Original Article

Efficacy of Intravenous Ondansetron Versus Ephedrine as Prophylactic Against Hypotension and Bradycardia Following Spinal Anaesthesia in Elective Caesarean Section - A Comparative Study

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Abstract

Background: *The pathophysiological mechanism involved in the occurrence of hypotension and bradycardia following central neuroaxial blockade is peripheral vasodilatation, parasympathetic dominance and increased baroreceptor activity.Current studies correlate these haemodynamic changes with activation of a phenomenon naming Bezold-Jarisch reflex (BJR). 5-Hydroxytryptamine-3 is an important factor associated with inducing BJR and Ondansetron antagonizes the induction of BJR.*

Objective: *To compare the efficacy between ondansetron and ephedrine as prophylactic against spinal anaesthesia induced hypotension and bradycardia.*

Method: *120 mothers of ASA grade I and II scheduled for elective caesarean section under spinal anaesthesia were selected and randomized into two equal groups naming Group A(n=60) and Group B (n=60). Group A received Ondansetron IV (0.1mg/kg body wt) and group B Ephedrine (0.15 mg/kg body wt) 5 minutes prior spinal anaesthesia. Data were recorded before and just after anaesthesia and at two minutes intervals up to 10^{th} minute followed by five minutes intervals until the end of surgery. Results analyzed using unpaired t-test. A "P" value < 0.05 was considered statistically significant.*

Result*: Group A showed slight but statistically significant higher heart rate than after Group B at 10^{th} min and 15^{th} min (P=0.001). Statistically significant higher values of MAP in Group A found up to the 15^{th} minute of perioperative period. Rescue medications for hypotension were significantly higher in Ephedrine group. Shivering is common for both groups ,whereas nausea and vomiting is significantly less in group A.*

Conclusion: *Ondansetron and Ephedrine has potential role to prevent spinal anaesthesia induced hypotension and bradycardia but Ondansetron shows better efficacy. Ondansetron also plays important role in prevention nausea and vomiting.*

Key words: *Spinal anaesthesia, Elective Caesarean Section, Hypotension, Bradycardia, Bezold-Jarisch Reflex(BJR), Ondansetron, Ephedrine.*

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Introduction:

Spinal anaesthesia (SA) is the preferred anaesthetic choice for the majority of the caesarean section operation for its fast, profound and symmetrical sensory and motor block of high quality. Beyond many advantages it often creates an emerge hemodynamic instable situation resulting from spinal anaesthesia induced hypotension and bradycardia (SHI&B). The incidence has been reported to be 33% and 13% respectively for hypotension and bradycardia in non-obstetric patient but in obstetric non-

labouring patient the incidence of hypotension has been estimated to be as high as 50%-60% and a bit less found in labouring parturient.[1] The incidence of hypotension can be as high as 70-80% when pharmacological prophylaxis is not used[2].SHI&B can result in detrimental consequences to mother such as dyspnea, nausea, vomiting, loss of consciousness, pulmonary aspiration and cardiac arrest, and potentially cause harm to baby as a result of fetal acidosis, and uteroplacental hypoperfusion.[3, 4, 5, 6]. To date numerous studies have been conducted to identify a reliable means of prophylaxis of SHI&B. Amongst the different strategies, intravenous pre-load and lateral uterine displacement is routine procedures in practice. Prophylactic and therapeutic use of vasopressor (Ephedrine, Phenylephrine) to combat SHI&B is also used frequently. However no method has been proved satisfactory. Furthermore several adverse effects from many of these interventions have been identified. In some cases the incidence of hypotension has reported to be as high as 80% despite fluid pre-load, lateral uterine displacement and use of vasopressor agent.[7] Use of ephedrine in the prevention and management of SHI&B is a common practice. *Kee et al.*[8] found that a bolus dose of 30 mg intravenous ephedrine is required to reduce the incidence of SHI&B up to 35% but this was at the expense of rebound hypertension in 45% of those patients. Ephedrine has been shown to cross the placenta and to affect the foetal and neonatal heart rate due to â-adrenoceptor activity.[9] Some studies found significantly higher umbilical arterial pH when using prophylactic ephedrine.[10] Phenylephrine is also used as prophylactic against SIH but bradycardia and decreased cardiac output is usually seen because of its well known á-agonist properties and baroreceptor activation. As a result there is drop of utero-placental perfusion and decreased splanchic circulation. In recent years many studies have linked SHI&B to a physiological mechanism called Bezold- Jarisch Reflex (BJR), a form of vasovagal syncope triggered by the sympathetic blockade and resulting decreased vascular resistance.[6,12,]. The classic Bezold-Jarisch reflex: a cardio-inhibitory reflex arises from the mechanoreceptors and chemoreceptors located primarily in the left ventricular wall which participates in systemic response to a sudden decrease in left ventricle preload.[13]Activation of BJR causes inhibition of sympathetic outflow and shifts the cardiac autonomic balance towards parasympathetic dominance, inducing bradycardia while further exacerbating hypotension and vasodilation.[13,14] Research cites 5-Hydroxytryptamine-3 (5-HT_3 or Serotonin) as potential factor which contributes to induction of the BJR by activating serotonin sensitive chemoreceptors in the presence of decreased blood volume.[3,6,12,15].Therefore, current studies focused on investigating the ability of prophylactic intravenous 5-HT_3 receptors blockers or 5-HT_3 receptors antagonist to attenuate haemodynamic deranges following SA. Ondansetron is a potent selective 5-HT_3 antagonist.[16] In particular the prophylactic administration of 5-HT_3 antagonist ondansetron is of interest because it is widely available, economic, already commonly given to patient to prevent nausea and vomiting with minimal side effects for the mother and has been shown to be safe with no harmful effects to the baby if given at term.[17,18,19] So that prophylactic use of ondansetron ,a 5-HT_3 antagonist is an option to attenuate SHI&B. This study compared the efficacy of ondansetron and ephedrine as prophylactic agent. Potential detrimental effects of SHI&B and inadequacy of practicing strategies directed us to perform the study.

However, beyond what facts lied behind such haemodynamic instabilities, consequence of prolonged maternal hypotension may be deleterious both to mother and to the fetus. Brief episodes of maternal hypotension have lowered Apgar scores, prolonged time to sustained respiration and prolonged fetal acidosis[20]. So that prevention of maternal hypotension and bradycardia following SA should be a major concern for every practicing anaesthesiologist. In a retrospective study of 919 mother-infant pairs maternal hypotension was not found to predict a perinatal complication if promptly treated[21], but prolonged hypotension is associated with foetal acidosis and may cause maternal and foetal morbidity.[22]

It has been established from different studies that the BJR is potentially involved in the occurrence of SHI&B.Current studies indicate 5-HT_3

antagonism may abolish the BJR response to spinal anesthesia[23]. Therefore, many groups of clinicians working on investigating the ability of prophylactic intravenous 5-HT_3 receptors blockers or 5-HT_3 receptors antagonist to attenuate haemodynamic deranges following spinal anaesthesia. Ondansetron is a selective serotonin 5-HT_3 receptor antagonist and is approved by the FDA for treatment of nausea and vomiting caused by chemotherapy, radiation therapy and surgery. Side effects associated with the use of ondansetron include: diarrhea, headache, constipation, weakness, tiredness and dizziness.[24] The FDA has assigned ondansetron as pregnancy category B. A limited study, conducted in 176 pregnant women showed that ondansetron does not appear to be associated with an increased risk for major malformations above baseline.[25] So that ondansetron is considered as safe to give to patient. In our study ondansetron has been chosen because it is widely available, economic, already commonly given to patient to prevent nausea and vomiting with minimal side effects for the mother and has been shown to be safe with no harmful effects to the baby if given at term.[17,18,19]

Owczuk et al.[15] observed that intravenous ondansetron attenuated spinal anaesthesia induced hypotension. *Sahoo et al.*[12] found in a dose-response study that ondansetron 4 mg given intravenously 5 minutes before subarachnoid block reduced hypotension and vasopressor use in parturient undergoing elective caesarean section. Another study of *Marashi et al.*[14] showed prophylactic use of 6 mg and 12 mg intravenous ondansetron significantly attenuate SHI&B. In a recent study it has been demonstrated that ondansetron along with preloading of crystalloid infusion reduces the occurrence of hypotension following spinal anaesthesia for caesarean section.[26]

Materials & Methods:

After approval from the ethical review board this prospective randomized double blind comparative study was conducted in the department of Anaesthesiology and ICU of Dhaka medical college hospital from 1st March 2015 to 31st January 2016. 120 mothers of ASA grade I and II scheduled for elective caesarean section under spinal anaesthesia were selected on their consent and randomized into two equal groups naming Group A(n=60) and Group B (n=60) . Group A received Ondansetron IV (0.1mg/kg body wt) and group B Ephedrine (0.15 mg/kg body wt) 5 minutes prior spinal anaesthesia. Mothers having any contraindication for spinal anaesthesia, hypertensive disorder of pregnancy and known allergy to study drugs were excluded. Participant of Group A received intravenous ondansetron (0.1 mg/kg body weight) and Group B received ephedrine (0.15 mg/kg body weight).In pre-anaesthesia room clinical history was taken, gross physical examination was done and non-invasive blood pressure (NIBP), heart rate (HR), foetal Heart Rate (FHR) was recorded. Each mother received IV ranitidine (1 mg/kg) and was prehydrated with crystalloid solution (Hartmann's Solution) 20 ml/kg given over 30 minutes prior to introduce anaesthesia. In the operating room baseline values of HR, SBP, DBP and SpO2 were recorded. Five minutes prior to spinal anaesthesia prophylactic dose either of ondansetron or ephedrine was given to the parturient by the principal investigator himself according to group allocation. Spinal anaesthesia technique and perioperative monitoring was done by a second anaesthesiologist who was remain blinded to the study. After five minutes of prophylactic injection spinal anaesthesia was performed in sitting position at the level of L_{3-4} using a 25-gauge Quincke spinal needle. After confirmation of CSF flow 2.5 ml 0.5% hyperbaric Bupivacaine was administered. Patient was immediately placed in supine position with 15^0 left tilt. Upper sensory level was assessed with cold touch and surgeon was asked to proceed on surgery after confirming sensory loss at the level of T_4.Heart rate (HR), Systolic (SBP), Diastolic (DBP) and oxygen saturation (SpO_2) were recorded just after anaesthesia and at 2 minutes intervals up to 10 minutes followed by 5 minutes intervals until the end of surgery. Occurrences of nausea, vomiting and shivering were monitored, rescue medication was done accordingly and all that were recorded in data collection sheet. In the study following strategies were kept as rescue of complications:

Complication	Rescue strategy
Hypotension	Infusion of 200 ml Hartman solution immediately. If not solved then Inj. Ephedrine 5 mg IV
Bradycardia	Atropine 0.6mg IV
Nausea and vomiting	Prochlorperazine 12.5 mg IV
Shivering	Pethedine 25 mg IV

Verified and the coded data directly entered into the computer by using SPSS version19. Results were analyzed using unpaired t-test. A "P" value < 0.05 was considered statistically significant. Hypotension was defined as decrement of MAP more than 25% from the baseline (Baseline MAP calculated from three measurements taken on the ward before surgery) [25] and bradycardia was considered as heart rate less than 60 beats per minute. MAP was calculated with the formula: MAP= (2XDBP+SBP) / 3.

Results:

There were no significant differences between the groups with respect of age, gravity and ASA physical status (Table -I).

Table I *Age, Gravity and ASA status of the participants*

Parameters		Group A(n=60)	Group A(n=60)	P value
Age in years(Mean±SD)		28.6±5.82	28.6±5.82	0.349
Gravida	Primigravida	23(38.33%)	26(43.33%)	>0.05
	Multigravida	37(61.67%)	34(56.67%)	>0.05
ASA physical status	ASA I	49(81.67%)	48(80.00%)	>0.05
	ASA II	11(18.33%)	12 (20.00%)	>0.05

Data expressed as number (% of sample).

Indications for elective caesarean section showed uniform distribution between two groups (Table -II).

Table- II

Indications of elective caesarean section

Indications	Group A(n=60)	Group A(n=60)	P value
H/O previous C/S	29(48.33%)	30(50.00%)	>0.05
Malpresentation	12(20.00%)	13(21.67%)	>0.05
Short stature	02(03.33%)	00(0000%)	>0.05
CPD	03(05.00%)	02(03.33%)	>0.05
Elderly primi	05(08.33%)	06(10.00%)	>0.05
Post dated pregnancy	05(08.33%)	04(06.67%)	>0.05
Patient's desire	04(06.67%)	06(10.00%)	>0.05

Data expressed as number (%) of sample.

Coexisting diseases had no statistically significant variation (Table-III).

Table- III *Coexisting diseases of mothers*

Disease	Group A(n=60)	Group A(n=60)	P value
Diabetes Mellitus	04(06.67%)	05(08.33%)	>0.05
Bronchial Asthma	03(05.00%)	02(03.33%)	>0.05
Hypothyroidism	00(00.00%)	01(01.67%)	>0.05
Hepatitis B	01(01.67%)	00(00.00%)	>0.05
Obesity	03(05.00%)	04(06.67%)	>0.05
None	49(81.67%)	48(80.00%)	>0.05

Data expressed as number (% of sample).

Heart Rate trends higher values in Group A with significant difference (Figure-I).

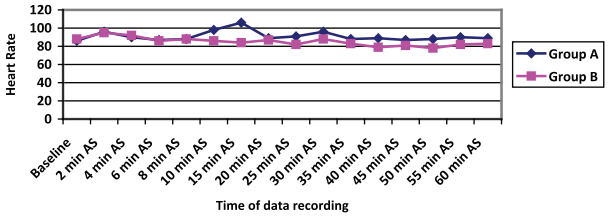

Fig.-1: *Trends of changes in heart rate (HR).AS-After spinal anaesthesia.*

Changes of mean arterial blood pressure (MBP) showed significantly lower trends in Group B than Group A within first 15 minutes of anaesthesia (Table- IV).

Table- IV: Trends in changes of MAP in study groups.

	MBP (mm of Hg)		
Time point	Group A (n=60)	Group A (n=60)	P value
Baseline	69.6 ± 8.6	68.9 ± 9.1	0.668
2 min AS	67.8 ± 7.3	61.5 ± 6.2	<0.001
4 min AS	69.5 ± 8.3	59.5 ± 4.3	<0.001
6 min AS	66.6 ± 7.5	61.5 ± 6.2	<0.001
8 min AS	67.6 ± 7.0	62.5 ± 4.2	<0.001
10 min AS	69.6 ± 7.3	67.5 ± 5.2	0.088
15 min AS	62.6 ± 7.1	55.5 ± 6.2	<0.001
20 min AS	68.0 ± 6.3	66.8 ± 6.2	0.295
25 min AS	63.6 ± 8.3	65.5 ± 6.2	0.158
30 min AS	63.6 ± 7.0	62.5 ± 5.7	0.076
35 min AS	64.8 ± 7.2	65.5 ± 6.0	0.059
40 min AS	63.0 ± 6.3	64.8 ± 6.1	0.115
45 min AS	63.4 ± 9.2	64.5 ± 8.2	0.236
50 min AS	67.6 ± 7.0	65.5 ± 4.2	0.048
55 min AS	68.5 ± 6.2	65.5 ± 5.0	0.093
60 min AS	69.8 ± 8.7	68.5 ± 9.2	0.431

Data expressed as Mean±SD, AS- After Spinal anaesthesia

Regarding complications although shivering is common for both groups, occurrence of nausea and vomiting is significantly less in group A (Table-V).

Table V *Occurrence of complications*

Complication	Group A (n=60)	Group A (n=60)	P value
Nausea	04 (06.67%)	20 (33.33%)	<0.05
Vomiting	08 (13.33%)	28 (46.67%)	<0.05
Shivering	28 (46.67%)	29 (48.33%)	>0.05

Data expressed as number of occurrence (% of sample).

Using rescue medications for complication revealed significant lower frequency in Group A except Pethedine used almost same in both groups. Use of Atropine nil in both study group(Table-VI)

Table VI *Requirement of rescue medication*

	Frequency of use		
Rescue Medications	Group A (n=60)	Group A (n=60)	P value
Hartmann solution	12 (20.00%)	28 (46.67%)	<0.001
Ephedrine	04 (06.67%)	24 (40.00%)	<0.001
Prochlor-perazine	09 (15.00%)	29 (48.33%)	<0.001
Pethedine	27(45.00%)	29(48.99)	0.211
Atropine	0	0	-

Data expressed as frequency of use (% of sample).

Discussion:

SIH&B is the most common anaesthetic problem of spinal anaesthesia and early, accurate intervention improves outcomes. Studies have revealed the effectiveness of different strategies for the prevention of these adverse effects such as pre or co-loading, use of vasopressor, positioning, compression devices etc. however a Cochrane review concluded that none of these techniques alone was sufficient in eliminating hypotension.[27] In recent years many studies have linked SIH&B to a physiological mechanism called the Bezold – Jarisch reflex (BJR), a form of vaso-vagal syncope triggered by the sympathetic blockade and resulting decreased peripheral vascular resistance.[12] Mechanoreceptor and chemo-receptors located in the left ventricular wall participate to produce this cardio-inhibitory reflex in response to hypovolaemia and results in

vasodilatation, bradycardia and hypotension.[13] These mechanoreceptors and chemoreceptors are serotonin sensitive and 5-hydroxytryptamine (5-HT_3) acts as potential factor to the induction of BJR. So that use of 5-hydroxytryptamine (5-HT_3) receptor antagonism is a potential step to inhibit BJR and thus to prevent haemodynamic changes following hypovolaemia.[3,5,13,15] Amongst 5-hydroxytryptamine (5-HT_3) antagonist Ondansetron, Granisetron, Palonosetron etc are safely used in management of various symptoms. Ondansetron was shown to attenuate arterial blood pressure drop due to spinal anaesthesia in general surgery population in a study by *Owczuk et al.*[15] and in obstetrical population by *Sahoo et al.*[12] Current study was conducted with patient undergoing elective caesarean section and compared ondansetron with ephedrine where as *Owczuk et al* .[15] and *Sahoo et al.*[12] compared ondansetron with placebo and *Ortiz-Gomez et al.*[6] studied with three different doses of ondansetron versus placebo. Our study included 120 participants which was sufficiently adequate to compare with previous studies.[6,12,16] As on the study conducted by *Owczuk et al.*[16] ondansetron (0.1 mg/kg) and ephedrine (0.15 mg/kg) was given intravenously 05 minutes prior to the administration of spinal anaesthesia. In the study, regarding the heart rate, no significant difference was detected between the groups except from 10th minute to 15th minute of spinal anaesthesia. Compared with group B, ondansetron group (Group A) showed slight but statistically significant increase in heart rate after 10 min (98, 84 beat/min respectively) and 15 min (106, 90 beat/min respectively) after spinal anesthesia. No occurrence of bradycardia observed in both groups. *Rashad et al.*[3] found 0% occurrence of bradycardia with prophylactic ondansetron and *Walid et al.*[33] observed 15% occurrence of bradycardia in a prospective randomized controlled double blind study in 2015.

In the trends of Mean arterial Pressure (MAP) change this study shows no significant difference of basal MAP between two groups but after introduction of spinal anaesthesia significant decrease in MAP in both groups with the least occurrence in ondansetron group. *Rashad et al.*[3] found significantly lower decreases of mean arterial pressure with use of ondansetron prophylactically in comparison with normal saline used as placebo ($p < 0.05$). We found statistically significant more decrease of MAP in Group B than Group A up to first 15 minutes after anaesthesia and at the 15th minute the difference was the highest (Group A- 62.6±7.1mmHg,Group-B-, 55.5±6.2mmHg, P <0.0001). Afterwards throughout the perioperative period MBP remain stable and no occurrence of hypotension observed.

In usage of rescue medications for treating hypotension there are very significant difference between ondansetron and ephedrine group. Co-loading of Hartmann solution was need for 46.67% (n=28) of group B patients whereas for 20% (n=12) of group A, this bears significant statistical difference (P<0.001). Consumption of vasopressor agent (ephedrine) was 04 % (n=04) and 40% (n=24) respectively in group A and B (P <0.001). *Walid et al.*[33] showed less consumption of ephedrine with ondansetron in comparison of placebo with a significant difference ($p < 0.001$).

This study also includes monitoring and recording of the intraoperative occurrence of nausea, vomiting and shivering. It reveals that nausea and vomiting occurred significantly higher in group B (P<0.05). *Walid et al.*[28] also reported significantly less episodes of nausea and vomiting with prophylactic use of ondansetron. *Gigillo et al.*[29] and *Gupta et al.*[30] also reported the superiority of 5-hydroxytryptamine (5-HT_3) receptor antagonist (Ondansetron, Granisetron etc.) over many others anti-emetics. Shivering remained as complication of almost similar magnitude for both of the groups. Some other studies revealed the poor efficacy of 5-hydroxytryptamine (5-HT_3) receptor antagonist in management of shivering.[29, 30]

Conclusions:

Despite practice of different strategies management of bradycardia and hypotension following spinal anaesthesia in obstetrics continues to be controversial. In the current study the efficacy of Ondansetron and Ephedrine in attenuation of haemodynamic derangements following spinal anaesthesia has been proved satisfactory with a statistically significant supremacy of the former over the later. Beside this Ondansetron bears additional advantages in the management of perioperative nausea and vomiting, although proved less effective to prevent shivering.

Limitations:

It was a single centre study. It might not reflect the overall picture of the population. Large scale study needs to be conducted to reach to a definitive conclusion. This study was conducted in ASA I and II patients of low risk group with stable haemodynamics, so that the result of this study may be extrapolated to patients with high risk.

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