The influence of intravenous ondansetron on maternal blood haemodynamics after spinal anaesthesia for caesarean section: a double-blind, placebo-controlled study

Wpływ ondansetronu na parametry hemodynamiczne matki podczas znieczulenia podpajęczynówkowego do cięcia cesarskiego – badanie randomizowane, przeprowadzone metodą podwójnie ślepej próby

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Abstract

Objective: *verification of a hypothesis assuming that 5-HT3 receptor blockade by intravenous administration of ondansetron reduces the incidence of hypotension and bradycardia in patients undergoing spinal anaesthesia for Caesarean section.*

Material and methods: *The study design was approved by the Bioethics Committee and included 72 patients undergoing elective Caesarean section, randomly assigned to ondansetron group (group O) or placebo group (group P). Finally, group O encompassed 35 patients administered ondansetron 8 mg i.v. dissolved in 10ml 0.9% NaCl whereas group P consisted of 34 patients receiving 0.9% NaCl 10 mg. Systolic and diastolic pressures were measured every 2 minutes since the onset of anaesthesia. Heart rate (HR) was monitored continuously. The criterion of hypotension requiring ephedrine was a decrease in systolic pressure by 20% compared to its baseline value or a decrease in systolic pressure below 90 mm Hg. The criterion of bradycardia was a decrease in HR below 60/min.*

Results: *Hypotension was observed in 14 group O patients (39%) and in 15 group P patients (44%); the difference was not statistically significant. Bradycardia was noted in 1 group O patient (3%) and in 2 group P patients (6%); the difference was not statistically significant.*

Conclusion: *A hypothesis assuming a reduction in pressure following subarachnoid anaesthesia for Caesarean section after the administration of 8 mg of ondansetron was not confirmed.*

Key words: **ondansetron** / **spinal anaesthesia** / **caesarean section** / **hypotension** /

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Streszczenie

Cel pracy: *weryfikacja hipotezy zakładającej, że blokada receptorów 5-HT3 poprzez dożylne podanie ondansetronu redukuje częstość występowania hipotensji i bradykardii u pacjentek znieczulanych podpajęczynówkowo do cięcia cesarskiego.*

Materiał i metodyka: *Plan badań uzyskał zgodę komisji bioetycznej. Do badania zakwalifikowano 72 pacjentki poddawane planowemu cięciu cesarskiemu, losowo przydzielając je do grupy ondansetronu (grupa O) lub grupy placebo (grupa P). Ostatecznie grupa O liczyła 36 pacjentek, którym przed znieczuleniem podano dożylnie 8 mg ondansetronu rozcieńczonego w 10 ml 0,9% NaCl, grupa P liczyła 34 pacjentki, które otrzymały 10 ml 0,9% NaCl. Pomiaru skurczowego i rozkurczowego ciśnienia tętniczego krwi dokonywano co 2 minuty od momentu znieczulenia. Częstość akcji serca (HR) monitorowana była w sposób ciągły. Za kryterium hipotensji wymagającej podania efedryny przyjęto spadek ciśnienia skurczowego o 20% w porównaniu z ciśnieniem wyjściowym lub spadek ciśnienia skurczowego poniżej 90 mm Hg. Za kryterium bradykardii przyjęto spadek akcji serca poniżej 60/min.*

Wyniki: *Hipotensję zanotowano u 14 pacjentek w grupie O (39%) i u 15 pacjentek w grupie P (44%) co nie stanowiło statystycznie istotnej różnicy. Bradykardię zanotowano u 1 pacjentki w grupie O (3%) i u 2 pacjentek w grupie P (6%) co nie stanowiło statystycznie istotnej różnicy.*

Wnioski: *Nie potwierdzono przyjętej hipotezy zakładającej redukcję spadku ciśnienia po znieczuleniu podpajęczynówkowym do cięcia cesarskiego po podaniu 8 mg Ondansetronu.*

Słowa kluczowe: **ondansetron /znieczulenie podpajęczynówkowe /cięcie cesarskie / / hipotensja /**

Introduction

Caesarean section is the most common gynaecological and obstetric procedure that many authors call „the Caesarean section epidemic" [1]. The anaesthetic procedure most frequently performed for Caesarean section is spinal anaesthesia. When administered by an experienced anaesthesiologist, the method is safe although associated with side effects and possible complications. Fortunately, life-threatening neurological complications are extremely rare [2]. The crucial Caesarean section-related problem, which has not been solved, is hypotension. Currently, block anaesthesia (spinal anaesthesia in particular), is the predominant anaesthesia technique for Caesarean sections. However, extensive sympathetic blockage occurring during spinal anaesthesia, together with the aorto-venous syndrome, markedly contributes to decreased arterial blood pressure and bradycardia in mothers, which can lead to clinical symptoms, such as general malaise, nausea, vomiting or dyspnoea. Hypotension can also result in reduced blood flow through the placenta in the uterus and a worse neonatal birth status [3]. In non-obstetric patients, the hypotension and bradycardia incidence rates have been reported to be 33% and 13%, respectively [4]. Depending on the prophylactics used, the hypotension incidence rate in patients undergoing spinal anaesthesia for Caesarean sections ranges from 12.5% (according to a French study) to 85% (according to the Riley findings) [5, 6]. The bradycardia incidence in obstetric patients is substantially lower; however, in a study by Somboonviboon, which included 722 female patients, the bradycardia incidence was found to be 2.5% [7].

Bradycardia can result from parasympathetic system dominance, increased baroreceptor activity or the Bezold-Jarisch reflex (BJR) [8]. BJR is triggered by mechanoreceptor and chemoreceptor stimulation. Mechanoreceptors located in the heart walls are stimulated by the mechanical cardiac cavity deformation caused by changes in blood pressure and volume. Serotonin released by activated thrombocytes is actively involved in chemoreceptor stimulation [9, 10, 11].

Animal studies have demonstrated that serotonin can be a relevant factor triggering BJR via 5-HT_3 receptor activation, leading to hypotension and bradycardia [12, 13]. According to a non-obstetric patient study carried out by Owczuk and a obstetric Caesarean section patient study by Sahoo, intravenous ondansetron, a 5-HT_3 receptor antagonist, administered prior to spinal anaesthesia reduced the patient hypotension incidence rates and decreased their systolic and mean arterial pressures [14, 15].
The aim of the present study was to verify the hypothesis that 5-HT_3 receptor blockage by intravenous ondansetron reduces the hypotension and bradycardia incidence rates in patients undergoing spinal anaesthesia for Caesarean section.

Aim of the study

The aim of the present study was to verify the hypothesis that serotonin type 3 receptor blockage by intravenous ondansetron administration could reduce the spinal anaesthesia-induced hypotension and bradycardia incidence rates in patients undergoing Caesarean section

Material and Methods

The Medical University of Gdańsk Independent Bioethics Committee for Scientific Research approved the study design, which. encompassed ASA I and II patients undergoing elective Caesarean sections due to cephalopelvic disproportion, post-C-section condition, gluteal position, ophthalmic indications and those without medical indications (i.e., Caesarean section on demand). The exclusion criteria included lack of consent for participation in the study, block anaesthesia contraindications and one or more of the following: multiple pregnancies, body weight >115 kg, height <152 cm, age under 18 years and over 40 years, diabetes mellitus, pregnancy-induced hypertension, chronic hypertension, cardiac diseases and use of selective serotonin reuptake inhibitors.

Patients were randomly assigned to two groups; one group received 8 mg of intravenous ondansetron (Zofran®,

GlaxoSmithKline Manufacturing S.p.A., Parma, Italy) (group O), and the other group received 10 ml of isotonic sodium chloride (placebo group – P). The randomisation was generated using the Internet website http://randomisation.com. The syringe content was administered over 1 minute, 5 minutes before the spinal anaesthesia was given. The anaesthetist preparing the solution was on call and the second anaesthetist that injected the solution was blinded.

Each patient was examined using a standard anaesthesiological protocol. Prior to their transfer to the operating room, the patients orally received 30 ml of 0.3 M sodium citrate to prevent aspiration pneumonia. In the operating room, the systolic and diastolic arterial pressures (SAP-3- and DAP-30, respectively) were measured. The mean arterial pressure (MAP-30) was calculated according to the following formula: MAP = (1/2 x systolic arterial pressure + 2/3 diastolic arterial pressure).

The measurements obtained were accepted as the baseline values. Subsequently the peripheral vein was cannulated and 6% HES 10 ml/kg (Voluven) was initiated. After the transfusion, each patient was injected the syringe content prepared by that anaesthesiologists who were not involved in the study. Five minutes later, patients underwent spinal anaesthesia in the sitting position using the 27 G pencil-point needle. The puncture was performed at L_3-L_4 or L_4-L_5. The bupivacaine dosages (Marcaine® Spinal 0.5% Heavy, Astra-Zeneca) were tailored to each patient's height (152 to 160 cm – 1.8 ml, 161 to 170 – 2.0 ml and above 170 – 2.2 ml). Additionally, the local anaesthetic was supplemented with 15 µg of fentanyl (Fentanyl, Warsaw Pharmaceutical Works, Polfa S.A.). After the drug administrations, the patients were immediately placed in the supine position with a 15° left table tilt. The block range was determined by assessing the height where cold sensation lacked. The procedure was initiated once the Th_4 anaesthesia level was achieved. After the delivery, the patients did not receive any fluids; however, the possible arterial pressure decreases were corrected with fractionated intravenous ephedrine doses (10 mg). In the bradycardia cases, 0.5 mg of atropine was administered. Additionally, 40% of the patients received oxygen through a facemask until the foetus was extracted, and after the extraction, 5 units of IV oxytocin were delivered.

After the anaesthesia (T0) was provided, the arterial pressure was measured every 2 minutes (e.g., T2, T4, and T6). The HR and non-invasive haemoglobin oxygen arterial blood saturation measurements were monitored continuously (Cardiocap II, Datex-Ohmeda). A 20% decrease in systolic pressure compared with the baseline value, or a decrease in systolic pressure below 90 mm Hg was considered as a hypotension requiring ephedrine. Moreover, a HR below 60/min was assumed as bradycardia. The Apgar score was determined at 1 and 5 minutes, and the baby's weight was measured immediately after the transfer to the Neonatology Department. After clamping and cutting of the placenta, the umbilical vein was injected. Moreover, 2 ml of blood was sampled with heparinised syringes (A-Line, Becton, Dickinson), and the acid-base balance was measured instantly after the blood sampling in an analyser situated within the "labour and delivery suite". Additionally, a pH < 7.2 was considered as acidosis.

Moreover, the following times were measured: 1.) Between anaesthesia and delivery (T1); 2.) Between surgery onset and extraction (T2); and 3.) Between uterus incision and extraction (T3).

Statistical analyses

Minimal patient number in each study group was calculated based on the data from the pilot study in 15 patients anaesthetized for caesarean section, in whom MAP drop (difference between the initial value and the minimal value recorded within 20 minutes after the block) was 20 ± 7 mm Hg. Previously mentioned patients from the initial study were treated with the same methodology as patients from the placebo group in the presented study. Intergroup differences in MAP drop of 25% were assumed to be clinically significant. With this assumption, 80% test power and α level of 0.05, 34 patients were needed in each study group. Final patient number was 36 per group due to potential patient dropouts.

Statistical analyses was performed using the Statistica 10.0 PL software (StatSoft Inc., Tulsa, OK, USA). The Student's *t* test for independent variables was used for comparing results (after verification of homoscedasticity with the Levene test). The chi-square and Fisher exact tests were also used if necessary. Multiple comparisons were performed using a 2-way analysis of variance (ANOVA) test for repeated measurements, and the post-hoc HSD Tukey test in justified cases. $P < 0.05$ was adopted as a significance cut-off.

Results

Demographic data

This study involved 72 patients, whereby 36 patients were included in 2 groups. Two patients received intravenous opioids due to insufficient anaesthesia and were excluded from further analysis. Ultimately, 36 patients were included in the ondansetron group and 34 in the placebo group. The demographic data are presented in Table I. No statistically significant intergroup differences were found regarding age, body weight, height and gestational week.

The anaesthesia, procedure and newborn characteristics

There were no statistically significant intergroup differences between the number of anaesthetised segments above S1 at minute 5 and 10 (Figure 1). Moreover, the T1, T2 and T3 durations were not significantly different between the two groups (Table II). The newborn characterisation parameters are presented in Table III. The Apgar score of one newborn in the placebo group and two neonates in the ondansetron group was 7 at 1 minute. At 5 minutes, the Apgar score of all newborns was 8 or more. None of the babies had acidosis. Furthermore, there were no statistically significant differences regarding anaesthesia–associated side effects between the groups (Table IV).

Haemodynamic parameters

The SAP, DAP, MAP and HR changes, which were determined at individual measurement points, are listed in figures 2, 3, 4 and 5. Decreased SAP, DAP and MAP values, compared with the baseline values, were observed in both groups, whereas HR remained unaltered in the placebo group but was significantly changed in the ondansetron group. The intergroup SAP, DAP, MAP and HR changes were not found to be statistically significant. The SAP, DAP, and MAP baseline value comparisons, with the respective to the minimum values, are presented in Figure 6, 7, 8; however, no statistically significant differences were observed between the groups.

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Table I. Demographic, obstetric and surgical data.

	Ondansetron Group	Placebo Group	P
	n=36	n=34	
Age (years)	32.5±443	3.1±3,62	0.64
Weight (kg)	77.4±8.99	77.6±8,54	0.96
Height (cm)	166±5.30	165.6±3,79	0.36
Gestational Age (weeks)	39.3±0.73	39.3±0,78	0.86

Data are presented as the mean ± SD

Table II. Surgical data.

	Ondansetron Group	Placebo Group	P
The time from anaesthesia administration to delivery T1 (min)	12.8±2.97	11.5 ±2.60	0.13
The time from skin incision to delivery T2 (min)	5.2 ±2.0	4.8 ±1.90	0.46
The time from uterine incision to delivery T3 (min)	49.5 ±19.63	51.2 ±28.30	0.81

Data are presented as the mean ± SD

Table III. Neonatal outcome data.

	Ondansetron Group	Placebo Group	P
Apgar score 1 min[a]	10 (7-10)	9.5 (7-10)	0.98
Apgar score 5 min[a]	10 (8-10)	10 (9-10)	0.41
Weight (g)[b]	3454±362.1	3391±313.5	0.53
pH - V[b]	7.36±0.03	7.34±0.03	0.07

[a] Data are presented as medians (min-max)
[b] Data are presented as means ± SD

Table IV. Side effects.

	Ondansetron Group	Placebo Group	p
Vasopressor use	14 (39%)	15 (44%)	
Bradycardia	1 (3%)	2 (6%)	0.609
Nausea	4 (11%)	4 (12%)	1.0
Vomiting	1 (3%)	0 (0%)	1.0
Dyspnoea	0 (0%)	1 (3%)	1.0
Pruritus	9 (25%)	9 (27%)	1.0

Data are presented as n (%)

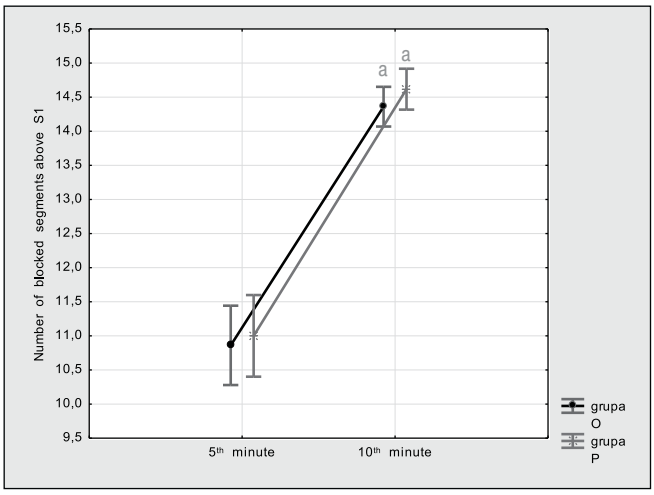

Figure 1. The blockade distribution of the number of anesthetised segments above S1. Data includes the means and 95% confidence intervals.
a – P < 0.0005 when compared with the baseline values.

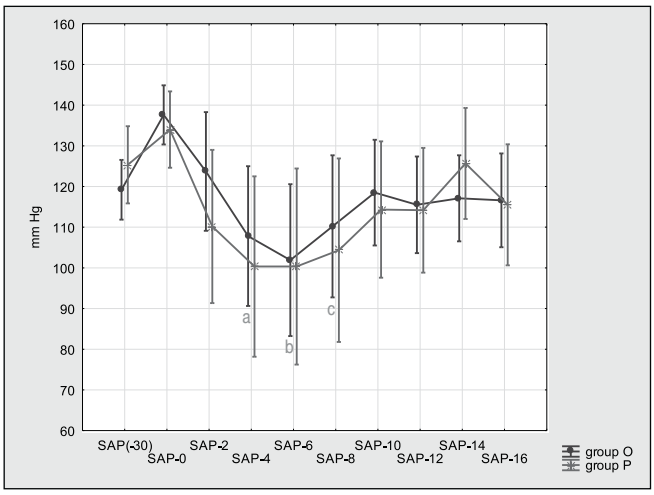

Figure 2. The systolic arterial pressure over time. The maternal systolic pressure was measured over sixteen minutes following spinal anaesthesia in Groups O and P.
a – P < 0.01 when compared with the (-30) min. group O value; b – P < 0.0005 when compared with the (-30) min. group O value; c – P < 0.05 when compared with the (-30) min. group O value.

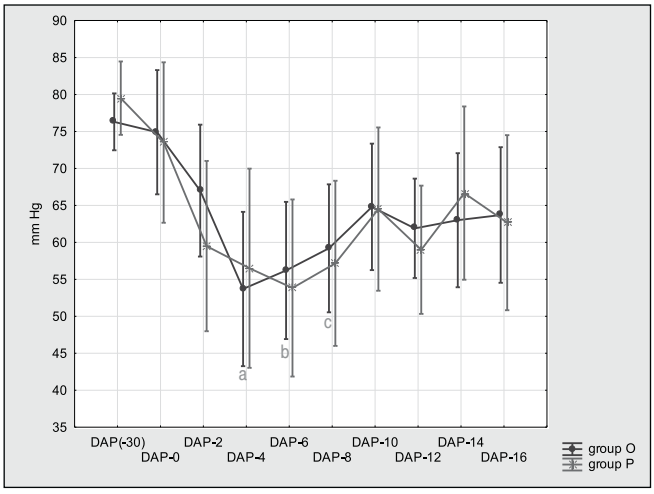

Figure 3. The diastolic arterial pressure over time. The maternal systolic pressures were measured over sixteen minutes following spinal anaesthesia in Groups O and P.
a – P < 0.0005 when compared with the (-30) min. group O value; b – P < 0.005 when compared with the (-30) min. group O value; c – P < 0.05 when compared with the (-30) min. group O value.

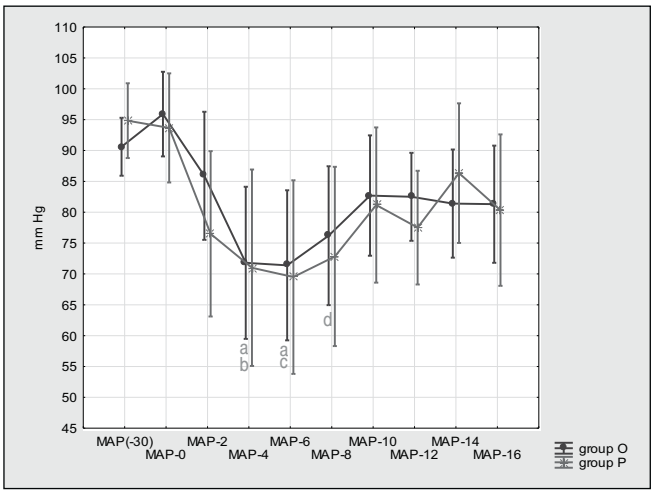

Figure 4. The mean arterial pressure over time. The maternal systolic pressures were measured for sixteen minutes following spinal anaesthesia in Groups O and P. a – P < 0.05 when compared with the (-30) min. group O value; b – P < 0.001 when compared with the (-30) min. group O value; c – P < 0.0005 when compared with the 0 min. group O value; d – P < 0.05 when compared with the 8 min. group O value.

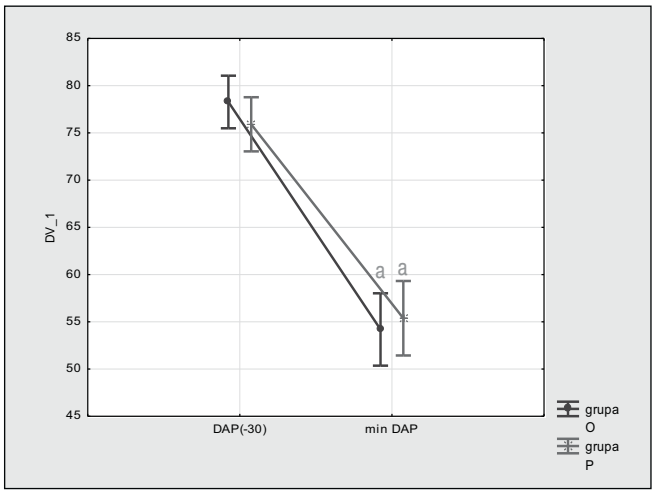

Figure 7. The initial and minimal DAP value comparisons during the study. a – P < 0.0005 when compared with the (-30) min. SAP value in the same group.

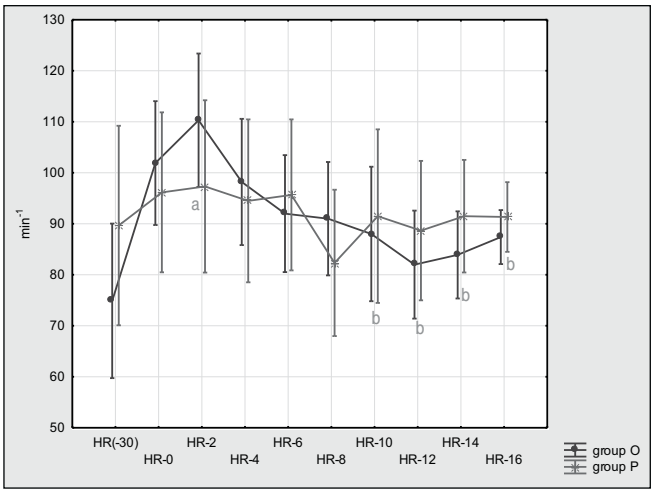

Figure 5. The changes in heart rate during the study. a – P < 0.0005 when compared with the (-30) min. group O value; b – P < 0.05 when compared with the 2 min. group O value.

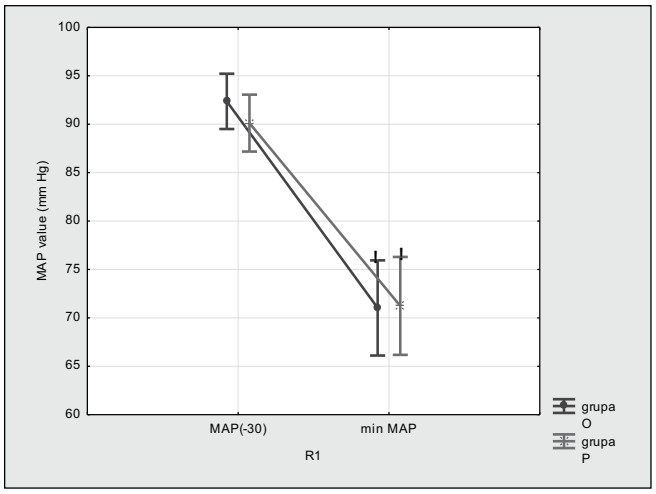

Figure 8. The initial and minimal MAP value comparisons during the study. a – P < 0.0005 when compared with the (-30) min. SAP value in the same group.

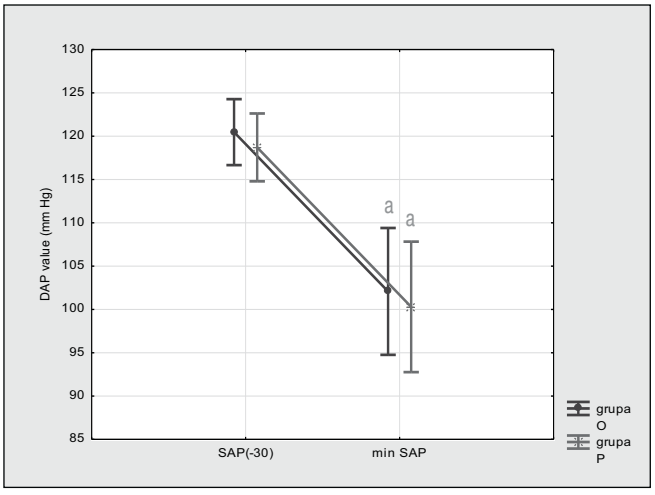

Figure 6. The initial and minimal SAP value comparisons during the study. a – P < 0.0005 when compared with the (-30) min SAP value in the same group.

Hypotension was observed in 14 ondansetron and 15 placebo patients (39% vs. 44%, respectively); however, the percentage of hypotensive patients between the groups was not statistically significant (p=0.84). Bradycardia, which required atropine, was noted in one ondansetron and 2 placebo patients (2.8%vs. 5.9%); however, this difference was also not significant (p=0.61). Additionally, the differences in SpO2 between the groups were also not found to be statistically significant.

Discussion

Attempts to find effective measures to prevent hypotension were vividly called by Alison Macarthur, "the quest for the Holy Grail", in obstetric anaesthesia [16]. The effects of intravenous crystalloid and colloid transfusions, vasoconstrictor administration (mainly ephedrine and phenylephrine) as well as physical methods, such as elevation or bandaging of the lower limbs, were compared in various combinations [17].

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These literature data and clinical observations confirm that despite combined use of preventive measures and conventional treatments, hypotension accompanying central anaesthesia continues to be the unsolved problem [18, 19].

5-HT_3 receptor antagonists have been mainly used by anaesthesiologists for postoperative nausea and vomiting (PONV) prevention and treatment [20, 21, 22]. Based on the results of the studies carried out by Owczuk and Sahoo, 5-HT_3 receptor antagonists are considered as drugs capable of preventing spinal anaesthesia-induced hypotension. The BJR mechanism of action is implicated as one of the possible causes of severe bradycardia and hypotension during spinal anaesthesia. Extensive sympathetic blocks lead to a decrease in vascular resistance and peripheral vasodilatation with blood redistribution to the visceral circulation and lower limbs [9]. The above changes and compression of the gravid uterus on the superior vena cava result in a reduced preload and BJR triggered by cardiac cavity mechanoreceptor of activation [23]. According to animal studies, 5-HT_3 receptor blocks substantially alleviate the symptoms associated with BJR that are triggered by various factors [24, 25]. Based on the above studies, Tsikouris et al. demonstrated that granisetron, a 5-HT_3 receptor blocker, decreases the fluctuations in heart rate that develop during the titling test, which are likely to be caused by BJR [26]. According to a study published by Owczuk and colleagues, in non-obstetric patients that were administered spinal anaesthesia, significantly lower minimum MAP and DAP values were observed during the first 20 minutes in a group receiving 8 mg of ondansetron compared with a placebo group [14]. Sahoo and colleagues studied Caesarean section patients receiving spinal anaesthesia, and observed lower hypotension incidence rates and lower phenylephedrine amounts were required in a group receiving 4 mg of ondansetron 5 minutes prior to anaesthesia compared with a placebo group. Additionally, hypotension was noted in two ondansetron patients (7.7%) and in 11 placebo group patients (42.3%) [15].

Our study did not confirm the findings of Sahoo and colleagues, which may have been the result of differences in the methods used. In their study, patients were prehydrated with 20 ml/kg of Ringer's solution; moreover, their hypotension criterion was a drop in systolic arterial pressure below 90 mmHg or a drop in the diastolic arterial pressure below 60 mmHg. The different hypotension criteria assumed by various authors markedly hinders the comparison of study results. Cyna and colleagues demonstrated 16 hypotension criteria in their 2009 meta-analysis, and Klöhr et al., who analysed studies regarding hypotension during Caesarean sections published between 1999-2009, found 15 various hypotension definitions [17, 27]. The lack of intergroup haemodynamic parameter differences can be attributed to the hormonal changes that occur during pregnancy and their effects on serotonin levels and the serotonin receptor sensitivity. Unfortunately, the majority of studies regard the effects of oestrogen, whose level increase during pregnancy and rapidly decrease after delivery, on 5-HT_{1A} receptor sensitivity that are located in the synaptic cleft and consequently on post-synaptic 5-HT_{1A} receptor desensitisation [28-30]. The available literature does not include any publications on the effects of oestrogen on 5-HT_3 receptors. Moreover, pregnancy can also affect serum serotonin levels, which has been demonstrated by Gall and Carrasco [31, 32]. According to their findings, serotonin levels in the observed pregnant women were markedly higher than those noted in the non-pregnant individuals.

In this report, the results of 2 methods are presented. In first method, the values determined at each time measurement point of the study and the minimal values recorded within the time between anaesthesia and delivery (T1) were compared. The second method originated from the fact that the spinal blockade dynamics were individually differentiated, thus the autonomic blockade onset time and its intensity may have been different in each patient. The above differences may have an impact on the average values obtained at the same measurement time point; therefore, two result presentation methods are required, which include the presentation of the minimum determined parameter values.

Our study findings do not confirm the hypothesis that a decrease in pressure following spinal anaesthesia for Caesarean section occurs after an 8 mg ondansetron administration. Further studies are needed to analyse higher acceptable ondansetron dosages.

Competing interests

No external funding and no competing interests are declared.

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