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The Comparative Study of Intravenous Ondansetron and Dexamethasone Effects on Reducing the Incidence of Post-Spinal Anesthesia Hypotension in Elderly Patients Undergoing Urologic Surgeries in Yasuj Shahid Beheshti & Tehran Shahid Modarres Hospitals

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Abstract

Background: Spinal anesthesia is a safe and effective method for a wide range of surgical procedures and is the recommended anesthesia method for various surgeries. Despite numerous advantages, spinal anesthesia is not without side effects. Without prophylaxis, approximately 33% of patients undergoing non-obstetric surgeries experience hypotension due to spinal anesthesia. Hypotension with symptoms such as dizziness, nausea, vomiting, aspiration, hypovolemia, and bradycardia may increase the risk of cardiovascular problems.

Various methods have been proposed to reduce the incidence of hypotension following spinal anesthesia, including intravenous fluid administration, vasopressor drugs, and leg compression. But no single technique for prevention of hypotension following spinal anesthesia has been described as being completely effective and the efficacy of various drugs is still unclear.

The aim of this study is to investigate the effect of preventive administration of two drugs (ondansetron and dexamethasone) on reducing hypotension and bradycardia in Elderly patients undergoing spinal anesthesia.

Methods: In this double-blind randomized clinical trial study, 120 participants were randomly selected from elderly patients referred for urological surgeries to Shahid Beheshti Hospital, Yasouj, and Shahid Modares Hospital, Tehran, Iran. Patients were divided into three groups before spinal anesthesia: in group A, 4 mg iv ondansetron was given five minutes before spinal anesthesia. In group B, 8 mg iv dexamethasone was given five minutes before spinal anesthesia and for patients in group C, no drug was given before spinal anesthesia. Blood pressure and heart rate monitoring were recorded before and thirty minutes after the administration of ondansetron or dexamethasone and at the same time in group C. Then the findings were compared among the three groups. Atropine or ephedrine was prescribed to the patients when needed.

Results: The main findings of this study showed that the groups had no significant difference in terms of systolic and diastolic blood pressure before the administration of ondansetron and dexamethasone. The comparison between the two intervention groups of ondansetron and dexamethasone showed that these two groups had no significant difference in any way either before or after the administration of the drug. Both drug groups (A and B) compared to the control group had a significant difference in terms of systolic and diastolic blood pressure after drug administration, increasing systolic blood pressure, diastolic blood pressure and heart rate. Also, the difference in heart rate after drug administration between the two dexamethasone and control groups was significant. So that the systolic and diastolic blood pressures were higher in the dexamethasone and ondansetron group compared to the control group, respectively. Besides, there was no significant change in heart rate in the dexamethasone intervention group compared to the control one. Also, the administration of ephedrine in the control group was higher than the two groups with drug intervention.

conclusion: In this study we concluded that prophylactic administration of dexamethasone and ondansetron before spinal anesthesia in elderly patients reduces post-spinal hypotension and bradycardia occurrence and it is safely recommended in elderly patients with contraindication for extra fluid therapy or alpha agonist administration due to cardiovascular risks and complications.

Keywords: Spinal Anesthesia; Ondansetron; Dexamethasone; Hypotension

Introduction

Spinal anesthesia is in common use for surgical procedures involving the lower abdomen, pelvis, perineal and lower extremities; it is beneficial for procedures below the umbilicus. Spinal anesthesia is a safe and effective method and has many advantages. Neuraxial anesthesia offers many benefits not available with general anesthesia. Neuraxial anesthesia has made it possible to perform many major procedures on an awake patient. Other beneficial effects are better pain control than intravenous narcotics, less need for systemic opioids, earlier recovery of bowel functions, easier participation in physical therapy, reducing intraoperative bleeding, decreasing the risk of venous thromboembolism, and less respiratory complications [1]. Unlike general anesthesia, spinal anesthesia does not require patients to use breathing tubes. Patients who take medications to control blood pressure, have COPD, or are long-term smokers have a hard time with breathing tubes, which makes spinal anesthesia a better option .Spinal anesthesia is especially advantageous for older patients who are more likely to suffer from post-surgery side effects including post-operative confusion or long term cognitive dysfunction. It also reduces the risk for heart or lung complications which may accompany general anesthesia. Using spinal anesthesia often even allows younger patients to go home on the very same day. Patients who underwent a procedure with spinal anesthesia instead of general, not only experienced less pain, but also had an overall shorter hospital stay.

But this method has some side effects [2]. Without drug prophylaxis, approximately 33% of patients undergoing non-obstetric surgery experience hypotension due to spinal anesthesia, and this rate reaches 70-80% in obstetric patients [3,4].

Hypotension often with symptoms such as dizziness, nausea, vomiting, aspiration, hypovolemia and bradycardia may increase the risk of cardiovascular problems.

This drop in blood pressure is caused by the dilation of arterial and venous vessels caused by sympathetic block along with the paradoxical activation of cardiac inhibitory receptors. Bradycardia after spinal anesthesia should always be considered a warning sign of a significant hemodynamic disturbance.

Various methods have been proposed to reduce the incidence of hypotension from spinal anesthesia, including intravenous fluids, vasopressor drugs, and leg compression, but no single Technique to avoid spinal anesthesia induced hypotension has been described as being completely effective. The efficacy of drugs is uncertain [5,6].

Ephedrine has traditionally been considered the vasoconstrictor of choice, particularly for use in spinal anesthesia-induced hypotension with bradycardia. Phenylephrine, an α1-adrenergic receptor agonist, is increasingly used to treat hypotension induced by spinal anesthesia, and its prophylactic administration (i.e., immediately after intrathecal injection of local anesthetics) has been shown to reduce the incidence of Arterial blood pressure drops. Other drugs, such as serotonin receptor antagonists (ondansetron), limit hypotension after spinal anesthesia by inhibiting the Bezold-Jarisch reflex, but more studies are needed before their widespread use can be recommended.

Therefore, it is important to investigate methods to reduce the incidence of hypotension following spinal anesthesia that is cost-effective, safe, and effective.

Many urologic surgeries, often elective in nature, are short-term and limited to the pelvis and are a good option for spinal anesthesia [7]. Urological surgeries are mainly performed on patients who are at risk of general anesthesia [8,9]. In addition, several studies have shown that spinal anesthesia reduces the risks compared to general anesthesia [10-13].

Most of the patients who undergo urological surgeries are elderly patients with weak autonomic protective responses, which decrease blood pressure and heart rate, and have many adverse effects on these patients [14]. The decrease in blood pressure and heart rate in these patients increases the load on the cardiorespiratory system, especially in elderly patients with low cardiorespiratory reserve [15].

Hypotension and bradycardia are common sequelae of spinal anesthesia. Estimates of the incidence of spinal anesthesia-induced hypotension (SIH) average between 15% and 33% of all cases [16,17]. The hypothesized mechanism for hypotension is attributed to venous and arterial vasodilatation caused by local anesthetic-induced sympathetic blockade. Since the blood in the venous system is approximately 75% of the total blood volume, vasodilation leads to venous congestion and reduced venous return [18]. In addition, the lack of compensatory response to

Reflex tachycardia and vagus nerve hyperactivity are factors that contribute to hypotension caused by spinal anesthesia [19,20].

Recently, the Bezold-Jarisch reflex (BJR) has been suggested as the most likely cause of bradycardia following spinal anesthesia [21]. Another mechanism that exists during spinal anesthesia is the reversed Bain-bridge reflex [22].

While the cardiovascular effects of spinal anesthesia are related to the degree of sympathetic block, the resulting degree of sympathetic block can vary significantly among patients.

Spinal anesthesia leads to bradycardia and lowers blood pressure by creating a sympathovagal imbalance in favor of a parasympathetic tone. This bradycardia/hypotension could indicate a cardiovascular dysfunction or could be interpreted as an adaptive response (prolongation of diastole duration to correct ventricular filling).

Approximately 13% of non-obstetrics experience bradycardia during spinal anesthesia, usually without significant consequences as long as corrective measures are taken promptly.

A decrease in cardiac output is one of the determining factors for lowering arterial blood pressure, which is observed in 15-50% of patients. In the elderly, age-related changes (changes in systolic function, diastolic relaxation) can exacerbate the decrease in cardiac output in these conditions [23-26].

Interventions to correct hypotension, such as volume replacement or administration of ephedrine, may be risky in elderly patients with heart failure or a history of my-

ocardial ischemia [27].

Despite its many advantages over general anesthesia, spinal anesthesia has important side effects, including blood pressure drop, which is seen in approximately 40% of non-obstetric patients and 80% of obstetric patients and leads to systemic hypoperfusion. If accompanied by bradycardia and without proper treatment, hypotension and bradycardia can turn into cardiac arrest. Hypotension can be especially harmful in elderly patients with limited cardiac reserve. The high incidence of coronary artery disease in elderly patients increases the risk of myocardial

Ischemia due to hypotension. Therefore, maintaining arterial blood pressure is important to ensure adequate regional perfusion [1,28].

Ondansetron is a drug that is also used to prevent postoperative nausea and vomiting, its antiemetic activity involves selective inhibition of serotonin receptors. Ondansetron can also suppress the Bezold reflex while dexamethasone increases total peripheral vascular resistance and may decrease serotonin expression, so it has been hypothesized as a treatment [29,30].

Since patients routinely do not receive drug prophylaxis for spinal anesthesia and are exposed to spinal anesthesia complications, and also elderly patients are more vulnerable, this study was conducted to investigate the effect of ondansetron and dexamethasone administration. It was done to prevent spinal anesthesia complications and blood pressure drop and hence no or less need of atropine and ephedrine administration to treat spinal anesthesia complications.

Material and Methods

We designed a double-blind randomized controlled trial study (Ethical code: IR.YUMS.REC.1401.114) on 120 patients who were Candidates for elective urology surgeries (from Oct 2021 to Jan 2023) at Shahid Beheshti Hospital in Yasouj and Shahid Modarres Hospital in Tehran. The patients were selected and randomly divided into three groups of 40 patients: First intervention group (Group A: 5 minutes before spinal anesthesia, 4 mg of ondansetron was injected intravenously), Second intervention group (Group B: 5 minutes before spinal anesthesia, 8 mg of dexamethasone was injected intravenously.) and the control group (Group C: No medicine was injected before spinal anesthesia).

The patients in this study were between 65 and 92 years old and have had physical condition standards I, II of the American Society of Anesthesiologists (ASA) who did not have a contraindication for spinal anesthesia (such as coagulation disorder, thrombocytopenia). Also, they did not have allergies to anesthetics and ondansetron or dexamethasone, and did not take drugs related to steroids or serotonin (for example, selective serotonin reuptake inhibitors), and did not suffer from uncontrolled cardiovascular, kidney, liver, or thyroid diseases, and EF>40%.

Also, the patients who had surgical complications such as bleeding, hemodynamic instability were excluded from the study.

It should be noted that this study was conducted in a double-blind manner. This means that patients, caregivers, anesthesiologists, surgeons and operating room personnel haven't been informed about the type of study. The website https/www.Randomization.com was used for random assignment to hide random allocation.

After registering the demographic information, including age and sex the objectives of the study were explained to the patients, and they entered the study if they wished. Written consents were obtained. The patients received Ringer's serum 5 ml/kg (if not prohibited), then they were placed in a sitting position, and the spinal anesthesia site from the middle of the back spine to the sitting area was sterilized with 10% betadine. Next stage, spinal anesthesia was performed by inserting a special needle for spinal anesthesia (No. 25 of Daroogostar Company) between the fourth and fifth lumbar vertebrae, and in all three groups, 0.5 % bupivacaine 15 mg was used for spinal anesthesia.

After the injection of drugs in the intervention groups, the patient was placed in a supine position immediately after the spinal anesthesia. In order to check the condition of blood pressure and heart rate in patients, blood pressure monitoring was done by sphygmomanometer every 3 minutes for 30 minutes, and the average systolic and dias-

tolic blood pressure was recorded before and after the administration of ondansetron or dexamethasone.

Heart rate monitoring was done based on an electrocardiogram during the first half hour after spinal anesthesia, and a general examination of the patient (blood pressure and bradycardia, alertness, weakness and lethargy, sweating, hot flashes during the first half hour after Spinal anesthesia) was investigated and atropine(0.5 mg) or ephedrine(5mg)was prescribed to treat bradycardia or hypotension in the patients based on medical perception.(Heart rate <45 , SBP<90)

Study Variables

In addition to sex and age, we also measured Heart rate, systolic and diastolic blood pressure and Atropine or ephedrine administration.

Sample Size

To determine the sample size based on the data of the preliminary study, we assumed that 45% of patients will develop hypotension after spinal anesthesia, and we also assumed that the administration of ondansetron leads to a 30% reduction in the risk of hypotension after spinal anesthesia. Therefore, a sample size of 100 patients was initially considered to obtain 90% trial power and 5% alpha-level error. The sample size was revised and recalculated according to the cautious treatment difference. Taking into account the possibility of 20% of cases of withdrawal from the study, the final number of 120 patients was included. Sample size calculations were done through the platform https://clincalc.com./stats/samplesize.as.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

Therefore, including totally the number of 120 samples in study, 40 patients should be included in each group.

Statistical Analysis

To describe data, we used frequency (percent), mean ± SD and range. Independent t-test and Mann-Whitney test were used for quantitative also chi-square test was utilized for qualitative variables. For the assumption of normality distribution Shapiro-Wilk normality test was used. Also, study charts were drawn by PRISM version 8 software. A P - value less than 0.05 was considered as statistically significant. All statistical analysis performed by SPSS software (IBM Corp. Released 2018. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

120 patients who were candidates for elective urology surgeries, were selected and randomly divided into three groups of 40 patients: Group A (ondansetron), group B (dexamethasone) and group C (control). The results showed that about 104 (86.7%) of the patients were men, whose average age was 73.38±6.98 (65 - 92) years. A total of 22 (18.3%) patients required the administration of ephedrine or atropine (10 patients' atropine, 12 patients' ephedrine).

Demographic and clinical characteristics of patients such as age, systolic blood pressure, diastolic blood pressure, heart rate before and after the intervention, the difference between systolic blood pressure, diastolic blood pressure and heart rate before and after drug administration were shown in table 1. The average changes before and after the intervention for the systolic and diastolic blood pressure of the patients are equal to 12.69 ± 9.71(mmHg) and 4.75 ± 4.84(mmHg), respectively. Also, the mean change of heart rate was calculated 5.6 ± 4.92 (Per min) with an age distribution of 73.38 ±6.98 years.

Table 1: Demographic and clinical characteristics of patients before and after intervention

parameters	Time	min	max	mean	SD
Age (Yrs.)		65	92	73/38	98/6
Systolic BP (mmHg)	Pre	115	155	134/85	96/8
	Post	100	150	122/16	8/9
	Δ	0	50	12/69	71/9
Diastolic BP(mmHg)	Pre	65	95	79/41	19/5
	Post	60	90	74/66	78/5
	Δ	0	20	4/75	84/4
HR (Per min)	Pre	48	85	71/45	39/7
	Post	52	90	77/05	89/6
	Δ	0	32	5/6	92/4

*BP: Blood Pressure, HR: Heart Rate

According to table 2, the comparison of groups in terms of systolic and diastolic blood pressure and heart rate before and after intervention and the changes was done and it was observed that the groups differ in terms of systolic blood pressure, diastolic blood pressure, blood pressure before the administration of ondansetron and dexamethasone. There are not any significant differences between groups regarding systolic and diastolic blood pressure before intervention (P-value>0.05) but there are significant differences between both intervention groups and the control group. So the average blood pressure in the two intervention groups is higher than the control group. The P-value ondansetron and dexamethasone versus control was 0.001 in terms of Systolic blood pressure. The P-value ondansetron versus control was 0.03 and 0.001 for dexamethasone versus control regarding Diastolic blood pressure. In general, the average heart rate did not show significant changes except in the comparison of dexamethasone versus control which showed that heart rate significantly decreased in the control group. (P-value=0.04).

Table 2: Investigating the difference between intervention groups in terms of blood pressure and heart rate factors before and after drug administration

Parameters	Time	Intervention	Mean ± SD	P-value(A Vs C)	P-value(B Vs C)	P-value (A Vs B)
Systolic BP (mmHg)	Pre	ondansetron	134/45 ±9/84	0/68	0/84	0/84
		dexamethasone	134/87 ±9/3			
		Control	135/25 ±7/84			
	Post	ondansetron	124/5 ±9/52	0/001	0/001	0/001
		dexamethasone	124/62 ± 8/5			
		Control	117/37 ±9/73			
Diastolic BP(mmHg)	Pre	ondansetron	78/87 ±5/82	0/57	0/73	0/43
		dexamethasone	79/87 ±5/6			
		Control	79/5 ±4/05			

	Post	ondansetron	74/87 ±5/6	0/03	0/001	0/15
		dexamethasone	76/75±6/05			
		Control	72/37±4/93			
HR (Per min)	Pre	ondansetron	75/42 ±7/84	0/06	0/59	0/21
		dexamethasone	77/5 ±7/07			
		Control	78/25 ±5/73			
	Post	ondansetron	70/97 ±8/51	0/61	0/04	0/21
		dexamethasone	73/25 ±7/55			
		Control	70/15 ±8/51			

Based on the information in Table 3, the mean changes in systolic, diastolic blood pressure and heart rate in comparison between the two intervention groups are statistically significant. P-values and Mean ± SD for each group were demonstrated in the table.

Table 3: Examining the difference between groups from the perspective of differences in blood pressure and heart rate factors before and after intervention

Parameters	Intervention	Mean ± SD	P-value(A Vs C)	P-value(B Vs C)	P-value (A Vs B)
Δ Systolic BP (mmHg)	ondansetron	9/95 ±8/04	0/001	0/001	0/86
	dexamethasone	10/25 ±7/15			
	Control	17/87 ±11/42			
Δ Diastolic BP(mmHg)	ondansetron	4± 3/43	0/005	0/005	0/29
	dexamethasone	3/12 ±4.03			
	Control	7/12±5/87			
HR (Per min) Δ	ondansetron	4/45±3/66	0/005	0/001	0/79
	dexamethasone	4/25±3/31			
	Control	8/1 ±6/31			

Based on the information in Table 4, the number of atropine and ephedrine prescriptions was compared between the intervention and control groups and it was observed that the dexamethasone and ondansetron group differed significantly from the control group in terms of ephedrine and atropine prescription. So the prescription of ephedrine in the control group was higher than in the two groups with drug intervention. Also, the results showed that the two groups of ondansetron and dexamethasone had no significant difference from the point of view of prescribing ephedrine or atropine.

Table 4: Examining the difference between the intervention groups in terms of atropine and ephedrine administration

Parameters	Intervention	N (%)	P-value(A Vs C)	P-value(B Vs c)	P-value (A Vs B)
Atropine	ondansetron	1(2.5)	0/02	0/02	0/99
	dexamethasone	1(2.5)			
	Control	8(20)			
Ephedrine	ondansetron	1(2.5)	0/006	0/006	0/69
	dexamethasone	1(2.5)			
	Control	10(25)			

Regarding changes in systolic blood pressure, diastolic blood pressure and heart rate of patients before and after drug administration compared to the control group:

The changes in systolic blood pressure of patients (before and after drug administration) for patients who were prescribed ondansetron was equal to 9.95±8.04, for patients who were prescribed dexamethasone 10.25±7.15, and for the group Control was 17.87±11.42. P-value comparing the reduction in systolic blood pressure between the ondansetron group and the control group was equal to 0.001 and significant, so that the systolic pressure reduction observed in the ondansetron intervention group was less than the control group.

P-value comparing the reduction of systolic blood pressure between the dexamethasone group and the control group was equal to 0.001 and significant, so that the reduction of systolic blood pressure in the dexamethasone intervention group was less than the control group. Also, the difference in systolic blood pressure reduction between the two groups treated with ondansetron and dexamethasone was not significant with P-value=0.86.

The heart rate changes of the patients (before and after drug administration) for the patients who were prescribed ondansetron was equal to 4.45±3.66, for the patients who were prescribed dexamethasone 4.25±3.31, and for the group The control was 8.1±6.31. P-value comparing the heart rate reduction between the ondansetron group and the control group was equal to 0.002 and significant, so that the heart rate reduction observed in the ondansetron intervention group was less than the control group.

P-value comparing the decrease in heart rate between the dexamethasone group and the control group was equal to 0.001 and significant, so that the heart rate in the dexamethasone intervention group was lower than the control group. Also, the difference in heart rate reduction between the two intervention groups of ondansetron and dexamethasone was not significant with P-value=0.79.

Discussion

Although spinal anesthesia is considered a safe procedure, it may be associated with complications such as hypotension and bradycardia. Previous studies show that the rate of hypotension and bradycardia after subarachnoid block is significant and varies from 10% to 80% [3,16,31]. In the elderly, spinal anesthesia is associated with a 25-69% incidence of hypotension and reduced physiological reserve, which, if added to cardiovascular and/or valvular ischemic disease, makes even short periods of uncorrected hypotension difficult to tolerate. slow and may have harmful consequences on their heart [32].

The mechanisms by which glucocorticoids increase blood pressure are not fully known with several factors have been proposed, but all of them indirectly increase environmental resistance as the main mechanism. Dexam-

ethasone does not cross the blood-brain barrier freely and the possibility of dexamethasone effect, there is a peripheral route. Endogenous and exogenous glucocorticoid effects are related to renal sodium and water balance by glucocorticoid receptors [33]. Activation of renal nerves by dexamethasone causes more reabsorption of water and sodium and increases vascular resistance and blood pressure. There is also evidence that glucocorticoids increase the effect of vasoconstrictors. Glucocorticoids increase angiotensin II receptors in rat aortic smooth muscle cells and circulating angiotensin II and catecholamines cause a deeper effect on blood pressure with higher levels of glucocorticoids, and glucocorticoid receptors in the smooth muscle cells of arterioles are important for the acute increase in blood pressure by glucocorticoids [34]. Apart from its central function in the brain, ondansetron binds to HT3-5 receptors peripherally, to receptors in the heart ventricles and on the vagus nerve, which contributes to BJR [35].

The binding of these receptors prevents the induction of BJR and reduces parasympathetic dominance, reducing the degree of bradycardia and hypotension induced by spinal anesthesia. On the other hand, studies have suggested that sympathectomy and aortocaval compression induced by local anesthesia stimulate left ventricular receptors to induce the Bezold-Jarisch reflex. Ondansetron antagonizes the Bezold-Jarisch reflex, which may explain its effectiveness in preventing bradycardia and lowering blood pressure during spinal anesthesia [36].

This study was conducted to investigate the effectiveness of two drugs, dexamethasone and ondansetron, on improving prevention of hypotension and bradycardia in elderly patients under spinal anesthesia in urological surgeries. Based on the main findings of this study, the comparison of the groups in terms of systolic blood pressure, diastolic blood pressure and heart rate before and after drugs administration showed that there was no significant difference between the groups in terms of systolic blood pressure, diastolic blood pressure and blood pressure before the administration of ondansetron and dexamethasone.

The comparison between the two intervention groups of ondansetron and dexamethasone showed that these two groups had no significant difference in any way, both before and after the administration of the drugs, which indicates the usefulness of both drugs in this regard. The ondansetron intervention group compared to the control group and the dexamethasone intervention group compared to the control group in terms of systolic blood pressure after drug administration, diastolic blood pressure after drug administration, increasing systolic blood pressure, diastolic blood pressure, and heart rate had a significant difference. Also, the difference in heart rate after drug administration between the two dexamethasone and control groups was significant. So that the systolic and diastolic blood pressures were higher in the dexamethasone and ondansetron group than the control group, respectively, and the difference in heart rate changes before and after the spinal anesthesia was less significant in the dexamethasone intervene group.

Therefore, it seems that dexamethasone may be more effective than ondansetron in terms of heart rate, although this difference is not significant. Also, the number of atropine and ephedrine prescriptions was compared between the intervention and control groups and it was observed that the dexamethasone and ondansetron group differed significantly from the control group in terms of ephedrine and atropine prescriptions. So the prescription of ephedrine in the control group was higher than in the two groups with drug intervention.

Dexamethasone is an inexpensive, readily available, and simple drug strategy to prevent hypotension after spinal anesthesia. In addition, dexamethasone can be used to prevent postoperative nausea and vomiting, prevent postoperative chills, and as an antalgic adjuvant [37]. In line with our study, several studies have investigated the preventive effect of dexamethasone on preventing blood pressure drops in patients with various surgeries.

For the first time, a study showed a favorable response regarding the effectiveness of an intravenous infusion dose of 8 mg of dexamethasone to reduce blood pressure after spinal anesthesia in elderly patients undergoing orthopedic surgery. This study observed higher minimum values of systolic, diastolic and mean arterial pressure in the dexamethasone intervention group with minimal effect on heart rate.

The researchers observed that patients who used steroids for various reasons and had spinal anesthesia had more favorable postanesthetic hemodynamic outcomes with minimal hypotension and, accordingly, minimal need for vasoconstrictor drugs. This theory suggested the value of administering dexamethasone to lower blood pressure after spinal anesthesia [37].

Chu et al., showed that dexamethasone (with 5-HT3 receptor blocking properties) similarly reduced the risk of postoperative nausea and vomiting as shown with other 5-HT3 receptor antagonists such as ondansetron [38].

Moeen SM et al also reported that intrathecal dexamethasone was as effective as intrathecal meperidine in reducing shivering after spinal anesthesia compared with a placebo in patients scheduled for prostate surgery under spinal anesthesia with fewer side effects [39].

In addition, Shalu et al concluded that administration of 8 mg IV dexamethasone prolonged the duration of sensory block and postoperative analgesia in patients undergoing spinal anesthesia [40].

The researchers even observed that with the prophylactic administration of dexamethasone, hypotensive patients required lower doses of ephedrine, and hypotension, if present, was not associated with nausea and/or vomiting. This study strongly suggests the use of dexamethasone in elderly patients and other patient populations at higher risk of hypotension after spinal anesthesia such as obstetric patients [37].

Based on studies, dexamethasone increases PVR by several mechanisms, namely, decreases the vasodilator nitric oxide (NO), increases sympathetic activity, and increases plasma dopamine and epinephrine. It also increases the sensitivity of vascular endothelium to various vasoconstrictors. In addition, dexamethasone has anti-HT3-5 effects that may affect BJR [41]. These two effects affect exactly the two pathophysiological effects that are involved in causing blood pressure drop after spinal anesthesia [3]. Various studies have confirmed these results [42-44].

Previous studies have shown the role of dexamethasone and ondansetron in preventing nausea and vomiting in spinal anesthesia procedures. Although our study did not investigate this, these two complications are closely related. One study showed that 6 mg of ondansetron and 8 mg of dexamethasone could equally reduce the incidence of nausea and vomiting in patients undergoing surgery under spinal anesthesia [45].

Pirat et al showed that 8 mg oral ondansetron and 4 mg intravenous ondansetron did not prevent intrathecal meperidine-induced nausea and vomiting during surgery [46].

In a study by Nortcliffe et al., dexamethasone was not effective in preventing nausea and vomiting induced by spinal anesthesia [47]. In addition, the reason for such inconsistent results in preventing nausea and vomiting can be hormonal changes, gender, age, weight, type of surgery and duration of surgery.

On the other hand, various clinical trials have been conducted to investigate the effect of ondansetron on blood pressure drop or bradycardia, which have generally published results in line with the recent study.

A study by Owczuk et al showed that administration of intravenous ondansetron (an HT3-5 receptor blocker) before spinal anesthesia in elderly patients reduced diastolic and mean arterial pressure drop without significant effect on systolic blood pressure [27]. However, meta-analysis studies have failed to validate those conclusions based on low-quality and insufficient evidence [48]. In addition, ondansetron may be responsible for reducing the level of spinal block and early resolution of spinal anesthesia [49].

In a randomized double-blind trial including patients undergoing urgent or elective surgery in various medical specialties, prophylactic administration of intravenous ondansetron compared to placebo was shown to significantly reduce blood pressure induced by spinal anesthesia, and fewer patients in the ondansetron group had Compared with the placebo group, they needed ephedrine during surgery. This study showed that, based on the observed rate, the use of ondansetron leads to a reduction of 139 patients requiring ephedrine per 1000 surgeries. Also, older patients are at risk of hypotension, and ondansetron may have a more pronounced antihypertensive effect in the elderly than

in younger patients. And even the administration of ondansetron before anesthesia prevents high blood pressure without affecting the heart rate of these patients [50].

A previous meta-analysis that included 17 randomized trials with a total of 1604 participants showed that 5-HT3 antagonists were effective in reducing the incidence of hypertension and bradycardia, but these effects were limited to patients undergoing cesarean section [51].

Similarly, another meta-analysis of data from 14 randomized trials including data from 1045 patients concluded that there was no strong evidence to support that ondansetron reduces the incidence of blood pressure and bradycardia after subarachnoid anesthesia [48]. However, it should be noted that only one of the 14 studies examined the effect of ondansetron in patients aged 60 years or older, and therefore, their conclusions are based mainly on younger participants.

Accordingly, a recent double-blind, randomized, placebo-controlled study with patients between 20 and 60 years of age, and a total of 140 patients, reported that participants who received ondansetron before an axillary nerve block had lower blood pressure and heart rate were similar to placebo [52].

It is possible that despite sympathetic block, adequate venous return in these patients due to effective vasoconstriction can maintain the load and make the Bezold reflex less involved in this patient population. A systematic review and meta-analysis of 13 RCTs showed that intravenous ondansetron given 5 minutes before the start of spinal anesthesia reduced SIH. Furthermore, this meta-analysis shows that pretreatment with ondansetron significantly reduces hypotension in subjects undergoing elective cesarean delivery. In addition, the results of our meta-analysis show that intravenous ondansetron also helps to reduce the incidence of bradycardia. This study showed that ondansetron inhibits BJR and reduces SIH and bradycardia after spinal anesthesia [53]. Although there was statistical heterogeneity among the studies, which could be attributed to variable definitions of blood pressure or the variety of types of surgeries.

A study was conducted with the aim of investigating the effect of ondansetron versus dexamethasone in reducing the incidence of hypotension caused by spinal anesthesia in cesarean delivery. In this study, 75 healthy parturients, with ASA I and II physical status, underwent elective cesarean surgery and underwent spinal anesthesia and showed that the effect of 8 mg of ondansetron compared to 8 mg of dexamethasone in reducing blood pressure and heart rate fluctuations in spinal anesthesia It is more effective. However, dexamethasone 8 mg was as effective as ondansetron 8 mg in providing a simple, safe, inexpensive, effective method of preventing nausea and vomiting during and after surgery with the advantage of being cheap and reducing the economic burden [54].

While our trial was conducted in a non-partum population, many studies on the effect of ondansetron in preventing hypotension have been conducted in a population of puerperal patients [55,56]. However, a parallel can still be drawn between pregnant women and the elderly, as both have a physiologically important reduction in preload, which reinforces the idea that suppression of the BJ reflex could explain the results observed in our study.

However, this hypothesis has been challenged by a previous study, which showed that ondansetron also prevented postoperative hypotension in elderly patients under general anesthesia. In that study, elderly patients received standard induction of anesthesia maintained with inhaled anesthetics. While 45% of patients in the control group had postoperative hypotension, this complication was observed in only 16% of patients receiving 4 mg of intravenous ondansetron [57]. The exact mechanism of this effect after general anesthesia is still unclear and cannot be explained by suppression of the BJ reflex. Therefore, it is unclear whether the preventive effect in reducing postoperative hypotension associated with spinal anesthesia, which was detected in our trial, is the result of inhibition of BJR and/or other mechanisms related to cardiovascular tone.

On the other hand, considering that our study consisted of an elderly population, we know that in older patients, inflammation, oxidative stress and endothelial dysfunction can lead to an increase in intra- arterial stiffness and a decrease in vascular expansion. Its consequences will be an increase in systolic blood pressure, an increase in left ventricular contraction and afterload, as well as a decrease

in coronary perfusion and initial diastolic filling of the left ventricle [58].

Patients over 60 years show higher baseline systolic blood pressure levels and upper mean change than younger subjects. Aging is also associated with decreased response to beta-adrenergic drugs and increased parasympathetic tone, which decreases cardiopulmonary and baroreflex reflexes [26,59].

Another plausible explanation for these results showed that approximately 80% of blood volume is stored in the veins, and aging-related hardening of the arteries may reduce the ability to absorb changes in blood volume. In addition, we cannot completely rule out the preventive effect observed mainly in the elderly group since these patients are more susceptible to BJ reflex hypotension and usually have reduced blood flow from the vena cava. They show upper and lower levels that gradually increase with age [59,60].

It can be assumed that by blocking this reflex, ondansetron is more effective in preventing hypotension caused by spinal anesthesia in elderly patients. Previous studies that included obstetric patients have shown that in patients who received 4 mg of ondansetron before subarachnoid block, the incidence of hypotension and the use of vasopressors were lower, which indicates the involvement of BJ reflex inhibition [61-63].

Therefore, it seems that the preventive administration of ondansetron or dexamethasone will be equally helpful in preventing hypotension and bradycardia in elderly patients.

In conclusion, dexamethasone and ondansetron before spinal anesthesia in elderly patients caused a significant reduction in changes in blood pressure and heart rate, decreased blood pressure and heart rate, and especially in those who received an extra fluid injection or alpha administration. An agonist is contraindicated due to cardiovascular risk.

The lack of risk and adverse effects of this dose of prescription drugs is low, the significant reduction in blood pressure and the number of heartbeats, hypotension, which has negative consequences on the cardiovascular system during and even after the operation, is reduced, as well as the possibility of using Reduced high doses of vasopressor drugs, which can cause negative effects on the cardiovascular system in the elderly, to control blood pressure and heart rate, which saves money.

Most of these patients will receive ondansetron during the procedure anyway, so there is no additional cost for the procedure. However, it is important that each anesthesiologist uses case-by-case judgment. We must keep in mind that the administration of dexamethasone or ondansetron cannot completely replace the current strategies in the treatment of hypotension caused by spinal anesthesia, but should be used as an additional strategy in addition to the existing tools.

As a limitation, in this study, the statistical significance of the reduction in blood pressure after spinal anesthesia and the reduction in the need for ephedrine or atropine was emphasized. And other possible side effects, such as glycemic profiles in the hours after dexamethasone administration and the rate of postoperative infection, were not reported in this study. Also, the low sample size for each subgroup limits the conclusions that can be drawn from our trial.

In suggestion, expanding clinical trials to surgical procedures other than urology or elderly patients and with different doses of ondansetron or dexamethasone would provide more validity to the study.

Also, considering other complications and a higher sample size will help to make the results more reliable at the clinical level. Therefore, there is a need for more studies on this topic. If some variables are removed, a more decisive result can be reached regarding the effectiveness of this intervention.

Authors Contribution

All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors of the manuscript title "The Comparative Study of Intravenous Ondansetron and Dexamethasone Effects on Reducing The Incidence of Post-Spinal Anesthesia Hypotension in Elderly Patients Undergoing Urologic Surgeries in Yasuj Shahid Beheshti & Tehran Shahid Modarres Hospitals" whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bur- eaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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