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A randomized controlled study investigating incidence of hypotension during caesarean section under subarachnoid block with prophylactic prevention in a tertiary health facility in Nigeria

Okolakpa CO[1], Benjamin E[1], Efegbere HA[2,3,4,5, 6]

1. Department of Anaesthesia, Delta State University ,Abraka, Nigeria
2. Department of Community Medicine, Edo State University Uzairue, Edo State, Nigeria
3. International College of Health Sciences and Technology, Edo State, Nigeria
4. Global Community Health Foundation, Nigeria
5. Cashville Development Foundation, Nigeria
6. International Centre of Inter-professional Team Building, Nigeria

Abstract

Background: Maternal hypotension is a common complication of spinal anaesthesia for caesarean delivery. The objective of this study was to assess a randomized controlled study investigating incidence of hypotension during caesarean section under subarachnoid block with prophylactic prevention in a tertiary health facility in Nigeria. Methods: This was a prospective, randomized double blind clinical study. Patients were randomized into three groups: Ondansetron (O) Ephedrine (E) or Normal Saline (NS). Group O received ondansetron 10 mg in 10ml saline; Group E received ephedrine 10mg in 10ml saline, while group NS received normal saline 10ml. All study drugs were given intravenously 5 minutes before spinal puncture. Data was analyzed using SPSS 25. The significance level was set as p< 0.05. Result : There was no significant difference in the 3 groups in terms of age (p = 0.077), weight (p = 0.677), height (p = 0.949), BMI (p = 0.307), ASA (p = 0.092) and educational status (p = 0.841). The difference in the incidence of hypotension between the 3 groups was highly significant (p = 0.000), but was comparable between ephedrine and ondansetron groups (p > 0.05). The severity of hypotension was more in the control group compared to the ephedrine and ondansetron groups, and the difference was highly significant (20%, 2.2% and 4.4% respectively, p = 0.000). Discussion and Conclusion: The study showed that ephedrine and ondansetron are comparable when used as prophylaxis for prevention of spinal anaesthesia induced hypotension during caesarean delivery.

Keywords: Randomized controlled study, hypotension, subarachnoid block, caesarean section, ondansetron and ephedrine

Introduction

Spinal anaesthesia is a popular technique for caesarean delivery as it is easy to perform and it provides a rapid-onset, dense sensory block. Although, not commonly associated with maternal or foetal risk from toxicity to local anaesthetics[1], common side effects include hypotension and bradycardia, which may be deleterious to both parturient and baby[1]. Maternal hypotension is the most common intraoperative complication following spinal anaesthesia during caesarean delivery, with an incidence as high as 50 – 80%.[2-4]Various prophylactic methods are currently used to prevent or minimize hypotension, including left uterine displacement, crystalloids or colloid preloading, utilization of compression stocking on the lower extremities and vasopressors, however, none of these methods is fully effective.[5-9]

Current studies indicate that 5-HT_3 antagonism may abolish the Bezold-Jarisch reflex (BJR) response to spinal anaesthesia. The bazold-Jarisch reflex occurs in response to noxious stimuli, the afferent unmyelinated c-fibers travel through the vagus to

Corresponding author Efegbere Henry Akpojubaro
Department of Community Medicine, Edo State University Uzairue, Edo State, Nigeria
Email: henryefegbere@gmail.com; efegbere.henry@edouniversity.edu.ng
ORCID Id: https://orcid.org/0000-0002-5599-6584

enhance the baroreceptor reflex mechanisms, inhibit sympathetic output, and inhibit vasomotor tone, leading to peripheral vasodilation. Ondansetron is a selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, and thus may be beneficial for preventing bradycardia and hypotension, the mechanism of action is believed to be inhibition of Bezold-Jarisch Reflex (BJR). This reflex is mediated through vagal afferents, which, when activated cause hypotension and bradycardia.[10-14]

The objective of this study was to compare the efficacy of ondansetron and ephedrine in preventing spinal anaesthesia induced hypotension during caesarean delivery. The justification for this study is that findings from this study will provide insightful information to address gaps regarding this or related topic in Anaesthesia.

Materials and Methods

Study Area: The study was conducted in Delta State University Teaching Hospital, Oghara, Delta State, Nigeria. This is a tertiary healthcare facility in Delta State that provides specialized care for a large proportion of patients in Delta State and other neighbouring states.

Study Design: The study was a prospective, randomized, placebo-controlled, double blind trial that evaluated whether the use of ondansetron will reduce the incidence and severity of hypotension in comparison with ephedrine and the placebo group. Each eligible patient was randomly allocated to either the ondansetron group (O), the ephedrine group (E) or the placebo group (NS) using computer generated random number table (Stat trek's Random Number Generator: Stat Trek.com). These computer-generated codes were placed in sealed envelopes and the envelopes were placed in a box. Each patient picked only one envelope from the box. The number picked by the patient in the sealed envelope randomized the patient into the appropriate group.

Selection Criteria:

Inclusion criteria:

i. Patients aged 18 to 35 years
ii. Elective caesarean section
iii. ASA classification I or II
iv. Term, Singleton Pregnancy

Exclusion Criteria:

i. Patient's refusal
ii. Presence of Diabetes mellitus
iii. Hypertensive disorders
iv. BMI>40
v. Complicated pregnancy such as placenta praevia, preeclampsia
vi. Allergy to the study drugs
vii. Contraindications to spinal anaesthesia
viii. Patients receiving selective serotonin re-uptake inhibitors or migraine medications

Sample size calculation:

- In a previous study by Ayorindeet al[15], the incidence of hypotension in patients who received placebo was 70%.
- It is predicated that prophylactic intravenous ondansetron will reduce the incidence of hypotension to 40%
- Alpha (type 1 error) = 0.05
- Beta (type 2 error) = 20%
- Power (1-beta) = 80%
- Confidence interval = 95%

The following formula was used for the sample size calculation:[16]

$N=r+1/r\ (P_1)\ (1-P_1)\ (Z_\beta + Z_\alpha/2)^2/(P_1-P_2)^2$

Where:

N= required sample size

R= ratio of cases to control (r+1/r=1 + 1/1=2)

$Z_\alpha/2$=desired statistical difference (1.96)

Z_β = desired power (0.84 for power of 80%)

P_1 = estimated prevalence = 70%

P_2 = desired prevalence = 40%

$P_1 - P_2$ = effect size = 70% - 40% = 30% = 0.3

Therefore:

$n = 2 \times 0.7 \times (1 - 0.7) \times (0.84 + 1.96)^2 / (0.3)^2$

$1.4 \times 0.3 \times 7.84 / 0.09\ 3.30 / 0.09 \approx 37.$

Attrition rate was estimated at 20% = 8. The sample size for each arm was 37 + 8 = 45. A total sample size of 135 patients was needed to detect a statistically significant difference among the three groups with 90% power; assuming ondansetron would decrease the incidence of hypotension by 30% following spinal anaesthesia compared to placebo.

Study Protocol

All eligible patients were seen in the ward a day before surgery and the study protocol was explained to them to the best of their understanding. Those who accepted to participate in the study and gave consent were enrolled. Pre-anaesthetic evaluation (history, physical examination and airway assessment using Mallampati scoring system) was carried out, and patients were classified using the ASA physical health status. Patients were fasted for solid food for eight hours (due to delay gastric emptying in parturient) and for clear fluids for 2 hours. On the day of surgery patients were transported to the theatre in supine position with left lateral tilt. In the theatre, anaesthetic machine, suction machine and other ancillary equipment were checked for functionality.

A second anaesthetist who was not involved in the study randomized the patients, using the computer-generated random numbers into group O, E and NS. Group O received ondansetron10 mg, group E received 10 mg ephedrine and group NS received 10 ml of normal saline intravenously. The study drugs were prepared by the pharmacist and presented to the investigator in 10ml solution in 10ml syringes thus blinding the patient to study the drugs. The syringes were presented in coded labels O, E and NS to correspond with patients' group allocation. The study drugs were administered by the second anaesthetist in the absence of the investigator. The principal investigator who monitored the outcome measures was thus blinded to the study drugs.

Resuscitation drugs (atropine, adrenaline and ephedrine) were made available, on arrival in the operating room, a Mindray multi-parameter monitor was attached to the patients, and baseline vital signs (pulse rate, systolic blood pressure, diastolic blood pressure mean arterial blood pressure, and oxygen saturation values) were obtained. An 18-gauge intravenous cannula was inserted into a vein on the dorsum of either hand, or the forearm. After cannulation, Normal saline or Ringer's lactate was commenced for preloading at 15 ml/kg in 30 min and fluid maintenance at 10 ml/kg for the first hour and 5 ml/kg subsequently.

Parturient were premedicated with i.v ranitidine 50 mg and metoclopramide 10 mg in the operating room 30 min prior to induction of spinal anaesthesia. After preloading, the study drugs were administered by second anaesthetist as per the protocol. Five minutes after the administration of the study drugs, spinal anaesthesia was performed under aseptic technique, with patients in the sitting position, at L3L4 interspace. A 25G Whitacre needle was used following confirmation of free flow of cerebrospinal fluid, patients received 2 ml (10 mg) of hyperbaric bupivacaine and 0.5 ml (25 mcg) fentanyl, a dressing was applied over the puncture site. Sensory block was assessed using a gentle pinprick with 25G hypodermic needle to ascertain the maximum level of sensory block. Bromage scale[17] [Bromage score IV: grade I- free movement of legs and feet (0%), II- just able to flex knees with free movement of feet (33%), III- unable to flex knees, but with movement of feet (66%), IV- unable to move legs or feet (100%)][15] was used to evaluate motor block. Surgery commenced when the desired maximum sensory block height of T4 was achieved. The haemodynamic parameters (PR, SBP, DBP, MAP and SPO_2) were obtained and recorded every 2 min until stable and thereafter every 5 minutes until skin closure. Hypotension, defined as a decrease from baseline values of 20% in systolic arterial pressure or SAP < 80 mmHg,[18] was treated with rapid administration of normal saline infusion and ephedrine bolus 3 mg aliquots until restoration of normal values.

Ethical Approval: Approval was sought from the Hospital ethics and Research Committees for the conduct of the study. Confidentiality and anonymity was ensured for all respondents.

Statistical analysis

Data entry and analysis were done using the statistical package for social sciences (SPSS) IBM statistics version 25. Quantitative data were expressed as means ± standard deviation (SD), or median and interquartile range. Descriptive and Inferential Statistics were deployed in this study.

Results

A total of 135 patients participated and completed the study. Table I shows patients' demographic characteristics. There was no significant difference in the 3 groups in terms of age ($p = 0.077$), weight ($p = 0.677$), height ($p = 0.949$), BMI ($p = 0.307$), ASA ($p = 0.092$) and educational status ($p = 0.841$).

Table I: Socio-demographic characteristics of patients. Data presented in mean ± SD; count (percent)

Parameter	Control	Ephedrine	Ondansetron	P-Value
Age (years)	30.97 ± 1.61	29.77 ± 1.61	30.33 ± 2.67	0.077
Weight (kg)	78.83 ± 16.05	81.10 ± 6.20	79.20 ± 6.46	0.677
Height (m)	1.69 ± 0.07	1.69 ± 0.06	1.69 ± 0.07	0.949
BMI (kg/m^2)	28.22 ± 1.24	28.43 ± 1.67	27.82 ± 1.66	0.307
ASA				
I	28 (62.2)	34 (75.6)	37(82.2)	0.092
II	17 (37.8)	11 (24.4)	8 (33.3)	
Educational Status				
1°	11 (24.4)	7 (15.6)	8 (17.8)	0.841
2°	23 (51.1)	25 (55.6)	26 (57.8)	
3°	11 (24.4)	13 (28.9)	11 (24.4)	

P-value < 0.05 is significant

Table I above showed 3 groups were comparable with regard to the pulse rate (p = 0.268), systolic blood pressure (p = 0.207), diastolic blood pressure (p = 0.151), mean arterial pressure (p = 0.113), respiratory rate (p = 0.472), and SpO_2 (p = 0.345).

Table II: Baseline vital signs. Data presented in mean ± SD.

Parameter	Control	Ephedrine	Ondansetron	P-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Pulse Rate (beats/min)	82.36 ± 6.22	82.62 ± 6.12	80.69 ± 5.95	0.268
Systolic BP (mmHg)	126.71 ± 4.47	126.36 ± 4.34	127.98 ± 4.77	0.207
Diastolic BP (mmHg)	76.98 ± 3.11	75.76 ± 3.82	76.30 ± 3.39	0.550
MAP (mmHg)	87.22± 7.59	85.16± 2.37	86.23± 5.10	0.156
RR (cycles/ min)	17.60 ± 1.05	17.27 ± 1.29	17.24 ± 1.09	0.188
Spo2 (%)	99.44 ± 0.50	99.22 ± 0.97	99.38 ± 0.51	0.262

P-value < 0.05 is significant

Table II showed about 64.4% of patients developed hypotension in the control group compared to 24.4% and 35.6% in the ephedrine and ondansetron groups respectively.

Table III: Severity of hypotension among the 3 groups: Data presented in counts (percent)

Parameter	Control	Ephedrine	Ondansetron	Total	P-Value
	Count (%)	**Count (%)**	**Count (%)**		
Severity of hypotension					
Mild	6 (13.3)	4 (11.1)	8 (13.3)	18 (13.3)	0.463
Moderate	9 (20.0)	4 (6.7)	4 (8.9)	17 (12.6)	0.008
Severe	14 (31.1)	3 (6.7)	4 (8.9)	21 (15.6)	0.002

P-value < 0.05 is significant

Table III showed severity of hypotension was more in the control group compared to the ephedrine and ondansetron groups, and the difference was significant (20%, 2.2% and 4.4% respectively, p = 0.002).

Table IV: Intraoperative block characteristics and Apgar score. Data presented in count (percent).

Parameter	Control	Ephedrine	Ondansetron	Total	P-value
Bromage Scale					
III	5 (11.1)	8 (17.8)	6 (13.3)	19 (14.1)	0.651
IV	40 (88.9)	37 (82.2)	39 (86.7)	116 (85.9)	0.763
Sensory Block Height					
T3	1 (2.2)	2 (4.4)	1 (2.2)	4 (3.0)	0.822
T4	33 (73.3)	36 (80.0)	35 (77.8)	104 (77.0)	0.411
T5	11 (24.4)	7 (15.6)	9 (20.0)	27 (20.0)	0.198

P-value < 0.05 is significant

Table IV showed a higher proportion of patients attained Bromage grade IV compared to grade III in all groups (85.9% vs. 14.1%).

Discussion

The findings of the index study showed that ondansetron was superior to placebo but comparable to ephedrine in preventing or reducing the severity of hypotension in patients undergoing Caesarean section under spinal anaesthesia. The average incidence of hypotension in the index study was 41.5%. This is much lower than the population incidence of 70-80%[18-24], however, the study by Edomwonyi and colleagues[11] was retrospective in nature. The difference in the definition of hypotension may have resulted in the difference in outcome measures noticed.[25,26] According to the findings in the index study, not only does ondansetron reduce the incidence of hypotension, it reduces the severity as well, and ultimately the requirement for ephedrine supplementation. This agrees with the reports from the studies done by Trabelesiet al[27], and Rashad et al[28], where they found that prophylactic ondansetron administration significantly decreased both the hypotension and the doses of vasopressors in parturients undergoing elective caesarean section under subarachnoid block compared to placebo. WhileOrtiz Gómez and Terkawi used 8mg of ondansetron in their study; 10mg was used in the index study. The lower doses used by these authors[29,30] compared to the index study may have resulted in the different outcome observed.

The incidence of hypotension in the ondansetron group in the index study was 35.6%. This is similar to the incidence of 35.7% reported by Hudson et al[20], and 37.5% by Trabelsi et al[27]. In contrast, some authors reported a higher incidence compared to that of the index study. Specifically, Ortiz Gómez and colleagues[29], Shah and co-workers[31], and Nivatpuminet al[10] reported a higher incidence of 44.6%, 46.0% and 53.6%% respectively. The incidence of hypotension in the ephedrine group in the index study is 24.4%. This is in agreement with 25% and 32% reported by Vercauteren et al[21], and Ngan-Kee et al[32-34] Colloid preload has been shown to be superior to crystalloid preload.[35,36]

Limitations

Though ondansetron may be considered expensive compared to ephedrine, research on the cost implication and the length of PACU stay following administration of ondansetron is yet to be explore.

Conclusion

Ondansetron was able to significantly reduce the incidence of hypotension in the study as it was comparable to ephedrine but superior to placebo in reducing the incidence and severity of hypotension; It is therefore pertinent that ondansetron should be administered prior to spinal anaesthesia for the prevention of maternal hypotension.

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References

1. Magalhães F, Govêia CS, de Arajo LLC, Nascimento BG, Kluthcouski SM. Ephedrine versus phenylephrine: prevention of hypotension during spinal block for caesarean section and effects on the fetus. Rev Bras Anaesthesiol. 2009;59 (1):11-20.
2. Meng W, Lang Z, Qun W, Ming-Kun S,Yan-Yun Y, Jun-Jing Y, et al. Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension during cesarean delivery: a dose-dependent study. Int J ClinExp Med. 2014; 7(12): 5210-5216.
3. Bhar D, Bharati S, Halder PS, Mondal S, Sarkar M, Jana S. Efficacy of prophylactic intramuscular ephedrine in prevention of hypotension during caesarean section under spinal anaesthesia: a comparative study. J Indian Med Assoc. 2011;109(5):300-307.
4. Mercier FJ, Bonnet MP, De a Done A, Moufouki M, Banu F, Hanaf A, et al. Spinal anaesthesia for caesarean section, fluid loading, vasopressors and hypotension. Ann FrAnesthReanim 2007;26(7-8):688-93.
5. Aragao FF, Arago PW, Martins CA, Salgado FN, Barrogueiro E. Comparison of metaraminol, phenylephrine and ephedrine in prophylaxis and treatment of hypotension in cesarean section under spinal anaesthesia. Rev Bras Anaesthesiol 2014;64(5):299-306.
6. Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszulowicz R, DylczykSommer A, et al. Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: a double-blind, placebo-controlled study. RegAnesth Pain Med 2008; 33:332– 339.
7. Gyermek L. Pharmacology of serotonin as related to anesthesia. J ClinAnesth. 1996; 8:402- 405.
8. NganKee WD, Prevention of maternal hypotension after regional anaesthesia for caesarean section. CurrOpinAnaesthesiol. 2010;23(3):304-9.
9. Edomwonyi NP, Ekwere IT, Egbekun R, Idehen HO, Sadiq A. Anaesthesia related complications in obstetric patients. Afr J AnaesthInt Care 2005;6(2):8-12.
10. Nivatpumin P, Thamvittayakul V. Ephedrine versus ondansetron in the prevention of hypotension during cesarean delivery: a randomized, double-blind, placebo-controlled trial. Int. J ObstetAnesth. 2016: 27:25-31.
11. Edomwonyi NP, Amadasun FE. Risk factors for development of Early Hypotension During Spinal Anaesthesia for Caesarean section. JMBR: A peer-review Journal of Biomedical Science 2009, (8) 65-71.
12. Gao L, Zheng G, Han J, Wang Y, Zheng J. Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension. Int J ObstetAnesth. 2015;24(4):335-43.

13. Heesen M, Kimek M, Hoeks SE, Rossant R. Prevention of spinal anaesthesia-induced hypotension during caesarean delivery by 5- Hydroxytryptamine-3 Receptor Antagonists. A Systematic Review and Meta-analysis and Meta-regression. AnesthAnalg. 2016;123(4): 977-88.
14. Abbas N, Syed ARS, Syeda SN. Role of prophylactic ondansetron for prevention of spinal anaesthesia induced hypotension in lower segment caesarean section. Pakarmedforces Med J 2016; 66(3):790-94.
15. Ayorinde BT, Buczkowski P, Brown J, Shah J,Buggy DJ. Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia induced hypotension during caesarean section. Br J Anaesth 2001; 86: 372–6.
16. Katie S, Tim B,Jenny B. Case-control study power and sample size calculations using
State. North American Stata Users' Group Meetings 2003; 07.
17. Bromage PR. Epidural Analgesia, Philadelphia: WB Saundersted;1978:144.
18. Klohr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. ActaAnaesthesiolScand 2010;54(8):909-21.
19. Ryu C, Geun JC, Yong HP, Hyun K. Vasopressors for the management of maternal hypotension during caesarean section under spinal anaesthesia A systematic review and network meta-analysis protocol. Medicine 2019; 98(1):1-3 (e13947).
20. Hudson MD. Crogan NL, Bilsky EJ. Efficacy of ondansetron as a prophylactic antihypotensive pharmacologic intervention among obese parturients undergoing spinal anaesthesia for caesarean delivery. Anesthesia eJournal 2016;4 (1):50-56
21. Vercauteren MP, Coppejans HC, Hoffmann VH, Mertens E, Adriaensen HA. Prevention of hypotension by a single 5-mg dose of ephedrine during small-dose spinal anaesthesia in prehydrated caesarean delivery patients. AnaesthAnalg. 2000;90(2):324-7.
22. Saygı Aİ, Özkan Ö, İsmet G, Hakan E, Ercüment M, Yaşam KA. Comparison of maternal and fetal outcomes among patients undergoing caesarean section under general and spinal anesthesia: a randomized clinical trial. Sao Paulo Med J. 2015; 133(3):227-34
23. Fakherpour A, Ghaem H, Fattahi Z, Zaree S. Maternal and anaesthesia-related risk factors and incidence of spinal anaesthesia-induced hypotension in elective caesarean section: A multinomial logistic regression. Indian J Anaesth 2018;62:36-46.
24. Brenck. F, Hartmann B,Katzer C,Obaid R,Brüggmann D, Benson M,Röhrig R,JungerA. Hypotension after spinal anaesthesia for caesarean section: identification of risk factors using an anaesthesia information management system**.** J ClinMonitComput. 2009 23(2):85-92.
25. Zwane SF, Bishop DG, Rodseth RN. Hypotension during spinal anaesthesia for Caesarean section in a resource-limited setting: towards a consensus definition. S Afr J Anaesth and Analg 2019;25(1):1-5.
26. Khalifa OSM. 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 anaesthesia. Ain Shams Anesthesiol 2015;8 (2):166-72
27. Trabelsi W, Chihebeddine R, Haythem E, Walid S, Mohamed B,Iheb L, et al. Effect of ondansetron on the occurrence of hypotension and on neonatal parameters during spinal anaesthesia for elective caesarean section, a prospective, randomized, controlled, doubleblind study. Anesthes Res Prac 2015:1-7.
28. Rashad MM, Farmawy MS. Effects of intravenous ondansetron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in parturients undergoing caesarean section. Egypt J Anaesth 2013; 29:369– 374.
29. Ortiz-Gómez JR, Palacio-Abizanda FJ, Morillas-Ramirez F, FornetRuiz I, LorenzoJiménez A, Bermejo-Albares ML. The effect of intravenous ondansetron on maternal haemodynamics during elective cesarean delivery under spinal anaesthesia: a double-blind, randomised, placebo-controlled trial. Int J ObstetAnesth 2014; 23:138– 143.
30. 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. RegAnesth Pain Med. 2015;40(4):344-348.
31. Shah N, Osea EA, Martinez GJ. Accuracy of noninvasive hemoglobin and invasive pointof-care hemoglobin testing compared with a laboratory analyze. Int. Jnl. Lab. Hem 2014, 36, 56–61
32. NganKee WD, Khaw KS, Lee BB, Lau TK, Gin Tony. A Dose-Response Study of
Prophylactic Intravenous Ephedrine for the Prevention of Hypotension During Spinal Anesthesia for Caesarean Delivery. Anaesth and Analg.2000;90(6):1390–1395.
33. Singh TH, Rupendra ST, Manichandra S, Rakesh N, Maharabam BD, Khullem MS. Prophylactic intravenous ephedrine for prevention of hypotension in caesarean section during spinal anaesthesia, A comparative study. J Med Soc 2016;30:116-20.
34. Andrzej M, Radoslaw O, Maria W, Krzysztof P, Majdylo K. The influence of intravenous ondansetron on maternal blood haemodynamics after spinal anaesthesia for caesarean section, a double-blind, placebo-controlled study. Ginekol Pol. 2015;86: 461-467.
35. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev 2006:CD002251.
36. Morgan P. The role of vasopressors in the management of hypotension induced by spinal and epidural anaesthesia. Canadian Journal of Anaesthesia 1994;41: 404–13.