diastolic blood pressure "mmHg" distribution among studied groups:

	Group O1 N=22	Group O2 N=22	Group C N=22	F	P
SBP basal	**135.11±6.32**	**134.88±6.27**	**134.39±7.12**	**2.298**	**0.107**
SBP after 5 min	**128.22±8.49**	**130.22±8.30**	**125.22±7.45**	**2.086**	**0.133**
SBP_10 min	**125.77±9.24**	**126.13±8.41**	**120.22±8.53***	**3.160**	**0.049***
SBP_15 min	**125.31±7.51**	**125.77±7.64**	**112.27±12.02***	**14.950**	**0.00****
SBP_20 min	**117.45±3.91**	**118.36±6.32**	**109.45±13.14***	**6.957**	**0.002***
SBP_25 min	**114.09±8.26**	**116.09±7.0**	**110.45±10.59**	**2.347**	**0.104**
SBP_30 min	**116.36±11.80**	**118.10±7.34**	**114.63±11.95**	**0.526**	**0.593**
SBP_40 min	**118.95±6.56**	**123.18±7.84**	**117.77±9.17**	**2.826**	**0.067**
SBP_50 min	**123.90±4.08**	**124.86±3.62**	**122.50±7.02**	**1.178**	**0.315**
SBP_60 min	**121.54±3.06**	**123.18±3.21**	**121.36±4.16**	**1.782**	**0.177**
SBP_90 min	**125.59±3.66**	**124.59±4.36**	**124.31±3.19**	**0.695**	**0.503**
SBP post OP min	**124.13±5.71**	**123.04±4.61**	**122.09±3.85**	**1.004**	**0.372**

	Group O1 N=22	Group O2 N=22	Group C N=22	F	P
DBP basal	**83.86±5.33**	**83.18±5.88**	**81.63±5.33**	**0.940**	**0.396**
DBP after 5 min	**81.95±6.11**	**81.0±3.51**	**80.0±4.60**	**0.888**	**0.417**
DBP_10 min	**82.13±8.79**	**83.04±8.47**	**75.22±6.02***	**6.508**	**0.003***
DBP_15 min	**79.77±5.73**	**81.68±7.59**	**67.50±11.38***	**17.761**	**0.00****
DBP_20 min	**78.54±3.93**	**79.36±6.32**	**69.63±12.03***	**9.593**	**0.00****
DBP_25 min	**76.09±8.26**	**77.86±6.78**	**72.45±10.59**	**2.216**	**0.117**
DBP_30 min	**77.77±10.74**	**78.40±6.80**	**76.81±11.18**	**0.147**	**0.863**
DBP_40 min	**78.04±6.58**	**82.18±7.84**	**76.77±9.17**	**2.791**	**0.069**
DBP_50 min	**82.90±4.08**	**83.22±3.90**	**81.09±6.83**	**1.116**	**0.334**
DBP_60 min	**79.54±3.06**	**79.77±2.61**	**79.36±4.16**	**0.082**	**0.921**
DBP_90 min	**82.59±3.66**	**81.13±3.62**	**81.31±3.19**	**1.127**	**0.331**
DBP post OP min	**80.13±5.71**	**79.04±4.61**	**78.09±3.85**	**1.004**	**0.372**

Table 3. Mean Blood Pressure "mmHg" among studied groups

	Group O1 N=22	Group O2 N=22	Group C N=22	F	P
MBP basal	**128.41±6.47**	**127.46±7.53**	**124.22±7.41**	**2.074**	**0.134**
MBP after 5 min	**124.26±7.72**	**123.99±5.53**	**121.34±6.47**	**1.305**	**0.278**
MBP_10 min	**123.64±11.78**	**124.64±11.26**	**114.90±8.51***	**5.597**	**0.006***
MBP_15 min	**121.12±7.82**	**123.18±10.11**	**104.55±15.32***	**17.294**	**0.00****
MBP_20 min	**117.30±5.22**	**118.42±8.40**	**105.75±16.33***	**8.895**	**0.00****

MBP_25 min	113.74±10.98	116.09±9.02	108.90±14.08	2.216	0.117
MBP_30 min	116.17±14.56	117.31±8.84	114.64±15.09	0.229	0.796
MBP_40 min	117.30±8.75	122.83±10.43	115.63±12.20	2.800	0.068
MBP_50 min	123.79±5.42	124.43±4.80	121.51±9.08	1.150	0.323
MBP_60 min	124.66±5.42	125.30±4.80	122.38±9.08	1.150	0.323
MBP_90 min	124.03±4.86	122.25±5.01	122.34±4.25	0.996	0.375
MBP_100 min	123.58±4.86	121.80±5.01	121.89±4.25	0.996	0.375

Table 4. Bradycardia, Hypotension and need of ephedrine distribution among studied groups:

			Group			Total	X^2	P
			Group O1	Group O2	Group C			
Ephedrine	No	N	19	20	13	52		
		%	86.4%	90.9%	59.1%	78.8%		
	Yes	N	3	2	9	14	7.79	0.02*
		%	13.6%	9.1%	40.9%	21.2%		
Bradicardia	No	N	18	22	14	54		
		%	81.8%	100.0%	63.3%	91.9%		
	Yes	N	4	0	8	12	8.12	0.018*
		%	18.2%	0.0%	36.7%	18.1%		
Hypotension	No	N	19	20	13	52		
		%	86.4%	90.9%	59.1%	78.8%		
	Yes	N	3	2	9	14	7.79	0.02*
		%	13.6%	9.1%	40.9%	21.2%		
Total		N	22	22	22	66		
		%	100.0%	100.0%	100.0%	100.0%		

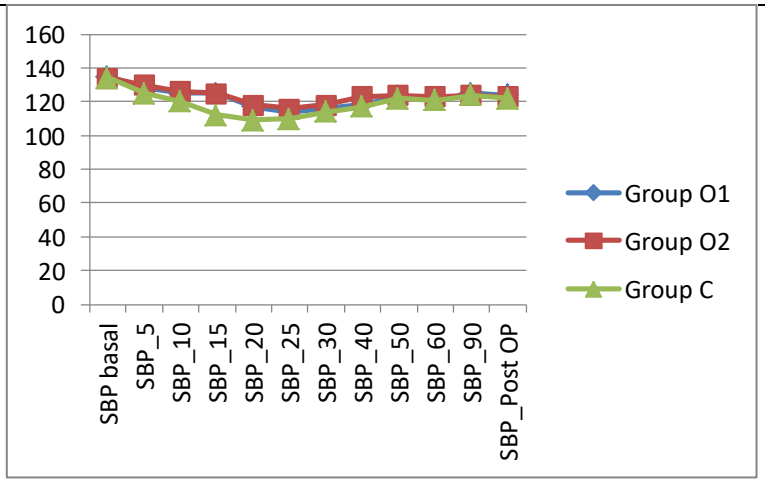

Figure 1. Mean Blood Pressure "mmHg" among studied groups.

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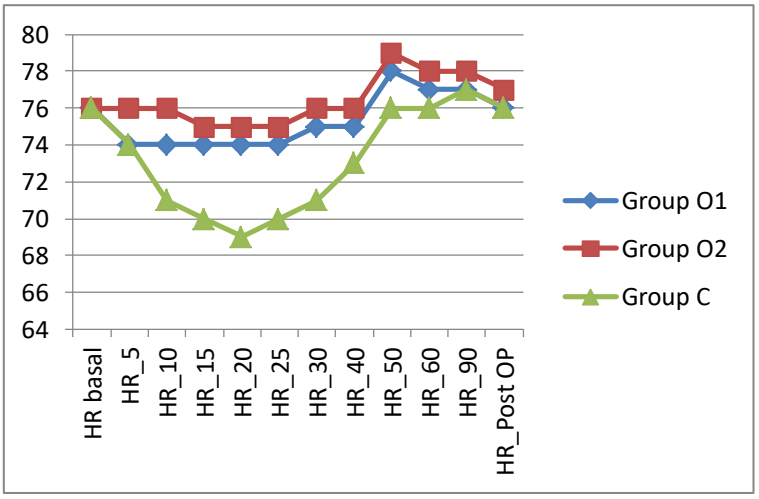

Figure 2: Heart rate "beat/min" distribution among studied groups.

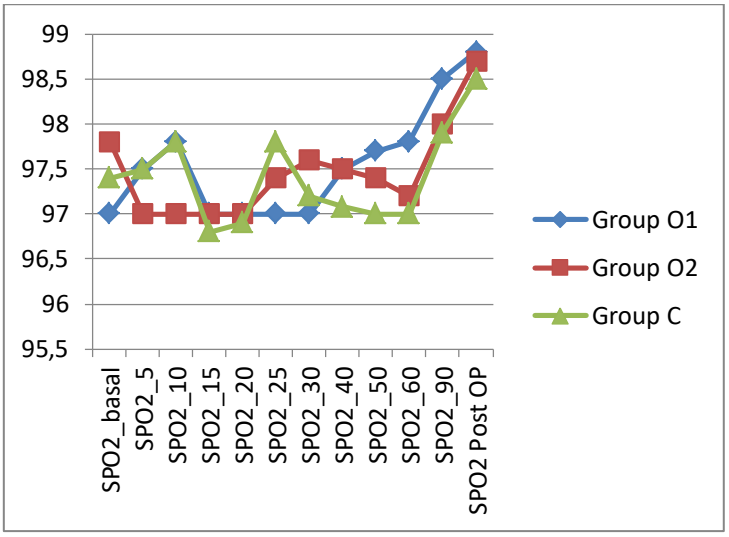

Figure 3: SPO2 (%) distribution among studied groups.

4. Discussion:

Measuresto 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, administration of sympathomimetic, administration of atropine, and patient positioning which facilitating venous return **(7).**

Volume preload may cause fluid overload and cardiovascular collapse in labile patients, prophylactic use of vasopressors has no role in preventing hypotension in turn which may cause HTN and increase cardiac workload **(8).**

Two studies done by **(4)** and **(9)** to evaluate the effect of ondansetron on the hemodynamics following subarachnoid block in patients undergoing elective cesarean section, found in their studies made of, patients divided into two groups: group O receiveing intravenous ondansetron 4 mg and group S receiving normal saline, Results showed that the in decrease in mean blood pressure was significantly less in Group O than Group S, thus patients in Group O required significantly less vasopressors, however, there was no decrease in HR in both groups, which is in agreement with the findings of the our present study.

A similar study was done by **(10)** as they tested the effect of Ondansetron on the hypotension following, spinal anesthesia in pregnant candidate women for elective cesarean section, They concluded that the use of ondansetron leads to a less reduction in MBP which goes side by side with the results of the present study.

Our primary aim was to assess systolic blood pressure (SBP), diastolic blood pressure (DBP), the mean blood pressure (MBP), the heart rate (HR), oxygen saturation percentage (PO_2) and intraoperative need for ephedrin in ondansetron4mg group (group O1),ondasteron 8mg group (O**2**) and control group (group C) in different time intervals, As well as, any complications during or after surgery .

Our study showed that, there was no significant difference between the groups O1 (n=22) group O2 (n22) and group C (n=22) as regards to the demographic data including mean age (50years), BMI and parity in all groups.

These results are in agreement with that of **Trabelsi et al., (9)** who compared ondansetron 5 mg (*n*=40) with placebo (*n*=40), **Owczuk et al., (11)** who compared ondansetron 8mg in their patients (*n*=35) with placebo (*n*=36), and **Sahoo et al., (4)** who compared ondansetron 4 mg (*n*=24) with placebo (*n*=24).

Regarding systolic blood pressure (SBP)The current study revealed that.SBP was significantly lower among control group from 10 min tell the 20 minutes compared to group (O1) or(O2) groups, with no significant difference between (O1) &(O2) groups and also no significant difference among the three groups regarding rest of the recoreded, other times, This finally finding in agreement with the results obtained by **Sahoo et al., (4)** who stated that, 4 mg ondansetron given 5 minutes before spinal block for caesarean section attenuated the decrease in systolic blood pressure, Other investigators reported that ondansetron in obstetric patients undergoing caesarean section under spinal block that SBP they were arrangement with our work.

While, **Ortiz-Gommez et al., (12)** in their study includeing three doses of ondansetron (2, 4, and 8 mg versus placebo) with 32 patient in each group, found that, there were no significant differences in the number of patients with decrease in SBP in the placebo (43.8%) and ondansetron 2 mg (53.1%), 4 mg (56.3%) and 8 mg (53.1%) groups (P = 0.77), nor in the other time recorded points with systolic hypotension (7.3% in the placebo group and 11.1%, 15.7% and 12.6% in the ondansetron 2, 4 and 8 mg groups, respectively, P = 0.32). That deference may be due to our methodology difference from that of the Ortiz-Gommez et al., in the administration of intrathecal fentanyl 20 µg.

In contrast to our results (**13)** 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. However, one patient in each group required 10 mg of ephedrine to treat hypotension.

our current study revealed that, diastolic blood pressure (DBP) DBP was significantly lower

among control group from 10 min tell 20 minutes compared with other than other groups with no significant difference between (O1) & (O2) groups and also no significant difference among the three groups regarding other periods , These finding are in agreement with that results obtained by **Sahoo et al., (4)**and **Abbas et al., (14)** were they stated that, 4 mg ondansetron given 5 minutes before spinal block for cesarean section attenuated the decrease in diastolic blood pressure, Also it is in agreement with **(9)** who used in stead 5 mg ondansetron in their study.

Our finding are in agreement with the results obtained by **Sahoo et al., (4)** who used 4 mg ondansetron given 5 minutes before spinal block for caesarean section and **(9)** who used 5 mg ondansetron, they found that SBP, DBP, and the MBP were higher in patients who were given ondansetron compared to their control group.

In contrast to our result , **Tatikonda et al., (15)** In their comparative randomized controlled double-blinded study done on patients who were posted for elective orthopedic, gynecological and general surgical procedures under spinal anesthesia, found that there was no statistically significant difference in the systolic blood pressure, diastolic blood pressure and MAP. Although there was a significant difference in the vasopressor usage in their study.

HR was significantly lower among our control group from 10 min tell the 40 minutes compared to O1 and O2 with no significant difference between O1 or O2 groups with also no significant difference among the three groups regarding other times.

Regarding the heart rate (HR), the present study revealed that there was no significant difference between the three studied groups except at time 30 and 45 min after the procedure where the HR was significantly lower in group C compared to group O.which is Consistent with the resultsof Owczuk **et al., (11)** observed that intravenously injecting of 8 mg ondansetron 5 min before spinal anesthesia can curb the reduction of SBP without affecting heart rate. **Abbas et al., (14)** found on other hand that heart rate was significantly lower in group II placebo group in comparison with other group I who received ondansetron 4 mg The explanation for this finding may be due to spinal anesthesia induces sympathetic block that leads to vasodilatation, pooling of venous blood, decrease of venous return, and low ventricular volume state, which leads to stimulation of chemoreceptors and mechanoreceptors in the Cardiac wall with abrupt withdrawal of sympathetic supply, and unopposed vagal tone to the heart, which leads to Bradycardia and hypotension , **is a** reflex called the Bezold-Jarisch reflex, and it is triggered by serotonin (5-HT3) released from thrombocytes under low ventricular volume conditions that stimulate cardiac chemoreceptors and increase the vagal tone **(16).**

There was no significant difference among groups regarding the spo2 changes in our presented work. between the three study groups with lower values in group O1 andO2and groupc, while there was no significant difference among the two studied groups regarding the intraoperative bradycardia. Our results are in agreement with that of **(17)** who conducted in their study on 100 parturient scheduled for elective cesarean delivery under spinal anesthesia and found that the intravenous 4 mg ondansetron significantly decreases hypotension, HR fluctuation, and the dose of vasopressor used.

Our present outcomes are in concur with **(18)** who revealed that, hypotension after spinal block during caesarean section is common, and the main treatment and prevention relies on IV fluids infusion and vasopressors administration such as phenylephrine, ephedrine, mephentermine.

Furthermore, **(19)** found that ondansetron reduced hypotension in obstetric patients undergoing caesarean section, but the preventive effect was not superior to vasoconstrictors.

Also **(4)** reported, significant bradycardia and hypotension in their work which may compromise

the health of the mother and the fetus. It produces vasodilation, hypotension, and bradycardia by sympathetic blockade and BJR via stimulation of 5-HT3 receptors in vagal nerve endings. However, **(20)**who stated that, in some cases of their work tachycardia may occur, as a compensatory response to a rapid reduction in systemic vascular resistance or due to severe local anesthetic systemic toxicity and associated with ST segment changes.

5. Conclusion

From the previous results, we demonstrated that in patient undergoing orthopedic surgeries under spinal anesthesia, prophylactic intravenous administration of 4mg ondansetron or 8mg ondansetron 5min before induction of spinal anesthesia to well significantly reduce the severity of spinal-induced hypotension and bradycardia.

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