

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH



EFFECTS OF PROPHYLACTIC INTRAVENOUS GRANISETRON, ONDENSETRON AND EPHEDRINE ON HEMODYNAMIC CHANGES DURING SPINAL ANESTHESIA IN CESAREAN DELIVERY: A DOUBLE BLIND, PROSPECTIVE RANDOMIZED CONTROLLED STUDY.

Anaesthesiology

Safiya Shaikh

Consultant And Head Of The Department

Mrudula Tatakuri*

Department Of Anesthesia, Karnataka Institute Of Medical Sciences, Hubballi 580022, India. *Corresponding Author

ABSTRACT

BACKGROUND AND AIMS: Spinal anaesthesia is considered as gold standard technique for cesarean sections but the side effects of spinal anesthesia are hypotension, bradycardia and shivering. Serotonin released during the low volume states has been suggested as a possible trigger for the Bezold-Jarisch reflex (BJR) that may lead to the bradycardia and hypotension.

OBJECTIVE: To compare between two serotonin receptor antagonists ondansetron and granisetron and traditionally used vasopressor 'ephedrine' on hemodynamics, sensory and motor blockade during spinal anesthesia in cesarean delivery.

SETTINGS AND DESIGN: This setting was designed as a double-blind, prospective, randomized controlled study.

MATERIALS AND METHODS: A total number of 90 patients of ASA grade 1 & 2 of age between 20-30 years undergoing lower segment cesarean section were randomly allocated into 3 equal groups. Group A received 1mg granisetron, Group B received 4mg ondansetron, Group C received 10mg ephedrine. All of these studied groups were diluted in 10ml normal saline and administered over a period of 1-5 min before induction of spinal anesthesia. Mean arterial blood pressure, heart rate, rescue of vasopressor, sensory and motor blockade were assessed.

RESULTS: The incidence of hypotension and need of rescue vasopressor is significantly lower ($p < 0.05$) in Group B than in group A & C. There is significant faster sensory and motor recovery in Group A than in group B & C.

CONCLUSION: In parturients undergoing cesarean section 1.V 4mg ondansetron before giving spinal anesthesia decreased both the hypotension and the doses of vasopressor required.

KEYWORDS

Cesarean section, 5-HT, Granisetron, Ondansetron, Ephedrine.

INTRODUCTION

Spinal anesthesia has become the gold standard technique for cesarean section [14]. Although spinal anesthesia has been considered safe technique, it has many side effects including hypotension, nausea, vomiting, bradycardia and other dysrhythmias [16]. The incidence of hypotension and bradycardia in non obstetric patients has been reported to be 33% and 13% respectively [5, 11]. In obstetric, non laboring patients, the incidence of hypotension has been estimated to be as high as 50-60% [5, 11]. Lateral uterine displacement and preloading with crystalloids or colloids have been commonly used to prevent spinal induced hypotension, but these alone may offer only a partial protection [17]. A combination of preloading vasopressor drugs has maximum efficacy in preventing spinal induced hypotension. Hypotension occurs from decrease in systemic vascular resistance and central venous pressure from sympathetic block. Sudden bradycardia can occur from shift in cardiac autonomic balance towards the parasympathetic system from activation of left ventricular mechanoreceptor or chemoreceptor Bezold-Jarisch reflex (BJR) or from an increase in baroreflex activity [6].

Pharmacology and animal studies suggest that 5-HT₃ [serotonin] may be an important factor associated with inducing the BJR during low volume states and this effect can be blocked at the 5-HT₃ receptor [1, 7]. On the other hand serotonin (5-HT) is a critically thermoregulatory neurotransmitter [11]. Many studies highlight the use of a 5-HT₃ antagonist in prevention of hypotension and bradycardia caused by BJR in obstetric and non obstetric patients [2, 7, 9].

Ondansetron and Granisetron are selective 5-HT₃ receptor antagonists, and thus may be beneficial for preventing bradycardia and hypotension [12]. Ephedrine, an indirectly acting sympathomimetic amine is probably the choice of vasopressor in obstetric anesthesia [13]. Although ephedrine has mixed α -adrenoreceptor and β -adrenoreceptor activity, it maintains arterial pressure mainly by increase in cardiac output and heart rate as a result of its predominant activity on β 1-adrenoreceptor [5].

This study aimed to compare a traditional vasopressor 'Ephedrine' with 5HT₃ receptor antagonists 'Granisetron' and 'ondansetron' on hemodynamic changes the motor and sensory block during spinal anesthesia in cesarean delivery.

MATERIALS AND METHODS

This randomized, double blinded study was performed at Karnataka Institute of Medical Sciences, Hubballi. A total of 90 patients of ASA grade 1 & 2 of age group between 20-30 years undergoing lower segment caesarean section and satisfied all the essential criteria were enrolled in the study after taking informed written consent and were randomly allocated into three groups.

GROUP A (n=30): - Patients receiving 1mg granisetron diluted in 10ml normal saline slowly IV 5mins before spinal anesthesia.

GROUP B (n=30): - Patients receiving 4mg ondansetron diluted in 10ml normal saline slowly IV 5mins before spinal anesthesia.

GROUP C (n=30): - Patients receiving 10mg ephedrine diluted in 10ml normal saline slowly IV 5mins before spinal anesthesia.

ASA grade 3 & 4, patients refusal, patients with contraindications for spinal anesthesia, patients with history of known allergy to Granisetron, Ondansetron and Ephedrine, patients receiving serotonin agonists or antagonists, patients with ischemic heart disease, chronic hypertension or pregnancy induced hypertension were excluded.

Preanaesthetic evaluation of all patients were done and patients who belonged to inclusion criteria after taking a written informed valid consent were allotted randomly into the above groups.

In the operation theatre, a good peripheral intravenous access was secured using 18 gauge cannula and all patients were prehydrated with IV 500ml ringer's lactate. Baseline non invasive blood pressure, heart rate, electrocardiograph, pulse oximetry were recorded before spinal anesthesia and every 5 mins until the end of the procedure.

Time to analgesic block at T10 dermatome i.e. time interval between the end of administration of anesthetic and the onset of cutaneous analgesic at T10 were evaluated using midline bilateral pin prick every minute till complete loss of cutaneous sensation at T10 at which point surgery will be proceeded. Then the patients were evaluated every 15mins till sensory level regression to S1.

Degree of motor block will be assessed when cutaneous sensations are lost at T10 using modified Bromage scale.

0=No Block.
 1=Inability to raise extended leg.
 2=Inability to flex the knee.
 3=Inability to flex ankle and foot.

During surgical procedure adverse effects like nausea, vomiting, hypotension, bradycardia were recorded. Vasopressors were administered if mean arterial blood pressure falling >20%mm of Hg. If bradycardia occurred 0.6mg atropine was given IV. The total dose of vasopressors and atropine administered was recorded.

STATISTICAL ANALYSIS:

Data was checked, entered and analysed and were expressed as mean ±SD for quantitative variables and percentage for categorical variables Chi-square(x²) or fisher exact test, ANOVA(F test) for comparison between groups. P<0.05 was considered statistically significant.

RESULTS:

A total of 90 parturients were included in the study 30 each in 3 groups.

Table 1: Demographic data:

	Group A Mean (SD)	Group B Mean (SD)	Group C Mean (SD)	P value*
Anthropometry measures				
Height	165(5.1)	167 (5.0)	167 (5.6)	0.45
Weight	75 (10.4)	79.0 (10.0)	74.3 (128)	0.44
Age	24.27	24.8	24.8	0.770
Gestational age	37.9 (0.8)	38.1 (1.2)	38.1 (0.9)	0.712

*one way ANOVA

There were no significant differences in demographic data between the groups as shown in the table 1.

Table 2: Mean arterial blood pressure between the groups

Intra operative mean arterial pressure at various time points	Group A Mean (SD)	Group B Mean (SD)	Group C Mean (SD)	P value*
Baseline	91.2 (9.1)	91.3 (7.4)	91.1 (7.8)	0.994
5 minutes	82.6 (12.8)	84.7 (11.1)	81.6 (14.9)	0.638
10 minutes	77.2 (12.3)	78.4 (11.8)	80.0 (12.1)	0.660
15 minutes	80.4 (8.6)	81.3 (8.4)	81.8 (8.5)	0.829
20 minutes	79.6 (6.8)	82.7 (5.7)	80.7 (6.8)	0.171
25 minutes	82.1 (12.3)	84.6 (11.0)	81.13 (5.9)	0.643
30 minutes	82.2 (8.5)	83.1 (8.1)	82.3 (8.6)	0.903
45 minutes	82.5 (8.9)	83.9 (6.2)	83.7 (8.0)	0.772

*one way ANOVA

There were no statistical significant differences observed in heart rate and mean arterial blood pressure(MBP) between the groups. But the incidence of hypotension in Group A, Group B, Group C was 33.3%, 23.3%, 36.7% respectively. The incidence of hypotension in Group B being significantly lower than in Group A and Group C. Group B also required lower doses of rescue vasopressor as shown in the table 2.

Table 3: Operative parameters

Operative patient parameters in minutes	Group A N (%) N=30	Group B N (%) N=30	Group C N (%) N=30	P value*
Ephedrine requirement				
No	19 (63.3)	23 (76.7)	19 (63.3)	0.443
Yes (5 mg)	11 (36.7)	7 (23.3)	11 (36.7)	
Atrophine requirement				
No	30 (100.0)	30 (100.0)	27 (90.0)	0.045
Yes	0 (0.0)	0 (0.0)	3 (10.0)	
Time of vaso pressor administration	7.9 (2.1)	9.2 (2.4)	6.9 (1.3)	<0.001

Presence of side effects among the study participants				
Hypotension present				
No	20 (66.7)	23 (76.7)	19 (63.3)	0.510
Yes	10 (33.3)	7 (23.3)	11 (36.7)	
Brady cardia				
No	30 (100.0)	30 (100.0)	27 (90.0)	0.045
Yes	0 (0.0)	0 (0.0)	3 (10.0)	
Nausea and vomiting				
No	28 (93.3)	30 (100.0)	27 (90.0)	0.227
Yes	2 (6.7)	0 (0.0)	3 (10.0)	
Shivering				
No	24 (80.0)	22 (73.3)	23 (76.7)	0.830
Yes	6 (20.0)	8 (26.7)	7 (23.3)	
Others				
No	30 (100.0)	30 (100.0)	30 (100.0)	1.000
Yes	0 (0.0)	0 (0.0)	0 (0.0)	

*chi square test

Also the time of 1st rescue vasopressor administration had a significant statistical difference of 7.9, 9.2, 6.9 minutes in Group A, Group B, Group C respectively showing the 1st use of vasopressor is late in Group B. There is also statistical difference in the requirement of atropine and incidence of bradycardia among 3 groups being 0%, 0%, 10% in Group A, B, C respectively. There was significant statistical difference in sensory onset, Group A being faster than group B and C (9.1±2.3, 10.1±1.5, 10.9±2.3) in minutes and regression (143.0±19.4, 160±23.5, 175.5±10) respectively. Even the motor regression is early for Group A than Group B & C (150.5±19.9, 175±6.3, 173.9±9.1) respectively

There is no significant statistical differences in respiratory rate, oxygen saturation, shivering, pain. The incidence of nausea and vomiting were 6.7%, 0%, 10% among Group A, B, C respectively.

DISCUSSION:

Spinal anesthesia is one of the regional techniques commonly used for parturients undergoing cesarean section in order to avoid most of the risks which may happen with general anesthesia. Maternal hypotension is one of the most common complications during spinal anesthesia because of sympathetic nerve blockade which decreases blood return to the heart. Prehydration with crystalloid solutions is an important method to prevent hypotension during regional anesthesia. Increasing the crystalloid preload from 10-30ml/kg may further reduce the incidence of hypotension. But it is time consuming to administer and potentially dangerous in susceptible mother by risking circulatory overload after delivery and also by causing significant hemodilution.

Protocols that aim to prevent hypotension during spinal anaesthesia for cesarean delivery result in better outcome than those designed to treat hypotension after it has occurred. In this study traditionally used vasopressor in obstetric anesthesia ephedrine, which is non catecholamine sympathomimetic agent stimulates α and β-adrenergic receptors predominantly indirectly is compared with two 5HT₂ receptor antagonists ondansetron and granisetron which block the BJR. All these 3 drugs were used prophylactically and given 5min before spinal blockade with 5mg ephedrine rescue boluses if hypotension occurred.

Ondansetron is one of the medications studied before by Sahoo et al[2] and proved that it attenuated spinal induced hypotension if given iv in cesarean patients before spinal anaesthesia and our results coincided with their finding. Other studies Owzale et al[1] studied ondansetron in general surgical population while Sahoo et al[2] and Ortiz Gomez et al[3] studied ondansetron in obstetric patients undergoing cesarean delivery. Ondansetron was shown to attenuate arterial BP.

Tsikouris et al[9] in their study on granisetron found that granisetron when given iv in cesarean patients before spinal anaesthesia decreased the changes that usually occur in heart rate and blood pressure during head up tilt table test due to BJR and M. Rashad[15] study also showed faster sensory regression and no

hemodynamic changes and no change in motor block.

Studies showed that low dose of prophylactic iv ephedrine significantly reduced the incidence of maternal hypotension. In these studies low dose of hyperbaric bupivacaine along with intrathecal opioids were used. These both factors lead to less cvs instability which can be managed even with low doses of prophylactic iv ephedrine shown by Muhammed Shakeel Iqbal et al [17].

In this present study a standardized dose of hyperbaric bupivacaine without any intrathecal opioids was used. In this study we found that despite reduction in MBP in 3 groups, it is still less in ondansetron group than in granisetron and ephedrine groups. Even there is less requirement for rescue vasopressor. Atropine requirement for bradycardia is found to be less in both ondansetron and granisetron groups. I.v granisetron prior to intrathecal bupivacaine resulted in faster sensory onset and regression.

CONCLUSION:

Our study concluded that prophylactic ondansetron is better than granisetron and ephedrine in attenuating bradycardia and hypotension. Granisetron has early sensory onset and recovery.

Limitation in this study:

- 1: Not comparing different doses of the 3 therapeutic medications
- 2: Apgar scores of newborn were not recorded as ephedrine has a dose related propensity to depress fetal pH but our main focus was the effect of these 3 drugs on maternal hemodynamics and sensory and motor blockade of spinal anesthesia.

REFERENCES:

- [1] Owczuk, R., Wenski, W., Polak-Krzeminska, A., Twardowski, P., Arszulowicz, R., Dylczyk-Sommer, A., ... & Wujtewicz, M. (2008). Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: a double-blind, placebo-controlled study. *Regional anesthesia and pain medicine*, 33(4), 332-339.
- [2] Sahoo, T., SenDasgupta, C., Goswami, A., & Hazra, A. (2012). Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: a double-blind randomised, placebo-controlled study. *International journal of obstetric anesthesia*, 21(1), 24-28.
- [3] Ortiz-Gómez, J. R., Palacio-Abizanda, F. J., Morillas-Ramirez, F., Fonet-Ruiz, I., Lorenzo-Jiménez, A., & Bermejo-Albares, M. L. (2014). 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*, 23(2), 138-143.
- [4] Butterworth, J. (1998). Physiology of spinal anesthesia: what are the implications for management?. *Regional anesthesia and pain medicine*, 23(4), 370.
- [5] Norris, M. C. (1987). Hypotension During Spinal Anesthesia for Cesarean Section: Does it Affect Neonatal Outcome?. *Regional Anesthesia and Pain Medicine*, 12(4), 191-194.
- [6] Arndt, J. O., Bomer, W., Krauth, J., & Marquardt, B. (1998). Incidence and time course of cardiovascular side effects during spinal anesthesia after prophylactic administration of intravenous fluids or vasoconstrictors. *Anesthesia&Analgesia*, 87(2), 347-354.
- [7] Adams, V. R., & Valley, A. W. (1995). Granisetron: the second serotonin-receptor antagonist. *Annals of Pharmacotherapy*, 29(12), 1240-1251.
- [8] Rashad, M. M., & Farmawy, M. S. (2013). Effects of intravenous ondansetron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in parturients undergoing cesarean section. *Egyptian Journal of Anaesthesia*, 29(4), 369-374.
- [9] Tsikouris, J. P., Kluger, J., Chow, M. S., & White, C. M. (2000). Usefulness of intravenous granisetron for prevention of neurally mediated hypotension upon head upright tilt testing. *The American journal of cardiology*, 85(10), 1262-1264.
- [10] Burns, S. M., Cowan, C. M., & Wilkes, R. G. (2001). Prevention and management of hypotension during spinal anaesthesia for elective Caesarean section: a survey of practice. *Anaesthesia*, 56(8), 777-798.
- [11] Marashi, S. M., Soltani-Omid, S., Mohammadi, S. S., Aghajani, Y., & Movafegh, A. (2014). Comparing two different doses of intravenous ondansetron with placebo on attenuation of spinal-induced hypotension and shivering. *Anesthesiology and pain medicine*, 4(2).
- [12] Olivier, B., Soudijn, W., & van Wijngaarden, I. (1999). The 5-HT1A receptor and its ligands: structure and function. In *Progress in drug research* (pp. 103-165). Birkhäuser, Basel.
- [13] Husaini, S. W., & Russell, I. F. (1998). Volume preload: lack of effect in the prevention of spinal-induced hypotension at caesarean section. *International Journal of Obstetric Anesthesia*, 7(2), 76-81.
- [14] Trabelsi, W., Romdhani, C., Elaskri, H., Sammoud, W., Bensalah, M., Labbene, I., & Ferjani, M. (2015). 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.
- [15] Rashad, M. M., & Farmawy, M. S. (2013). Effects of intravenous ondansetron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in parturients undergoing cesarean section. *Egyptian Journal of Anaesthesia*, 29(4), 369-374.
- [16] Eldaba, A. A., & Amr, Y. M. (2015). Intravenous granisetron attenuates hypotension during spinal anesthesia in cesarean delivery: A double-blind, prospective randomized controlled study. *Journal of anaesthesiology, clinical pharmacology*, 31(3), 329.
- [17] Iqbal, M. S., Ishaq, M., Masood, A., & Khan, M. Z. (2010). Optimal dose of prophylactic intravenous ephedrine for spinal-induced hypotension during cesarean section. *Group*, 1(30), 27-2.

- [18] White, C. M., Chow, M. S., Fan, C., Kluger, J., & Bazunga, M. (1998). Efficacy of Intravenous Granisetron in Suppressing the Bradycardia and Hypotension Associated with a Rabbit Model of the Bezold-Jarisch Reflex. *The Journal of Clinical Pharmacology*, 38(2), 172-177.
- [19] Khalifa, O. S. M. (2015). A comparative study of prophylactic intravenous granisetron, ondansetron, and ephedrine in attenuating hypotension and its effect on motor and sensory block in elective cesarean section under spinal anesthesia. *Ain-Shams Journal of Anaesthesiology*, 8(2), 166.