PREOPERATIVE INTRAVENOUS ONDANSETRON VERSUS EPHEDRINE FOR INTRAOPERATIVE HEMODYNAMIC STABILITY IN CESAREAN SECTION UNDER SPINAL ANESTHESIA

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Submitted: 27/6/2020; Accepted: 22/11/2020; Published: 21/6/2021

ABSTRACT

Background

Intra-operative hypotension is a common complication after spinal anesthesia for cesarean section due to sympathetic block and pooling of blood in the lower limbs by the effect of local anesthetic agent, this complication could be problematic for both the anesthesiologist and the surgeon which may increase perioperative morbidity of the parturient, many preventive measurements had been tried to prevent it but none of them were completely effective

Objectives

Comparison between intravenous ephedrine and ondansetron for intraoperative hemodynamic stability and frequency of vasopressor use in the cesarean section under spinal anesthesia

Methods

After Kurdistan Board for medical Specialties ethical committee approval a 120 consented parturients involved in this study, they were prepared for cesarean section under spinal anesthesia, ASA=II(American Society of Anesthesiologists physical status II), age between 18-45 year old. They were randomly divided into three groups equally, group (N) received 10ml normal saline; (group E) received 10mg IV ephedrine ; (group O) received 8mg IV ondansetron immediately after spinal anesthesia, mean arterial pressure, heart rate, nausea and vomiting monitored perioperatively, Apgar score (Appearance, Pulse, Grimace, Activity, and Respiration) of the fetus and frequency of using vasopressor also recorded.

Results

One hundred twenty (120) term, singletons pregnant patient underwent spinal anesthesia for elective cesarean section included in this study, there was no significant difference found between groups in term of blood pressure but those who received ephedrine have lesser incidence of bradycardia and needs less amount of vasopressor use also ondansetron group has less incidence of bradycardia

Conclusion

Prophylactic ephedrine or ondansetron is given for spinal anesthesia in elective cesarean delivery have no significant effect on maternal blood pressure, ephedrine reduced the number of patients who require vasoconstrictor and atropine, ondansetron reduces the need for atropine during operation.

Keywords: *Ondansetron, Ephedrine, Hemodynamic stability, Spinal anesthesia, Cesarean section.*

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https://doi.org/10.17656/jsmc.10298

INTRODUCTION

Spinal anesthesia is often a modality of choice for cesarean section delivery. It is an effective anesthetic method that avoids the risks of general anesthesia in a parturient with a potentially difficult airway. However, a spinal block has predictable undesirable sequelae including hypotension leading to nausea and vomiting, decreased uteroplacental blood circulation, and fetal acidosis.

Nearly 33% of non-obstetric patients experience spinal anesthesia-induced hypotension and this incidence goes up to 70-80% in obstetric patients without pharmacological prophylaxis [1, 2].

Preload with crystalloids or colloids and lateral uterine displacement have been frequently used to prevent spinal-induced hypotension, but these strategies alone offer only partial protection.

A combination of preloading and vasopressor drugs has maximum effect in preventing spinal-induced hypotension [3]. When it is compared to other vasopressors ephedrine is proved to be more effective in increasing blood pressure [4]. Mainly it's a beta-adrenergic effect that causes an increase in arterial pressure by increasing cardiac output rather than vasoconstriction [5]. Several studies have shown that ondansetron, serotonin (5 hydroxytryptamines) receptor antagonists were evaluated in human studies for their potential to prevent spinal anesthesia-induced hypotension. The results of these trials were not consistent [6, 7]. They supposed that the mechanism of action is by inhibition of the Bezold-Jarisch reflex (BJR). This reflex is mediated through vagal afferent, which, when activated cause hypotension and bradycardia, activating chemoreceptors that are sensitive to serotonin in the cardiac wall by a decrease in blood volume may lead to increase vagal nerve activity, followed by bradycardia and vasodilatation [8, 9].

In the current study ephedrine and ondansetron have been compared for the prevention of maternal hypotension after spinal anesthesia for elective caesarian delivery. The primary outcome was maternal blood pressure and pulse rate from spinal block to delivery. The secondary outcome includes the number of patients requiring a vasoconstrictor, the dose of vasoconstrictor required, maternal symptoms (nausea and vomiting), and Apgar score of the fetus.

PATIENTS AND METHODS

The study is a randomized, single-blind clinical trial. It was approved by the scientific council of anesthesia and the Kurdistan board ethical committee. The study was carried out at Sulaymaniyah Maternity Hospital from May 2019 to May 2020.

Total number of 120 pregnant ladies who were scheduled for delivery by caesarian section under spinal anesthesia included in the current study, they were randomly divided into three equal groups,

Group N was a control group that received 10 mL 0.9% normal saline

Group E received ephedrine 10 mg diluted in 0.9% normal saline to 10 mL

Group O received ondansetron 8 mg diluted in 0.9% normal saline to 10 mL

Inclusion criteria

All parturient aged between 18–45-year-old, American Society of Anesthesiologists physical status II, term, singleton pregnancy; elective cesarean delivery under spinal anesthesia

Exclusion criteria

Patients under 18 and above 45-year-old, with a history of uncontrolled diabetes mellitus, hypertension, allergy to study drugs, prolong QT interval and contraindication for spinal anesthesia, failed spinal anesthesia, those who required another drug likely to influence blood pressure before delivery or general anesthesia were withdrawn from the study.

Patients are managed as the following. They were evaluated in the anesthesia clinic the day before surgery, on the morning of surgery the procedures and treatment were explained to them and informed consent was taken from all participants, they received an intravenous infusion of lactated ringer's solution 500 ml. Patients transferred to operating room monitoring with electrocardiogram, non-invasive blood pressure measurement, and pulse oximetry were established. Mean arterial pressure (MAP) and pulse rate (PR) recorded before starting of operation. Spinal anesthesia administered in the sitting position at the level of L3–L4 or L4-L5 with a 27-gauge Quincke spinal needle, 0.5% hyperbaric bupivacaine 2.5 mL (12.5mg) was injected intrathecally. The patient was then positioned supine on the operating table with a 15 degree left

lateral position for uterine displacement. Mean arterial pressure and heart rate were recorded every 5 minutes perioperatively. Hypotension was defined as a decrease in MAP < 65. If hypotension developed, ephedrine 5–10 mg were given intravenously, bradycardia was defined as PR <50 beats/min was treated with intravenous atropine 0.5 mg. The severity of nausea and/or vomiting before delivery was graded according to the following four-point grading system: 0 =no symptoms, 1= nausea, 2= vomiting 1–2 times, 3= vomiting >2 times. Metoclopramide 10mg was administered intravenously to patients complaining of nausea or vomiting. Apgar score at 1and 5 min, the total volume of intravenous fluid administered were recorded.

Statistical analysis

Data recorded and statistical software for social science analysis SPSS 20 for statistical analysis. T-test for the difference in the means and Chi-square for finding relationships between different factors were used, data below 0.05 considered as statistically significant.

RESULT

A total number of 120 parturient participated in the current study, the mean age of participants was 30.74 and SD of 5.34. mean body mass index (BMI) of participants was 31.7 and SD of 3.7. No statistically significant difference between studied groups was noticed regarding age, BMI, Mean arterial blood pressure (MAP), pulse rate (PR) and preoperative history of medical disease, Apgar scores of the baby at 1 and 5 minutes. (Table 1)

In comparing MAP between E and N group no significant difference between the two groups were noted. While the significant difference was observed in PR which was lower in group N after 10 min post spinal injection (p-value=0.00) and no obvious difference in the preceding readings. (table2).

Regarding the amount of IV fluid and given a dose of ephedrine, frequency of nausea and vomiting between group E and N no significant difference were observed however the amount of atropine usage in group E was significantly lower(P-value=0.03). (Table 2)

In comparing MAP and PR between O and N group no significant differences between the two groups were noted (table3).

The amount of IV fluid and given a dose of ephedrine, frequency of nausea and vomiting between-group O and N no significant differences were observed, however, the amount of atropine usage in group O was significantly lower(P-value=0.01). (Table 3)

In comparing MAP between E and O group no significant difference between the two groups were noted. While the significant difference was observed for PR which was lower in group O after 15 min post spinal injection (P-value=0.02) and no obvious difference in the preceding readings. (table4).

The number of IV fluids and given a dose of ephedrine and atropine between group E and O no significant difference were observed however the frequency of nausea and vomiting in group O was significantly lower (P-value=0.01). (Table 4)

Table 1. Age group, BMI, preoperative (MAP, PR), medical disease, Apgar score between studied groups.

Variable	N	E	O	P-value
Age groups (year)	31.10	31.38	29.75	0.1
BMI (kg/m2)	31.69	32.16	31.44	0.3
Preoperative MAP (mmhg)	100.58	98	102	0.2
Preoperative PR (bpm)	101	100	107	0.5
Medical Disease	3(7.5%)	5(12.5%)	6(15%)	0.2
Apgar score 1 and 5 min	8 10	9 10	8 9	0.2 0.6

Table 2. MAP, PR, top-up dose of ephedrine, nausea and vomiting, atropine, mean of fluid use between Normal saline and Ephedrine groups.

Mean arterial blood pressure (mmhg)	N	E	P value
MAP1	83.78	91.58	0.1
MAP2	69.68	74.26	0.3
MAP3	80	78	0.7
MAP4	75.43	77.48	0.3
Pulse rate (bpm)			
PR1	101	104	0.5
PR2	78	99	0.00
PR3	89	98	0.09
PR4	94	95	0.4
Top up dose of ephedrine (mg)	10.75	6.88	0.04
Nausea & vomiting	17(42.5%)	20(50%)	0.7
Atropine (mg)	13(32.5%)	2(5%)	0.03
Mean of fluid use (ml)	942	960	0.7

Table 3. MAP, PR, a top-up dose of ephedrine, nausea and vomiting, atropine, mean of fluid use between Normal saline and Ondansetron groups.

Mean arterial blood pressure (mmhg)	N	O	P value
MAP1	83.78	84	0.9
MAP2	69.68	71	0.8
MAP3	80	75	0.3
MAP4	75.43	75	0.7
Pulse rate (bpm)			
PR1	101	107	0.3
PR2	78	89	0.05
PR3	89	88	0.8
PR4	94	93	0.7
Top up dose of Ephedrine (mg)	10.75	9.50	0.5
Nausea & vomiting	17(42.5%)	10(25%)	0.09
Atropine (mg)	13(32.5%)	3(7.5%)	0.01
Mean of fluid used (ml)	942	960	0.8

Table 4: MAP, PR, a top-up dose of ephedrine, nausea and vomiting, atropine, mean of fluid use between Ephedrine and Ondansetron groups.

Mean arterial blood pressure (mmhg)	E	O	P value
MAP1	91.58	84	0.07
MAP2	74.26	71	0.4
MAP3	78	75	0.5
MAP4	77.48	75	0.2
Pulse rate (bpm)			
PR1	104	107	0.6
PR2	99	89	0.06
PR3	98	88	0.02
PR4	95	93	0.33
Top up dose of Ephedrine (mg)	6.88	9.50	0.1
Nausea & vomiting	20(50%)	10(25%)	0.01
Atropine (mg)	2(5%)	3(7.5%)	0.6
Mean of fluid used (ml)	960	960	0.95

DISCUSSION

In this randomized controlled trial, single-term parturients who underwent spinal anesthesia for elective cesarean delivery and received prophylactic ephedrine, ondansetron, or placebo were involved.

It has been found that PR after 10min of injection of ephedrine were higher in the E group than N group and use of atropine were more in the placebo group because ephedrine mainly maintains blood pressure by increasing cardiac output and pulse rate [(11)].

MAP difference in both ephedrine and placebo groups were statistically insignificant because frequent top-up dose of ephedrine in placebo group had been used to prevent hypotension during the procedure, in result, the total dose of ephedrine used intraoperatively were higher in placebo group and increasing ephedrine dose significantly reduce risk of hypotension [(12)].

The following studies agree with our results:

Xu S. et.al involved 97 parturient in their studies, they found that the rate of tachycardia was lower in group noradrenaline as compared to ephedrine (P-value=0.002) [(13)].

Nivatpumin P et.al selected 168 parturient, showed that Prophylactic administration of ephedrine 10mg has no effect on maternal blood pressure as compared to placebo but reduce the patient needs for vasopressor (P-value=0.023) [(14)].

In comparing placebo to ondansetron group, placebo group needed significantly more atropine than ondansetron group. Because ondansetron is a 5-HT3 receptor antagonist which inhibits behold-jarisch cardiac reflex (promote parasympathetic activity leading to bradycardia, vasodilatation, and hypotension).

The following studies agree with our results:

Chengmao et al. in 7 randomized control trials included 449 parturient discovered that Ondansetron effectively reduces the incidence of bradycardia in the elective cesarian section (P-value =0.006) [(15)].

Heesen M et al in 7 trials concerned 1604 parturient, found that Ondansetron is a 5HT3 receptor blocker which is effective in reducing the incidence of bradycardia (P-value=0.01) [(16)].

Terkawi et al. involved 86 parturient established that Ondansetron does not show any significant difference in MAP between placebo and ondansetron group inpatient undergoing elective cesarian section under subarachnoid block (P-value=0.89) [(17)], when comparing ephedrine group with ondansetron group,

PR after 15 min of injection of studied drugs were higher in ephedrine group because ephedrine mainly maintains blood pressure by increasing cardiac output and heart rate [11]. While nausea and vomiting were less in the ondansetron group because 5-HT3 is a serotonin receptor antagonist which is present centrally on the chemoreceptor trigger zone of area postrema and peripherally on vagal nerve terminals, they are known to be associated with nausea and vomiting [18].

The following studies agree with our results:

Chengmao et.al in 8 randomized control trial choose 1630 parturient recognized that ondansetron significantly reduced incidence of nausea and vomiting in the cesarian section under spinal anesthesia (P-value =<0.00001) [15].

Nivatpumin P et al involved 168 parturients, as they comparing ondansetron to ephedrine group there was no significant difference in a maternal MAP under spinal anesthesia for cesarian section (P-value=0.25) [14].

The following studies are disagreed with the current study:

A study done by Cyna AM et al which involved 470 parturients from seven trials shows a significantly decreased incidence of hypotension in that parturient who received ephedrine prophylaxis (RR 0.51, 95% CI (confidence interval) 0.33 to 0.78;) [19]. Also, Lee A et al studied 641 parturient from 14 clinical trials and found that ephedrine is more effective than the control group for prevention of hypotension [RR], 0.73; 95% CI, 0.63 to 0.86 [20], this differs from the current study because we used frequent top-up doses of ephedrine in the control group to prevent hypotension during the operation.

A study was done by Sahoo T et al which take 52 parturients scheduled for cesarean section under spinal anesthesia and received 4mg ondansetron prophylactic their results show that decreased incidence of hypotension and vasopressor use in the ondansetron group in compared to the saline group (P-value =0.009) [21]. Wang M who takes 150 parturient shows the effect of different doses of ondansetron on maternal hypotension during cesarean section under spinal anesthesia, the incidence of hypotension significantly reduced (P-value =<0.05) [22], the difference from the current study because of the frequent top-up doses of ephedrine used in the control group to prevent hypotension during the operation.

In conclusion, In the current study, we concluded that prophylactic ephedrine 10 mg or ondansetron 8 mg given immediately after spinal anesthesia for elective cesarean delivery have no significant effect on maternal blood pressure as compared to placebo, ephedrine reduced the number of patients who require vasoconstrictor and atropine, ondansetron reduces the need for atropine during operation.

REFERENCES

1. Liu SS, Mcdonald SB. Current Issues in Spinal Anesthesia. Anesthesiology. 2001;94(5):888–906.

2. Mercier FJ, Auge M, Hoffman C, Fischer C, Le Gouez A. Maternal Hypotension During Spinal Anesthesia for Cesarean Delivery. Minerva Anaestesiol. 2013; 79:62–73.

3. Bhagat H, Malhotra K, Ghildyal SK, Srivastava PC. Evaluation of preloading and vasoconstrictors as a combined prophylaxis for hypotension during subarachnoid anaesthesia. B. Indian Journal of Anesthesia. 2004;48(4):299–303.

4. Burns SM, Cowan CM, Wilkes RG. Prevention and management of hypotension during spinal anesthesia for elective caesarean section: a survey of practice. Anesthesia 2001; 56: 794–8.

5. Cooper DW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and Maternal Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery. Anesthesiology. 2002;97(6):1582–90.

6. Trabelsi W, Romdhani C, Elaskri H, Sammoud W, Bensalah M, Labbene I, et al. Effect of Ondansetron on the Occurrence of Hypotension and on Neonatal Parameters during Spinal Anesthesia for Elective Caesarean Section: A Prospective, Randomized, Controlled, Double-Blind Study. Anesthesiology Research and Practice. 2015; 2015:1–7.

7. Ortiz-Gómez J, Palacio-Abizanda F, Morillas-Ramirez F, Fornet-Ruiz I, Lorenzo-Jiménez A, Bermejo-Albares M. The Effect of Intravenous Ondansetron on maternal Haemodynamics During Elective Caesarean Delivery Under Spinal Anaesthesia: a Double-blind, Randomised, Placebo-controlled Trial. International Journal of Obstetric Anesthesia. 2014;23(2):138–43.

8. Aviado DM, Aviado DG. The Bezold-Jarisch Reflex.A Historical Prospective Of Cardiopulmonary Reflexes, Annals of the New York Academy of Sciences. 2006;940(1):48–58.

9. Yamano M, Ito H, Kamato T, Miyata K. Characteristics of Inhibitory Effects of Serotonin (5-HT)3-Receptor Antagonists, YM060 and YM114 (KAE-393), on the von Bezold-Jarisch Reflex Induced by 2-Methyl-5-HT, Veratridine and Electrical Stimulation of Vagus Nerves in Anesthetized Rats. The Japanese Journal of Pharmacology. 1995;69(4):351–6.

10. Yamano M, Kamato T, Nishida A, Ito H, Yuki H, Tsutsumi R, et al. Serotonin (5-HT)3-Receptor Antagonism of 4,5,6,7-Tetrahydrobenzimidazole Derivatives against 5-HT-Induced Bradycardia in Anesthetized Rats. The Japanese Journal of Pharmacology. 1994;65(3):241–8.

11. Critchley L, Stuart J, Conway F, Short T. Hypotension during Subarachnoid Anaesthesia: Haemodynamic Effects of Ephedrine. British Journal of Anaesthesia. 1995;74(4):373–8.

12. Kee WDN, Khaw KS, Lee BB, Lau TK, Gin T. A Dose-Response Study of Prophylactic Intravenous Ephedrine for the Prevention of Hypotension During Spinal Anesthesia for Cesarean Delivery. Anesthesia & Analgesia. 2000;90(6):1390–5.

13. Xu S, Mao M, Zhang S, Qian R, Shen X, Shen J, et al. A randomized double-blind study comparing prophylactic norepinephrine and ephedrine infusion for preventing maternal spinal hypotension during elective cesarean section under spinal anesthesia. Medicine. 2019;98(51).

14. Nivatpumin P, Thamvittayakul V. Ephedrine versus ondansetron in the prevention of hypotension during cesarean delivery: a randomized, double-blind, placebo-controlled trial. International Journal of Obstetric Anesthesia. 2016;27:25–31.

15. Zhou C, Zhu Y, Bao Z, Wang X, Liu Q. Efficacy of ondansetron for spinal anesthesia during cesarean section: a meta-analysis of randomized trials. Journal of International Medical Research. 2018;46(2):654–62.

16. Heesen M, Klimek M, Hoeks SE, Rossaint R. Prevention of Spinal Anesthesia-Induced Hypotension During Cesarean Delivery by 5-Hydroxytryptamine-3 Receptor Antagonists. Anesthesia & Analgesia. 2016;123(4):977–88.

17. 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. Regional Anesthesia and Pain Medicine. 2015;40(4):344–8.

18. Eidi M, Kolahdouzan K, Hosseinzadeh H, Tabaqi R. A comparison of preoperative ondansetron and dexamethasone in the prevention of post-tympanoplasty nausea and vomiting. Iran J Med Sci. 2012 Sep;37(3):166-72. PMID: 23115448; PMCID: PMC3470085.

19. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for Preventing hypotension during Spinal Anaesthesia for Caesarean Section. Cochrane Database of Systematic Reviews. 2006; 10.1002/14651858.cd002251.pub2

20. Lee A, Kee WDN, Gin T. Prophylactic ephedrine prevents hypotension during spinal anesthesia for Cesarean delivery but does not improve neonatal outcome: a quantitative systematic review. Canadian Journal of Anesthesia/Journal canadien danesthésie. 2002;49(6):588–99.

21. 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. International Journal of Obstetric Anesthesia. 2012;21(1):24–8.

22. Wang M, Zhuo L, Wang Q, Shen MK, Yu YY, Yu JJ, Wang ZP. Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension during cesarean delivery: a dose-dependent study. Int J Clin Exp Med. 2014 Dec 15;7(12):5210-6. PMID: 25664023; PMCID: PMC4307470.