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Hemodynamic Changes in Elective Cesarean Section Under Spinal Anesthesia. A Prospective randomized controlled double-blind Comparison Study with Preoperative Ondansetron Administration

Riad Tome[1,2*], Haitam Zeibak[1], Jiryis Ghantus[1], Ziad Khatib[1,2], Nashed Ibraheem[1,2] and Jawad Tome[3]

[1]The Nazareth Hospital E.M.M.S, Department of Anesthesia, Israel

[2]Bnai Z ion Medical Center, Department of Anesthesia, Former Place of work, Israel

[3]Tel Aviv Medical Center, Department of General Surgery, Israel

Introduction

In Israel over than 90% of the elective cesarean sections performed under Spinal Anesthesia (SA). However, this type of anesthesia frequently associated with side effects that primarily affect the parturient and the fetal health [1]. Nearly, 70–80% of obstetric patients experience Spinal Anesthesia-Induced Hypotension (SAIH) without pharmacological prophylaxis [2]. This hypotension is commonly accompanied with reflex tachycardia, nausea and vomiting, and in rare occasions bradycardia can be observed. Most authors agree that hypotension presents when Systolic Blood Pressure (SBP) reduced from baseline of more than 20% [3]. The main mechanism of SAIH is decreased systemic vascular resistance resulting from arterial vasodilation [4].

In addition, sympathetic nervous system blockade can decrease venous return to the right heart reducing the preload. In response, stimulation of cardiac sensory receptors in the left ventricle leads to vasodilation, bradycardia and hypotension, and this is the Bezold Jarish Reflex (BJR) [5].

Augmentation of the intravascular volume with crystalloids and vasopressors is the cornerstone of the treatment of SAIH [2]. Among vasopressors, the pure α-adrenergic receptor agonist phenylephrine has become the first-line treatment in the last years because of its efficacy to maintain the umbilical cord blood PH and the Apgar score in the neonates [6].

Ondansetron, a 5-HT3 receptor antagonist that used generally for prophylaxis and treatment of nausea and vomiting may attenuate the SAIH [7,8]. Numerous studies were performed to investigate the effect of ondansetron on SAIH, but given the relatively large heterogeneity and small sample sizes in the involved studies, further large and strict randomized clinical trials are still needed, especially among obstetric patients [9].

We hypothesized that prophylactic use of intravenous ondansetron before SA in elective cesarean section can reduce SAIH and can reduce the amount of vasopressor phenylephrine needed to control blood pressure.

The primary outcome was to compare the changes in maternal blood pressure and phenylephrine consumption between two groups of mothers undergoing cesarean section under SA, the first received ondansetron and the second received placebo. The secondary outcomes were to compare adverse effects such as bradycardia, nausea & vomiting and dizziness between the two groups, as well as the difference in umbilical cord blood pH and the Apgar score between the two groups at the first minute after delivery.

Materials and Methods

This prospective double-blind study, conducted following institutional ethical committee approval (0053-19-BNZ).

Inclusion Criteria

One hundred mothers (fifty in each group of the two study groups) of American Society of Anesthesia (ASA) physical status I or II in preoperative assessment aged between 18 and 45 years who were candidates for elective cesarean delivery under SA.

Exclusion Criteria

Mothers who have presented with hypertensive disorders of pregnancy or unstable hemodynamics and coagulation abnormality before surgery, mothers presented with cardiovascular disease or hypersensitivity to ondansetron, mothers on drugs that may cause hypotension, were excluded also mothers who converted SA to General Anesthesia (GA) were also excluded.

Group O

The Ondansetron group, fifty mothers who received 4 mg of Ondansetron intravenously diluted in 10 ml of 0.9% sodium chloride over one minute, five minutes before performing the SA.

Group P

The Placebo group, fifty parturient who received 10 ml of pure 0.9% sodium chloride

Correspondence to: Riad Tome M.D, Head of Anesthesia department, The Nazareth Hospital E.M.M.S, P.O.Box 11, Nazareth 16100, Israel, Tel: +972547672220, E-mail: riad.tome59@gmail.com

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All the mothers were in fasting for 8 hours at least before surgery. Intravenous (IV) access was established in all patients with an 18–20-gauge peripheral intravenous catheter. Premedication with IV ranitidine 50 mg and IV metoclopramide 10 mg were given one hour before surgery. Upon patient arrival to the operating room, standard ASA monitoring was connected, baseline values of pulse oximetry (SpO_2), noninvasive Blood Pressure (BP) and electrocardiogram (ECG) were recorded. Pre-hydration with Ringer's lactate infusion 1000 ml started 30 min before surgery. IV cephamycin 2 grams for antimicrobial prophylaxis was given 20 min before surgery.

SA was performed according to the institute protocol in the sitting position, after sterile preparation and skin infiltration with local anesthetic lidocaine, lumbar puncture was performed at L3-L4 or L4-L5 intervertebral space, using Whitacre pencil point 25, 27-gauge needle. After identification of the subarachnoid space by cerebral fluid outflow, 10 mg of hyperbaric Marcaine 0.5% and Fentanyl 0.02 mg were administered in the subarachnoid space. Following the subarachnoid injection patient positioned in a 15°–20° left side position. The extent of the sensory block was evaluated by pinprick test, surgery allowed to start after obtaining sensory block higher than T6 dermatomes.

Vital signs (Systolic Blood Pressure-SBP, Diastolic Blood Pressure-DBP, Mean Blood Pressure-MBP, Heart Rate-HR) were recorded at the baseline, every 1 min for the first 5 minute after SA induction and then every 5 minutes until the end of the operation (to 35 min after SA for this study). Hypotension, defined as reduction in BP from baseline of more than 20 %, which treated with repeated doses of (50 mcg) intravenous phenylephrine and the total requirements of phenylephrine consumption after SA were recorded. Bradycardia, defined as heart rate drop less than 50 beats per minute which treated with single doses of IV Atropine sulfate 0.5 mg was recorded.

Episodes of nausea, vomiting and dizziness were recorded.

Umbilical venous blood gas PH and Apgar score assessed by pediatrician at the first minute after delivery for all the neonates were also recorded.

Power Analysis

For this study with a primary outcome defined as changes in maternal blood pressure. The power analysis was performed using the G*Power version 3.0.10 freeware (Franz Faul, University of Kiel, Germany) http://www.gpower.hhu.de/. To calculate sample size with a power of 0.8that demonstrate a difference of 20% or more in blood pressure as statistically significant ($\beta = 0.2$, $\alpha = 0.05$), we took a sample size of 45 women per group. Considering 10% unexpected exclusion we recruited 50 women in each group.

Statistical Analysis

Statistical analysis was performed using the STATA 12.0 software, (Stata Corp. 2011. Stata Statistical Software: Release 12. College Station, TX: Stata Corp LP.USA)

Vital signs variables (SPB, DBP, MBP, and HR) repeated measurements in eight time periods every 5 minutes (baseline, 5, 10, 15, 20, 25, 30, 35minutes post SA), means, standard deviations and 95% of C.I. (Confidence Interval) were calculated. The results at each period of time between the two study groups were analyzed by the 2 sample T-test for differences of mean. The comparisons of results in each of the two study groups between the eight time periods were analyzed by the repeated measurements anova model with the Greenhouse-Geisser correction factor.

The results of the frequencies of women who received at least one dose of phenylephrine post SA between the two study groups were analyzed by chi square test. The results of total amount of phenylephrine received by patients post SA, between the two study groups were analyzed by the rank sum test (a non-parametric test).

For the results of intraoperative complications of bradycardia, nausea & vomiting and dizziness, numbers and percentages were calculated. The distributions for the categorical variables between the two study groups were compared and analyzed by the Chi square test or by Fisher-Irwin exact test (a non-parametric test for small numbers).

For demographic and clinical data of age and fetal pH, means and standard deviations were calculated. The results between the two study groups were analyzed by the 2 sample T-test for differences of mean.

For the results of ASA and Apgar levels, numbers and percentages were calculated. The distributions for the categorical variables between the two study groups were compared and analyzed by Fisher-Irwin exact test

All statistical tests were analyzed to a significance level of 0.05.

Results

The demographic data (Age, ASA) are presented in Table 1. There were no significant differences between the two study groups ($p > 0.05$).

There was no statistical difference in maternal blood pressure (SBP,DBP,MBP) between the two study groups at the eighth time periods of the study ($P > 0.05$), however there was statistically difference within each group between the eight time periods and between baseline and minute 35 in the same group (min 0 vs min 35) ($P < 0.05$) Figure 1.

Phenylephrine requirements, more doses of phenylephrine were administered in the group P compared to group O. Quarter of the mothers (12 women, 24%) in the group O compared to half of the mothers (25 women, 50%) in the group P, received at least one dose (50 mcg) of phenylephrine during the 35 minutes post SA (P =0.007). From the other side, no difference was observed in the total amount of phenylephrine dose between the two groups ($P > 0.05$), group O (mean ± SD 96 ± 58 mcg / median 100) VS group P (mean ± SD120 ± 75 mcg / median 100) Table 2.

Heart Rate and Bradycardia, comparing the HR at the eight time periods between the two study groups, there were no significant differences ($P > 0.05$). In addition, the difference in HR between baseline and 35 minutes post SA in each one of the groups was also not statistically significant ($P > 0.05$) Figure 2.

The incidence of bradycardia was similar between the two study groups, 3 patients (6%) in group O and 5 (10%) in the group P, received one dose (0.5 mg) of IV Atropine during the 35 minutes post SA ($P > 0.05$).

Adverse Events Analysis

During the 35 minutes post SA, in group P there were more events of nausea and vomiting (46%) of the mothers compared to only about a sixth(18%) in the group O. Incidence of dizziness during the 35 minutes post SA induction between the two groups was almost similar ($P > 0.05$) Table 3.

Fetal health outcome, a significantly higher mean of umbilical cord blood pH was recorded in group O. Mean pH of umbilical cord blood was 7.31 in group O and 7.27 in group P ($P < 0.05$).

Table 1: Demographic data

	Group O (n = 50)	Group P (n = 50)	*P* value
Age (years)	31.6 ± 6.0 [17-55]	31.7 ± 4.5 [24-44]	ᶴ0.9253
ASA			
1	32 (64.0)	33 (66.0)	⊥0.8330
2	18 (36.0)	16 (32.0)	
Not Determined		1 (2.0)	

Data are mean SD and [range] or numbers (%)
ᶴ 2- sample T-test
⊥ *Fisher* exact test

Table 2: Phenylephrine requirements by study group

		Group O N = 50	Group P N = 50	*P* value
Parturient received medication	number (%)	12 (24)	25 (50)	ᛒ0.0070*
Total amount (mcg)	median	100	100	
	mean SD	96 ± 58	120 ± 75	ᛋ0.4439**
	95% C.I.	[59-133]	[89-151]	

*Data are numbers (%), *P* value by ᛒchi square test;
**P value between two study groups by ᛋ Wilcoxon ranksum test

Table 3: Adverse events by study group during the 35 minutes post SA induction

	Group O (n = 50)	Group P (n = 50)	ᛒ*P* value
Nausea and Vomiting Number of parturient with at least one event in 35 min	9 (18)	23 (46)	0.0060
Dizziness Number of parturient with at least one event in 35 min	14 (28)	20 (40)	0.2050

Data are numbers (%)
P value between the two study groups by ᛒchi square test

Table 4: Fetal Health data by study group

	Group O (n = 50)	Group O (n = 50)	*P* value
APGAR			
10	36 (72.0)	33 (66.0)	⊥0.3310
9	14 (28.0)	14 (28.0)	
8		3 (6.00)	
Umbilical cord blood pH	7.31 ± 0.04 [7.2-7.4]	7.27 ± 0.06 [7.1-7.4]	ᶴ0.0006

Data are mean SD and [range] or numbers (%); *P* value between the two study groups by ᶴ 2- sample T-test for differences of mean or ⊥Fisher exact test

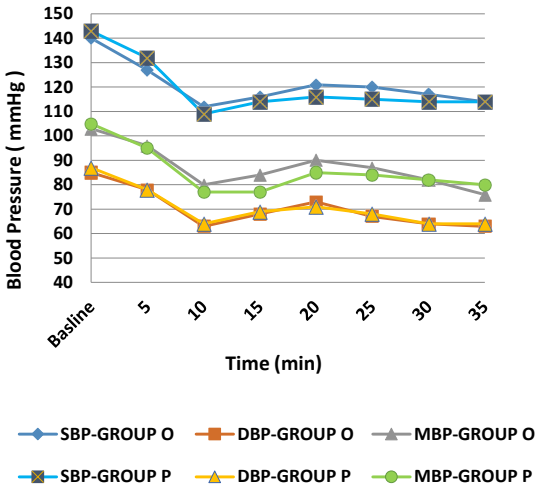

Figure 1. Peri-Operative SBP, DBP and MBP
SBP-systolic blood pressure, DBP-diastolic blood pressure, MBP-mean blood pressure.
Group O - received ondansetron, group P - received placebo.
Measurements of maternal blood pressure in each one of the two study groups, repeated at the eight time periods.
Data are mean.

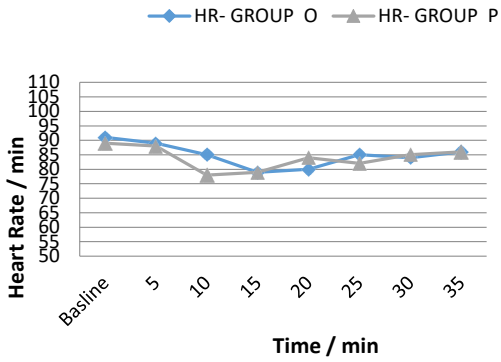

Figure 2. Peri-Operative HR
HR- heart rate.
Group O- received ondansetron, group P - received placebo.
Measurements of heart rate in each one of the two study groups, repeated at the eight time periods.
Data are mean.

Similar APGAR score was observed at the first minute after delivery in the two study groups ($P > 0.05$) Table 4.

Discussion

This prospective study, detected the effect of prophylactic ondansetron on SAIH incidences and phenylephrine consumption in mothers gave birth under SA indicates that prophylactic ondansetron does not decrease the incidence of SAIH directly after SA, however, it decreases the need for vasopressor (reduction in the number of mothers who required phenylephrine for the treating SAIH) and that means clearly but indirectly that prophylactic ondansetron may mitigate the risks of SAIH.

Prophylactic ondansetron administration before SA in obstetric patients to prevent SAIH is still conflicting. Previous studies have demonstrated its efficacy in prevention SAIH in obstetric patients but those studies were with small samples size [7,8]. Gao, et al. meta-analysis suggests that prophylactic ondansetron reduces both the incidence of SAIH and vasopressor consumption in both obstetric and non-obstetric patients, but there was a large heterogeneity and small samples size in the involved studies [9]. Another meta-analysis of Heesen, et al. also showed moderate effect in reducing the incidence of SAIH and bradycardia in obstetric patients but in that analysis, studies with different types of 5-HT3 antagonists were involved [10]. In contrast, other studies showed that prophylactic ondansetron may had very little effect, if any, on the incidence of SAIH in healthy mothers undergoing SA [11]. Terkawi, et al. showed that ondansetron premedication does not attenuate hemodynamic changes after SA nor does it reduce the amount of vasopressor use, pruritus, or nausea and vomiting [12]. Tubog, et al. conducted a systematic review and found that intravenous ondansetron may mitigate the risks of SAIH and bradycardia following SA [13].

In this context, our study has a larger sample size (100 mothers records) that detected the effect of prophylactic ondansetron on attenuation of SAIH and phenylephrine consumption in mothers gave birth under SA. We suggest our results indicate that ondansetron may attenuate BJR, produced by left ventricular mechanoreceptors stimulated by 5-HT, and can inhibit further expansion of peripheral blood vessels, augment venous return to the heart and result in less consumption requirement of vasopressor phenylephrine which means clearly but indirectly that prophylactic ondansetron may mitigate the risks of SAIH.

Prophylactic ondansetron that might cause BJR inhibition has been proposed to explain the reduction in perioperative bradycardia accompanied with hypotension after SA [3,14]. In the present study, we did not observe a significant difference in the incidence of bradycardia between the two study groups. The possible reasons may include the study design, doses of ondansetron, anesthetics (local and opioid) used for SA, or the vasopressor used (phenylephrine), which approximately affecting bradycardia in 10% of the mothers receiving this vasopressor [15]. Further studies still needed to evaluate this relation.

It is well known that ondansetron can reduce incidence and severity of post-operative nausea and vomiting (PONV) after SA [16,17], but there is restricted data on the intraoperative nausea and vomiting (IONV). In this study, we noted that mothers received ondansetron had significantly less incidence of IONV. One possible explanation for IONV attenuation may be that ondansetron can block part of the hemodynamic depression of SA by inhibition of BJR, that augment venous return to the heart, and can result to less reduction in cerebral hypo perfusion, and it is well known that cerebral hypo perfusion may activate vomiting centers in the medulla [18].

In this study, umbilical artery pH values were higher in group O, however no statistical difference was observed in APGAR score at the first minute after delivery. Trabelsi, et al. [19] showed that ondansetron can be helpful in improving metabolic acidosis, however, the exact reason is yet unknown for this result. Further studies still be needed to establish this assumption.

Limitations

There are some limitations to the study, subgroup analysis on different ondansetron doses, was not included, neither other factor such as anesthetic drugs and doses, and fluid type and volume. No safety data with respect to the side effects of ondansetron such as shivering, headache, electrocardiographic changes or acute myocardial ischemia, and no comparison analysis of the risk-benefit balance between the possible benefits of ondansetron versus its potential side effects.

Conclusion

The study illustrates that prophyl acticondansetron 4 mg, administered IV, five minutes before SA, although it did not attenuate SAIH directly, but it decreased significantly the need for the vasopressor phenylephrine, which means clearly but indirectly that prophylactic ondansetron can mitigate the risks of SAIH.

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