Research Article

Hypotension prevention in spinal anesthesia used in elective cesarean deliveries ondansetron versus ephedrine which is more effective and safe ?

Mohamed S. Fahim
Department of Anesthesia, Intensive Care and Pain Management,
Faculty of Medicine; Ain Shams University, Cairo, Egypt

Abstract
Background: Spinal anesthesia is considered the main protocol of choice in obstetric anesthesia due to rapid onset of action ,better pain control profile post operatively. The underlying physiological issue that causes hypotension is the sympathetic blockade that causes reduced vascular resistance besides the aortocaval compression that causes the supine hypotensive syndrome. The comparison and contrast between ephedrine and ondansetron to elucidate the best agent in management of hypotensive spinal anesthesia issues in obstetric practice is considered of crucial importance. **Aim:** Comparison between ephedrine and ondansetron for maternal hypotension prevention after spinal anesthesia administration for cases undergoing elective cesarean delivery. **Methodology:** A randomized double blinded clinical; research trial conducted from January 2015 till February 2017 at Mohamed Saleh Bashrahil Hospital in Holy Makka, Saudi Arabia in which 90 cases were recruited and categorized in three research groups that were equally divided involving the ephedrine research group (n=30), ondansetron research group (n=30),placebo research group (n=30). **Results:** The number of cases requiring intraoperative vasoconstrictors, doses of ephedrine and norepinephrine administered and post-spinal nausea and vomiting and postoperative satisfaction between the research groups (ephedrine, ondansetron ,placebo research groups)showing statistical significance as regards the requirement of ephedrine ,norepinephrine, any vasoconstrictors rescue anti emetics being highest among the placebo research group (p values =0.017, 0.045, 0.035, 0.042 consecutively)whereas there was no statistical significant difference concerning ephedrine per patient (mg), Norepinephrine per patient (µg), Nausea/vomiting score, satisfaction score (p values=0.782, 0.463, 0.236, 0.524 consecutively). **Conclusions:** Prophylactic ephedrine or ondansetron administered immediately after spinal mode of anesthesia for elective cesarean section doesn't differ significantly as regards maternal blood pressure readings in comparison to placebo.
Key words: Elective cesarean section –Ephedrine-spinal anesthesia-ondansetron-hypotension

Introduction
Obstetric anesthesia is one of the cornerstone issues of safety in cesarean section deliveries .The anesthesiologist is required to monitor and maintain the vitals of the case in a manner to allow the patient to be compensated to the physiological challenges required during delivery.[1,2]

Spinal hypotensive impact of anesthesia is a main concern for both the obstetrician and anesthesiologists as it could mask the bleeding issues intraoperatively and with regain of post-operative normal blood pressure the patient could have the hazardous impacts of bleeding .The anesthetic art of managing obstetric cases having spinal anesthesia is to counteract the hypotensive effect in a manner that maintains the patient safety.[3,4]

Spinal anesthesia is considered the main protocol of choice in obstetric anesthesia due to rapid onset of action, better pain control profile post operatively and easily trainable technique that has a high level of safety and reliability when properly practiced by well-trained anesth-esiologists.[5,6]

On the other hand spinal anesthesia has various draw backs such as maternal hypotension that is considered unfavorable in some clinical scenarios such as antepartum hemorrhage

requiring emergency deliveries in addition to nausea ,vomiting however those issues are manageable when proper agents are used.[7,8]

The underlying physiological issue that causes hypotension is the sympathetic blockade that causes reduced vascular resistance besides the aortocaval compression that causes the supine hypotensive syndrome.[9,10]

Ephedrine among other agents are commonly used to raise the systemic blood pressure to counteract the hypotensive side effects that are expected from this mode of anesthesia .among the agents of growing research interest that are investigated is the ondansetron, a serotonin (5-HT3) receptor antagonist that is believed to counteract the hypotensive spinal anesthesia issues by inhibition of the Bezold-Jarisch reflex caused by triggering the vagus nerve causing bradycardia and hypotension those effects are believed to be mediated by chemoreceptors sensitive to serotonin those receptors are believed to be located within the cardiac muscle.[11,12]

The comparison and contrast between ephedrine and ondansetron to elucidate the best agent in management of hypotensive spinal anesthesia issues in obstetric practice is considered of crucial importance to enhance the maternal and fetal safety levels that would upgrade the health service offered for those cases.[13,14]

Aim

Comparison between ephedrine and ondansetron for maternal hypotension prevention after spinal anesthesia administration for cases undergoing elective cesarean delivery.

Methodology

A randomized double blinded clinical; research trial conducted from January 2015 till February 2017, after approval of local ethical committee on the current research study and written informed consent was taken from all participant, conducted at Mohamed Saleh Bashrahil Hospital in Holy Makka, Saudi Arabia in which 90 cases were recruited and categorized in three research groups that were equally divided involving the ephedrine research group (n=30), ondansetron research group (n=30), placebo research group (n=30) Inclusive research criteria was as follows in which all cases recruited had an age above 18 years old age, ASA classification I or II; full term gestational age, singleton; elective cesarean delivery using spinal mode of anesthesia; exclusive research criteria were as follows clinical of DMs, hypertension, body mass index above 40 kg/m^2, complicated gestation (e.g antepartum hemorrhage), allergy to investigated agents drugs, and/or any contraindication to spinal anesthesia .

Using a computer-generated program the cases were randomized into three equal research groups as follows research Group E w have been administered intravenous ephedrine 10 mg diluted in 10mL 0.9% saline; research Group O ondansetron 8 mg diluted in 10 mL0.9% saline; and research Group P as a control research group that were administered 0.9% saline 10 mL as a placebo.

Cases, anesthesiologists have been blinded to the research group distribution. Cases recruited for the research have been administered oral ranitidine 150 mg as premedication with assessment of non-invasive systolic blood pressure, diastolic blood pressure and heart rate. Measurements at the supine position before entering the operative theater besides of lactated Ringer's solution 500 mL intravenous infusion. Vitals monitoring using pulse oximetry, noninvasive blood pressure measuring tools and electrocardiogram have been implemented. Spinal anesthesia have been administered using the lateral position at L2–3 or L3–4 level using a 25-gauge Quinketype (polymed spinal needle, Brusssels, Belgium), or a 26- or 27-gauge spinal needle as a free-flowing cerebrospinal fluid have been Noticed, 0.5% hyperbaric bupivacaine 11mg in conjunction to fentanyl 10μg have been injected intrathecally.

1ry research outcome

Recording every minute till delivery of systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate. The sensory block level was assessed using cold sensation 5 min after administering spinal anesthesia. Hypotension was defined as a decrease in SBP >20% of baseline, or SBP <90 mmHg. If hypotension developed, ephedrine 5–10 mg or norepinephrine 4–8 μg were given intravenously; this is normal practice at our institution, but the drug and dose used were at

the discretion of the attending anesthesiologist. Heart rate <50 beats/min was treated with intravenous atropine 0.6 mg.

2ry research outcome

a- Determining nausea severity and/or vomiting before delivery have been graded in accordance to a fourpoint grading score : 0, no symptoms; 1, nausea; 2, vomiting 1–2 times; 3, vomiting >2 times.

b- Recording the time of delivery, Apgar scoring at 1and 5 minutes, blood loss estimated volume and total intravenous fluid volume administered. Cases that required general anesthesia or another agent that could influence blood pressure indices before delivery have been excluded from the research study. Metoclopramide 10mg have been given intravenously to cases that complained of nausea or vomiting within the first 6 hours, postoperatively. Subsequently, ondansetron 8 mg or metoclopramide 10mg intravenously were administered every 8h as needed. Nausea and vomiting scoring, dosage of antiemetic agents and cases satisfaction have been observed and recorded by an anesthesiologist specialized nurse that attended the patient 24 hours after the operation.

Investigated agents, have been prepared and properly sealed using an envelope by an anesthesiologist assistant not involved in the research study, and handled to an anestsiologist unaware of the patient's randomization allocation. cases that required general mode of anesthesia or another agent that could affect the blood pressure readings before delivery have been excluded from the research.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science version 23 (IBM SPSS Ver. 23). Qualitative data were presented as numbers and percentages and compared between groups using Chi-square test while quantitative data were presented as means and standard deviations and compared between groups using One Way Analysis of Variance (ANOVA). The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the level of < 0.05.

Results

The clinical and demographic features of the three research groups (ephedrine, ondansetron and placebo research groups) in which there was no statistical significant difference as regards the age (years) weight, height (cm), BMI (Kg/m2),ASA status type I, II, SBP (mmHg), DBP (mmHg), HR (beats/min) (p values 0.370, 0.717, 0.313, 0.769, 0.811, 0.779, 0.779, 0.717, 0.831consecutively) as shown in table 1

The comparative statistical analysis of the three research groups (ephedrine, ondansetron, placebo research groups) shows that there was no statistical significant difference as regards the skin incision (horizontal, midline) sensory level (T1-4, T5-6), skin incision delivery time interval (min), uterine incision delivery time interval (min) operative time (min), Apgar score (1,5 min), nausea /vomiting pre delivery (0,1,2), estimated blood loss volume (ml), total intravenous fluid (ml), maternal hypotensive attacks (p values 0.690, 0.486, 0.931, 0.651, 0.941, 0.261, 0.678, 0.945, 0.931, 0.872, 0.557 consecutively) as displayed in table 2.

Finally the number of cases that required intraoperative vasoconstrictors, dosages of ephedrine and norepinephrine administered and post-spinal nausea and vomiting and post-operative satisfaction between the research groups (ephedrine, ondansetron, placebo research groups) revealed statistical significance with regard to the requirement of ephedrine ,norepinephrine, any vasoconstrictors rescue anti emetics being highest amongst the placebo research group (p values =0.017, 0.045, 0.035, 0.042 consecutively)on the other hand there was no statistical significant difference regarding ephedrine per patient (mg), Norepinephrine per patient (µg), Nausea/ vomiting score, satisfaction score (p values =0.782, 0.463, 0.236, 0.524 consecutively) as shown in table 3 and displayed in figure 1.

Table (1): Comparison between the three studied groups regarding clinical and demographic characteristics

	Group E No. = 30	**Group O No. = 30**	**Group P No. = 30**	**Test value**	**P-value**	**Sig.**
Age (years)	29.9 ± 5.7	31.8 ± 5.5	30.4 ± 4.9	1.006*	0.370	**NS**
Weight (kg)	69.5 ± 8.7	67.6 ± 10.8	68.4 ± 7.3	0.333*	0.717	NS
Height (m)	163.8 ± 5.4	162.4 ± 6.3	161.4 ± 6.5	1.177*	0.313	NS
BMI (kg/m^2)	25.9 ± 3.3	26.6 ± 4.2	26.3 ± 3.7	0.263*	0.769	NS
ASA status I II	 24 (80.0%) 6 (20.0%)	 23 (76.7%) 7 (23.3%)	 25 (83.3%) 5 (16.6%)	0.417•	0.811	NS
SBP (mmHg)	117.6 ± 10.5	119.3 ± 9.64	118.1 ± 8.4	0.251*	0.779	NS
DBP (mmHg)	73.8 ± 5.3	72.6 ±5.4	73.2 ± 6.3	0.334*	0.717	NS
HR (beats/min)	87.6 ± 11.4	85.9 ± 12.3	86.4 ± 9.4	0.186*	0.831	NS

*: One Way ANOVA test; •: Chi-square test

Table (2): Comparison between the three studied groups regardingintra-operative data

	Group E No. = 30	**Group O No. = 30**	**Group P No. = 30**	**Test value**	**P-value**	**Sig.**
Skin incision Horizontal Midline	 27 (90.0%) 3 (10.0%)	 28 (93.3%) 2 (6.7%)	 26 (86.7%) 4 (13.3%)	0.741•	0.690	NS
Sensory level T1-4 T5-6	 23 (76.7%) 7 (23.3%)	 26 (86.7%) 4 (13.3%)	 26 (86.7%) 4 (13.3%)	1.440•	0.486	NS
Skin incision delivery (min)	8.5 ± 3.7	8.7 ± 2.9	8.8 ± 2.7	0.071*	0.931	NS
Uterine incision delivery (min)	1.9 ± 0.9	2.0 ± 0.8	1.8 ± 0.8	0.431*	0.651	NS
Operative time (min)	50.6 ± 10.2	51.3 ± 11.8	50.4 ± 9.3	0.061*	0.941	NS
Apgar score 1min 5min	 8.9 ± 0.4 9.8 ± 0.5	 8.7 ± 0.5 9.9 ± 0.6	 8.8 ± 0.5 9.8 ± 0.4	 1.364* 0.390*	 0.261 0.678	 NS NS
Nausea/vomiting score pre delivery 0 1 2	 25 (83.3%) 4 (13.3%) 1 (3.3%)	 27 (90.0%) 2 (6.7%) 1 (3.3%)	 26 (86.7%) 3 (10.0%) 1 (3.3%)	0.744•	0.945	NS
Estimated blood loss (ml)	347.4± 97.8	352.6±110.0	357.7±107.3	0.072*	0.931	NS
Total intravenous fluid (ml)	1197 ± 288	1215 ± 317	1242 ± 390	0.138*	0.872	NS
Maternal hypotension≠	15 (50.0%)	16 (53.3%)	19 (63.3%)	1.170•	0.557	NS

≠ Decrease in SBP > 20% of baseline or SBP < 90 mmHg

*: One Way ANOVA test; •: Chi-square test

Table (3): Number of patients requiring intraoperative vasoconstrictors, doses of ephedrine and norepinephrine administered and post-spinal nausea and vomiting and postoperative satisfaction between the studied groups

	Group E No. = 30	**Group O No. = 30**	**Group P No. = 30**	**Test value**	**P-value**	**Sig.**
Ephedrine	19 (63.3%)	24 (80.0%)	28 (93.3%)	8.139•	0.017	S
Norepinephrine	10 (33.3%)	5 (16.7%)	14 (46.7%)	6.207•	0.045	S
Any vasoconstrictors	20 (66.7%)	22 (73.3%)	28 (93.3%)	6.686•	0.035	S
Ephedrine per patient (mg)	19.5 ± 8.3	20.3 ± 9.5	18.7 ± 8.6	0.247*	0.782	NS
Norepinephrine per patient (µg)	15.6 ± 9.6	13.6 ± 7.6	12.9 ± 8.8	0.777*	0.463	NS
Nausea/vomiting score				8.021•	0.236	NS
0	19 (63.3%)	27 (90.0%)	22 (73.3%)			
1	2 (6.7%)	1 (3.3%)	3 (10.0%)			
2	4 (13.3%)	1 (3.3%)	1 (3.3%)			
3	5 (16.7%)	1 (3.3%)	4 (13.3%)			
Rescue antiemetic	6 (20.0%)	0 (0.0%)	4 (13.3%)	6.300•	0.042	S
Satisfaction score	95.6 ± 2.3	95.4 ± 2.2	96.1 ± 2.8	0.651*	0.524	NS

*: One Way ANOVA test; •: Chi-square test

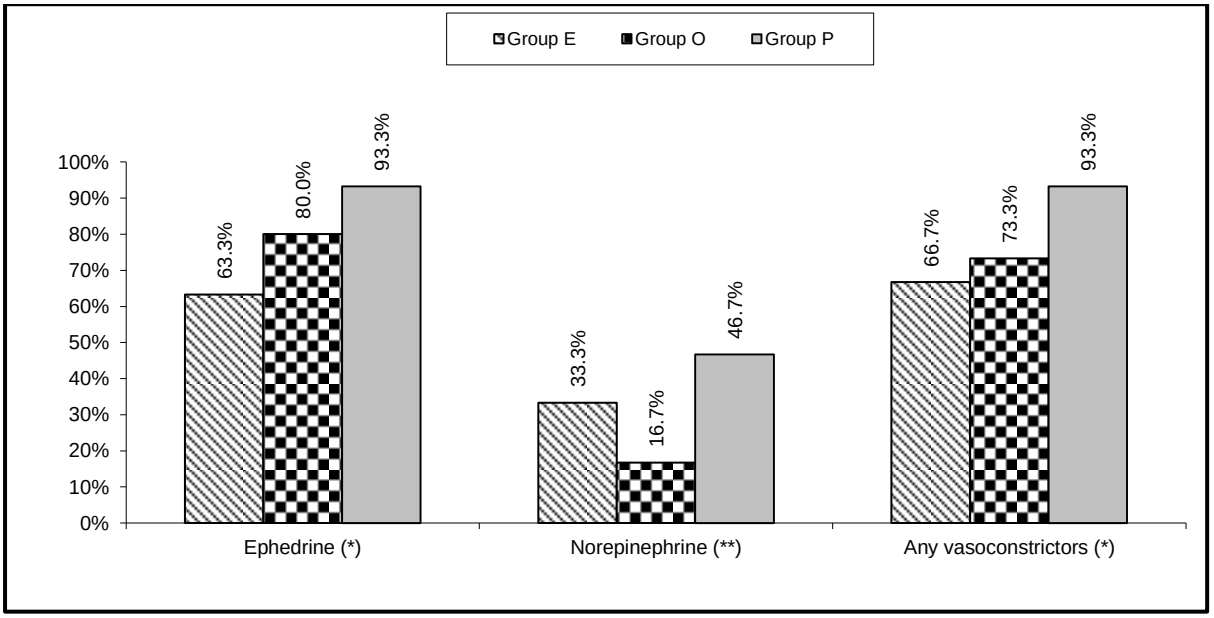

Figure (1): Number of patients requiring intra-operative vasoconstrictors; (*) Significant between group E and P; (**) Significant between group O and P.

Discussion

Spinal anesthesia practice is one of the most favorable modes of anesthesia in obstetrics due to simplicity and reduced maternal and fetal side effects in comparison to general anesthesia .However one of the draw backs is the maternal hypotensive issues that occur requiring the administration of vasoconstricting agents that maintain the hemodynamic stability required during delivery.[15,16]

A prior similar randomized controlled research trial, have revealed and displayed among its research findings that there was no statistical significant difference as regards the occurrence of hypotension, nausea, vomiting or Apgar

scoring level among three investigated research groups involving ephedrine, ondansetron and placebo research groups however the research team of investigators have observed a greater percentage of cases within the placebo research group that needed vasoconstrictor agents for management of hypotensive issues more than cases among the ephedrine research group. those findings show great similarity and harmony to the current research study findings denoting the effectiveness of ephedrine in anaging spinal anesthesia hypotensive issues.[17]
A prior research team investigated the impact of intravenous ondansetron agent on hypotension and bradycardia triggered by spinal mode of anesthesia the study recruited 140 study subjects, 70 cases in research group A have been administered 2mL of i.v. ondansetron 4mg and 70 cases within research Group B have been administered 2 mL of i.v. normal saline evaluation of blood pressure and heart rate measurements were obtained every 3 min for 30 min after conducting spinal anesthesia the research team have noticed the following results in which there was no statistically significant difference in systolic blood pressure, diastolic blood pressure, and mean arterial pressure. 19(27%) patients in research Group A and 33(47.1%) in research Group B needed ephedrine agent *P* value = 0.029. 12(17.1%) in research Group B whereas no cases among research Group A had shivering *P* value = 0.0001. The research team concluded that prophylactic usage of ondansetron before spinal mode of anesthesia considerably decreases the need for administering ephedrine agent and shivering, those research findings show great harmony with the current research findings denoting the effectiveness of ondansetron as a vasocon-strictor agent reducing the hypotensive attacks due to spinal anesthesia.[1,3,5]

Another prior research group of investigators have compared and contrasted between three variable dosages of ephedrine administered for prophylaxis in the form of a single bolus, revealing among their study findings that ephedrine dosages 15 mg and 20 mg are more efficient in comparison to the 10 mg bolus administered for cesarean section . another prior research systematic review have shown that ephedrine prohibited hypotensive attacks during administration of spinal mode anesthesia used for cesarean section on the other hand Apgar scoring and pH of the umbilical artery wasn't statistically significantly different from the control research group those findings could be justified by the fact that the cases were managed in the placebo research groups by vasoconstrictor agents when hypotensive attacks have occurred similar to the approach implemented in the current research study. Another research meta-analysis interestingly have revealed that ephedrine administration in a prophylactic manner in a dosage of 14 mg, the number needed to treat and number needed to harm have been similar denoting that higher doses of ephedrine could lead to maternal hypertension and tachycardia.[9,12,15]

On the other hand at cellular and molecular levels ephedrine agent is capable to cross the placental barrier consequently causing fetal tachycardia and acidosis that denotes that proper dosge is crucial in managing the cases properly in order not to cause any potential harm and that doses should be accustomed according to the clinical case scienario. Even though ephedrine is efficient as an agent that manages maternal hypotension other research studies priorly perfomed have revealed that phenylephrine is more privelged as regards its impact on fetal acid-base physiological balance.[2,7,10]

Prior research groups of investigators have revealed and displayed among their observations that a 4 mg dosage of ondansetron in a prophylactic manner diminishes spinal anesthesia hypotensive impact during obstetric anesthesia for cesarean sections since it blocks serotonin-mediated Bezold-Jarisch reflex, That consequently enhancing venous return and decreasing the variations in blood pressure.[8]

Prior research teams of investigators have shown that ondansetron 4 mg administered before conducting spinal anesthesia reduces hypotensive attacks and decreases the requirement for administrating ephedrine agent those research findings show great harmony to the current study findings denoting the beneficial effective action of ondansetron that could be a useful alternative to ephedrine besides it was observed that ondansetron has a favorable impact on fetal umbilical acid-base physiological balance .[9,10,17]

On the other hand, prophylactic ephedrine or ondansetron did not appear to influence the Percentage of cases that develop hypotension after conducting a spinal mode of anesthesia This could be justified by the therapeutic impact of rescue vasoconstrictors administered to sustain maternal normal blood pressure and placental vascular flow before delivery**.** [10,14]

Conclusions and recommendations

Prophylactic ephedrine or ondansetron administered immediately after spinal mode of anesthesia for elective cesarean section doesn't differ significantly as regards maternal blood pressure readings in comparison to placebo, however to verify the study results larger sample size is requird and consideration to perform future studies in a multicentric fashion.

References

1. Sahoo T, SenDasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotensionwith ondansetron in parturients undergoing caesarean section: a double-blind randomised,placebo-controlled study. Int J Obstet Anesth 2012; 21: 24-8.
2. Trabelsi W, Romdhani C, Elaskri H, et al., Effect of ondansetron on the occurrence ofhypotension and on neonatal parameters during spinal anesthesia for elective caesareansection: a prospective, randomized, controlled, double-blind study. Anesthesiol Res Pract2015; 2015: 158061.
3. Wang Q, Zhuo L, Shen MK, Yu YY, Yu JJ, Wang M. Ondansetron preloading withcrystalloid infusion reduces maternal hypotension during cesarean delivery. Am J Perinatol2014; 31: 913-22.
4. Wang M, Zhuo L, Wang Q, et al., Efficacy of prophylactic intravenous ondansetron on theprevention of hypotension during cesarean delivery: a dose-dependent study. Int J Clin ExpMed 2014; 7: 5210-6.
5. Gao L, Zheng G, Han J, Wang Y, Zheng J. Effects of prophylactic ondansetron on spinalanesthesia-induced hypotension: a meta-analysis. Int J Obstet Anesth 2015; 24:335-43.
6. Ortiz-Gomez JR, Palacio-Abizanda FJ, Morillas-Ramirez F, Fornet-Ruiz I, Lorenzo-JimenezA, Bermejo-Albares ML. The effect of intravenous ondansetron on maternal haemodynamicsduring elective caesarean delivery under spinal anesthesia: a double-blind, randomised,placebo-controlled trial. Int J Obstet Anesth. 2014;23: 138-43.
7. Gupta SD, Pal R, Sarkar A, et al., Evaluation of Ondansetron-induced QT interval-prolongation in the prophylaxis of post-operative emesis. J Nat Sci Biol Med 2011; 2: 119-24.
8. Demirhan A, Tekelioglu YU, Akkaya A, et al., Antiemetic effects of dexamethasone and ondansetron combination during cesarean sections under spinal anaesthesia. Afr Health Sci. 2013;13(2):475-482. doi:10.4314/ahs.v13i2.39
9. Chengmao Zhou,ˊYu Zhu, Zeqing Bao, Xianxue Wang,and Qili Liu, Efficacy of ondansetron for spinal anesthesia during cesarean section, Journal of International Medical Research, Published online 2017 Vol. 46(2) 654–662
10. Chooi C, Cox JJ, Lumb RS, et al. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database Syst Rev*. 2017; 8:CD002251.
11. Yousefshahi F, Dahmardeh AR, Khajavi M, Najafi A, Khashayar P, Barkhordari K. Effect of dexamethasone on the frequency of postduralpuncture headache after spinal anesthesia for cesarean section:a double-blind randomized clinical trial. *Acta Neurol Belg*.2012;112:345-350.
12. Jabbari A, Alijanpour E, Mir M, Bani Hashem N, Rabiea SM, RupaniMA. Post spinal puncture headache, an old problem and newconcepts: review of articles about predisposing factors. *Caspian JIntern Med*. 2013;4:595-602.
13. Sachs A, Smiley R. Post-dural puncture headache: the worstcommon complication in obstetric anesthesia. *Semin Perinatol*. 2014;38:386-394.
14. Fattahi Z, Hadavi SM, Sahmeddini MA. Effect of ondansetron on post-dural puncture headache (PDPH) in parturients undergoing cesarean section: a double-blind randomized placebo-controlled study. *J Anesth*. 2015; 29:702-707.
15. Heesen M, Klimek M, Hoeks SE, Rossaint R. Prevention of spinal anesthesia-induced hypotension during cesarean delivery by 5-hydroxytryptamine- 3 receptor antagonists:

a systematic review and meta-analysis and meta-regression. *Obstetric Anesthesia Digest.* 2017; 37:103-104.

16. Zheng Y, Yu T, Tang Y, et al., Efficacy and safety of 5-hydroxytryptamine 3 receptor antagonists in irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2017;12:e0172846.
17. Memari F, Jadidi R, Noroozi A, Mohammadbeigi A, Falahati J. Protecting effect of gabapentin for nausea and vomiting in thesurgery of cesarean after spinal anesthesia. *Anesth Essays Res*.2015;9:401-404.