

Effect of Ondansetron on Spinal-Induced Hypotension by Using Bupivacaine - Dexmedetomidine Mixture Intrathecally for Percutaneous Nephrolithotomy

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ABSTRACT

Background: Percutaneous nephrolithotomy surgery (PCNL) is preferably performed under spinal anesthesia (SA). Bezold-Jarisch reflex (BJR), is mediated by serotonin receptors (5-HT₃) located on the vagus nerve and within the wall of the cardiac ventricles, contributes to the occurrence of hypotension and bradycardia after SA. Ondansetron; an antiemetic drug was investigated as a 5-HT₃ antagonist for inhibition of BJR.

Aim of the work: This study aims to assess the effect of Ondansetron on spinal-induced hypotension during PCNL surgery under SA. **Patients and Methods:** This prospective randomized double-blinded study included eighty-four patients scheduled for PCNL under SA in Urology and Nephrology center, Mansoura University. Patients were randomized into two equal groups: Group C (n=42 cases) and Group O (n=42 cases) which received IV ondansetron 4mg 5 minutes before SA.

Results: No statistical difference regarding basal characteristics, perioperative SBP, DBP, the incidence of intraoperative hypotension, the required dose of ephedrine, frequencies of hypotension, and duration of each hypotensive episode was detected in our study. **Conclusions:** in our study, ondansetron 4mg IV 5 minutes before spinal anesthesia in cases of PCNL under SA using a bupivacaine-dexmedetomidine mixture didn't reduce the incidence of hypotension and didn't reduce the required dose of ephedrine

Keywords: Spinal-Anesthesia-hypotension-PCNL-Ondansetron.

INTRODUCTION

PCNL surgery is an effective procedure in cases of large renal stones, which can be done under different modalities of anesthesia either spinal, general, or local anesthesia^(1,2). However, SA-induced sympathetic blocking results in vasodilatation leading to a subsequent drop in arterial blood pressure.⁽³⁾

Decreasing the systemic vascular resistance (SVR) and the amount of blood returning to the heart results in reflex vasodilation, hypotension, and bradycardia, which is named Bezold -Jarisch reflex.⁽⁴⁾⁽⁵⁾ Ondansetron; an antiemetic drug was studied as a 5HT₃ antagonist for inhibition of Bezold - Jarisch reflex.

PATIENTS AND METHODS

This prospective randomized double-blinded study included eighty-four patients scheduled for PCNL under SA in Urology and Nephrology center, Mansoura University, Egypt.

Ethical approval:

After approval by Institutional Research Board, Faculty of Medicine, Mansoura University (IRB code: MS.20.09.1248), written informed consent was obtained from participants after explanation of the used drug and its possible consequences. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Included patients were of both sexes, following the American Society of Anesthesiologists (ASA) physical status I and II, with an age range between 18 and 65 years.

Exclusion criteria were patient refusal, contraindication to SA, known allergy to ondansetron, known allergy to bupivacaine or dexmedetomidine, uncontrolled hypertension, cardiac patient (ischemic heart disease, moderate to severe stenotic valve lesion, atrial fibrillation) and blood transfusion during surgery.

Randomization was done for 84 cases; Group C (n=42) in which patients were injected with 10 ml normal saline intravenous (IV) 5 min before SA, and Group O (n=42) in which patients were injected IV with 4 mg Ondansetron (Ondansetron hydrochloride dihydrate (Zofran 4mg/2ml amp, Novartis Sandoz, Germany) diluted with normal saline to a volume of 10 ml, 5 minutes before SA

Upon arrival to the operation room (OR), wide bore IV access (20-gauge cannula) was secured for IV fluids. All patients were monitored for vital signs. Spinal anesthesia was delivered in the sitting position under complete aseptic condition, using a 25-gauge spinal needle (quinckle type). The needle was advanced at level L 4-5 or L 3 – 4. After a clear flow of CSF, 3 mls 0.5 % hyperbaric bupivacaine HCL (Sunnybupivacaine 20mg/4ml amp, sunny medical, Egypt) was injected followed by 5 Mcg dexmedetomidine HCL (Precedex 200 Mcg/2ml vial, Hospira, Pfizer scientific office, USA) diluted to 1ml in insulin syringe. After intrathecal injection, patients were positioned supine immediately, the sensory level was assessed every 2 minutes by pinprick test, and a sensory block at T4-6 was considered sufficient to start surgery. Intravenous fluids included 500 mls of Voluven (Starch poly (O-2-Hydroxyethyl) 6%, Fresenius Kabi,

Germany) then 1000 mls crystalloids in the first hour and 1000 ml crystalloids in the second hour for all patients.

The anesthesia physician involved in data collection was not aware of patient allocation. The collected data included Patient age, height, weight, past medical history, basal HR, basal BP, and Oxygen saturation. Intraoperatively, BP, HR, and oxygen saturation were recorded. Hypotension was defined as a decrease in blood pressure by more than 20% of basal BP, a decrease of the systolic blood pressure to less than 90 mmHg or mean blood pressure (MBP) less than 60 and was treated with IV ephedrine sulfate (10mg bolus).

The incidence of hypotension was recorded according to the timing from spinal anesthesia, the duration of each hypotensive episode, and the severity of each episode; while the severity of hypotension was defined according to MBP (MBP 50 – 60 mmHg was considered mild, MBP 40 – 50 mmHg was considered moderate, MBP less than 40 mmHg was considered severe). Bradycardia was defined as a heart rate less than 50 beats/min and was treated with IV atropine sulfate (0.5mg). Postoperative data including HR, BP, and SpO², were measured every 15 minutes for 2 hours in the recovery unit.

Sample size calculation

Depending on the results of a previous study ⁽⁶⁾, Ondansetron reduced the incidence of spinal-induced

hypotension by about 20% (47% to 27%). G*power software version 9.1.2.2 was used to calculate the sample size. A total sample size of 80 patients was required to achieve a study power of 0.8, and an alpha effect of 0.05. 4 patients were added to compensate for dropouts.

Statistical analysis

SPSS statistics for windows (Statistical Package for the Social Sciences) version 26 (IBM, Armonk, NY, USA) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. All tests were conducted with a 95% confidence interval. P (probability) value < 0.05 was considered statistically significant. Charts were generated using SPSS’ chart builder and Microsoft Excel for windows 2019.

RESULTS

As shown in the study flow chart, eighty-four cases; undergoing PCNL surgery under SA using a bupivacaine-dexmedetomidine mixture, were recruited for our study. Patients were randomized into two equal groups: **Group C** (control group, n=42 cases) and **Group O** (ondansetron group, n=42 cases). In group O, three cases were excluded due to intraoperative blood loss and 81 cases completed the study protocol (42 cases for group C and 39 for cases group O), see **Figure 1**.

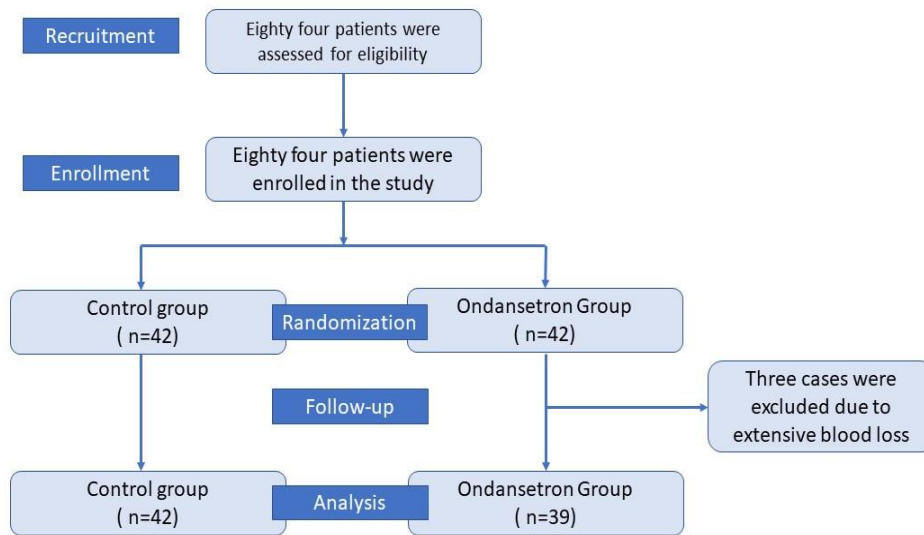


Figure 1: The study CONSORT flow chart

Basal characteristics showed no statistically significant differences between the two groups (Table 1). According to Table 2, there was no statistical difference in the Sensory and motor block characteristics in the two groups. Also, according to Table 3, there was no statistical difference in the incidence of intraoperative hypotension or the required dose of ephedrine in the two groups. In table 4, there was no statistical difference regarding the incidence of bradycardia, the incidence of nausea and vomiting, and shivering.

Table 1: Basal characteristics of our study

	Group C (n= 42)	Group O (n= 39)	95% CI	P
Age (years)	48.2 ± 10.9	48.9 ± 10.4	-5.5, 4.0	0.750
Gender M/F (n)	(15/27)	(14/25)	-	0.986
Height (cm)	164.4 ± 9.4	165.9 ± 7.8	-5.5, 2.2	0.405

Weight (kg)	87.7 ± 17.8	91.6 ± 16.4	-11.5, 3.7	0.313
BMI (kg/m²)	32.3 ± 5.6	33.5 ± 6.9	-4.0, 1.6	0.400
History of DM %(n)	23.8% (10)	41.0% (16)	-	0.097
History of HTN % (n)	45.2% (19)	33.3% (13)	-	0.273
ASA classification I/II (n)	15/27	17/22	-	0.469
Duration of surgery (min)	94.5 ± 26.6	94.6 ± 25.3	-11.6, 11.5	0.994

Data are expressed as mean ± SD or as percentage and frequency.
Group C (control group), Group O (ondansetron group).

Table 2: Sensory and motor block characteristics in our study.

	Group C (n= 42)	Group O (n= 39)	95% CI	P	
Onset of sensory block (min)	6.6 ± 2.6	6.1 ± 2.3	-0.5, 1.7	0.290	
Bromage scale	5 minutes	4 (3, 4)	4 (3, 4)	-0.5, 0.2	0.404
	10 minutes	4 (4, 4)	4 (4, 4)	-0.2, 0.1	0.339
	15 minutes	4 (4, 4)	4 (4, 4)	-	1
	1 hour	4 (4, 4)	4 (4, 4)	-	1
	2 hours	4 (4, 4)	4 (4, 4)	-	1
	3 hours	4 (3, 4)	4 (4, 4)	-0.5, 0.0	0.110
	4 hours	2 (2, 3)	2 (2, 3)	-0.3, 0.4	0.700
Time to 2-segment regression (min)	104.2 ± 8.5	102.9 ± 9.6	-2.8, 5.2	0.546	

Data are expressed as mean ± SD, median (Q1, Q3).
Group C (control group), Group O (ondansetron group).

Table 3: The incidence of intraoperative hypotension and the used vasopressor

	Group C (n= 42)	Group O (n= 39)	95% CI	P
• Intraoperative				
The incidence of hypotension n (%)	28(66.7%)	27(69.2%)	-	0.618
The required dose of ephedrine (mg)	10 (0 - 50)	10 (0 - 50)	-8.2, 4.9	0.618

Data are expressed as frequency (percentage) or median (minimum-maximum).
Group C (control group), Group O (ondansetron group).

Table 4: The incidence of perioperative complications in our study

	Group C (n= 42)	Group O (n= 39)	Odds ratio	P	
Intraoperative	Bradycardia n (%)	3 (7.1%)	4 (10.3%)	1.49	0.618
	Nausea & vomiting n (%)	3 (7.1%)	2 (5.1%)	0.73	0.707
	Shivering n (%)	13 (31.0%)	7 (17.9%)	0.49	0.175
	Pruritis n (%)	0 (0%)	0 (0%)	-	1
Recovery	Nausea & vomiting n (%)	0 (0%)	0 (0%)	-	1
	Shivering n (%)	6 (14.3%)	3 (7.1%)	0.5	0.345

Data are expressed as frequency (percentage).
Group C (control group), Group O (ondansetron group).

DISCUSSION

Our study evaluated the effect of using IV ondansetron HCl on the incidence of hypotension after SA in patients prepared for PCNL surgery. Our results showed that prophylactic ondansetron HCl didn't have any statistically significant effect on the incidence of hypotension, the dose of ephedrine requirements, or the incidence of bradycardia after SA.

In accordance with our results, several studies found that ondansetron HCl didn't reduce the incidence of SIH. In a study; including 86 patients prepared for CS under SA, Terkawi *et al* concluded that ondansetron HCl before SA, didn't attenuate hemodynamic changes and didn't reduce the amount of vasopressor used. ⁽⁷⁾ Similarly, Neumann *et al* concluded that ondansetron HCl 8mg IV before SA didn't attenuate post spinal changes in maternal blood pressure in patients undergoing elective CS. ⁽⁸⁾

Ondansetron HCl acts as a 5-HT₃ antagonist which in turn blocks BJR which contributes to the hemodynamic effects of SA, especially in hypovolemic patients. Meanwhile, during anesthesia for PCNL, a sympathetic block at a high level of anesthesia is required to reach the T4 level and a major part of the sympathetic system was blocked, ⁽⁴⁾ It is expected even when ondansetron HCl blocks BJR, it isn't enough to compensate the vasodilation all over the blocked area.

Another explanation for the failure of ondansetron HCl to reduce hypotension in our study is the low dose of ondansetron HCl (4 mg) used. While most of the studies which proved the efficacy of ondansetron HCl to reduce SIH had used a higher dose of ondansetron HCl (8, 12 mg)^{(9) (10) (11) (3)}, the majority of the studies in which IV 4mg ondansetron HCl was effective to decrease SIH were conducted in the obstetric population, ^(12,13,14) For anesthesia for CS or lower limb surgeries, the required level of anesthesia and the sympathetic block; a major factor affecting the incidence of hypotension, wasn't high when compared to the level required for PCNL surgeries as discussed before.

However, several studies supported the usage of ondansetron HCl to decrease the incidence of hypotension associated with SA. A review of 17 studies including 8 in obstetric suggested that ondansetron HCl reduced the incidence of hypotension in patients undergoing CS and the effect wasn't significant in the non-obstetric population. ⁽¹⁵⁾

In a group of 66 patients undergoing CS under SA, Wang *et al* found that 4mg ondansetron HCl IV 5 minutes before SA significantly reduced hypotension after SA. ⁽¹⁶⁾ Another study of 108 pregnant ladies undergoing elective CS was divided into two equal groups suggested that IV administration of 8mg ondansetron HCl before SA attenuated but not prevent SIH. ⁽¹⁰⁾

In another study of 100 patients in patients undergoing CS under SA, using 2ml hyperbaric bupivacaine 0.5%, Elkhoully *et al* concluded that prophylactic IV 4mg ondansetron HCl 5 min before SA significantly reduced hypotension and heart rate changes. ⁽¹⁷⁾

Additionally, in patients scheduled for elective operations under SA, Tatikonda *et al* concluded that prophylactic use of 4mg ondansetron HCl IV 5 min before SA, reduced the dose of ephedrine used and shivering. ⁽⁶⁾ Similarly, in a meta-analysis study Zheng *et al* concluded that prophylactic ondansetron HCl reduced the incidence of SIH and vasopressor required. ⁽¹⁸⁾

Ondansetron HCl is used primarily as an antiemetic drug, many studies have proved that ondansetron HCl had an antiemetic effect perioperative. ^{(19) (20,21,22,23)}

In a study of 120 patients undergoing CS under SA, Kalani *et al* concluded that IV 6mg ondansetron HCl or IV dexamethasone 8mg before SA had the same antiemetic effect perioperative. ⁽¹⁹⁾ Similarly, in a meta-analysis of 21 studies undergoing CS under SA, Zhoo *et al* concluded that ondansetron HCl could be effective in the reduction of vomiting after SA. ⁽²¹⁾

As regards our results, the incidence of vomiting after SA was 7.1% in group C and 5.1% in group O without reaching a statistical significance (P -value of 0.70). Vomiting after SA is a complex multi-factorial process that may be caused by spinal-induced hypotension, intrathecal opioids, and intrathecal dexmedetomidine. ^(23,24) So the incidence of PONV wasn't statistically significant between the two groups despite being lower in group O. Additionally, our sample size wasn't statistically large enough to detect that difference.

Depending on the results of several studies, ondansetron HCl was used to prevent postoperative shivering, which is considered a common complication after SA. ^(25,26)

Safavi *et al* used ondansetron HCl 8mg IV before SA to reduce the incidence of post spinal shivering in lower extremity orthopedic surgery under SA. ⁽²⁶⁾ Also, in their study of 120 patients undergoing elective lower abdominal surgery including hernioplasty, appendectomy, cystolithotomy and vaginal or abdominal hysterectomy under SA, Shakya *et al* used ondansetron HCl 4mg IV to decrease post spinal shivering without significant side effects. ⁽²⁷⁾

The incidence of shivering in group C is 31% (13 cases) and in group O 17.9% (7 cases) in the present study and the P -value was 0.17, however, this effect didn't show statistical significance. While the anti-shivering effect of ondansetron is mediated both centrally and peripherally, the cause of shivering may be hypothermia, hyperthermia, cooling effect of irrigation fluids and/or IV fluids despite the warming of fluids used. In accordant with our results,

Marashi *et al.* found that IV ondansetron HCl 6 or 12mg 5 min before SA attenuated post spinal shivering with no statistical difference. ⁽⁴⁾ Also, Browning *et al* concluded that IV ondansetron HCl 8mg given before combined spinal epidural during elective cesarean delivery didn't prevent shivering or decrease the severity of shivering. ⁽²⁸⁾

limitation of our study was heterogeneity of patients including ASA II in the study and BMI of more than 30. As well, the relatively small sample size was accused to be responsible for missing the statically significant differences for the secondary variables including POS and PONV, as discussed above.

CONCLUSION

In our study, ondansetron 4mg IV 5 minutes before spinal anesthesia in cases of PCNL under SA using bupivacaine-dexmedetomidine mixture didn't reduce the incidence of hypotension and didn't reduce the required dose of ephedrine and didn't reduce the incidence of bradycardia, but it reduced the incidence of nausea and vomiting and shivering with no statistical difference. Further studies are recommended to investigate the effect of Ondansetron on the incidence of SIH.

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