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Research Article

The Effect of Different Doses of Ondansetron in Reducing Injection Pain of Etomidate: A Double-Blind Randomized Clinical Trial

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ABSTRACT

Background: Etomidate is an anesthetic induction medicine that is the first choice, particularly in elderly and cardiovascular patients, due to its favorable hemodynamic stability. There are some complications with etomidate administration nevertheless. Created pain during the injection, for instance, may be bothering.
Methods: 60 patients who were candidates for general anesthesia with Etomidate were divided into 3 groups randomly. After infusing 300 ml of normal saline for each patient, 2 minutes before induction, Ondansetron 8mg, Ondansetron 4mg, and normal saline were administered to groups first, second, and third, respectively. Then Etomidate was given to all patients in the form of 10 ml ampoules containing 20 mg of Etomidate equally. The pain score was rated using the FPRS criterion, which is from 0 to 10. Collected data were analyzed and interpreted.
Results: The factor of sex wasn't an effective element in the level of pain, but height ($p = 0.034$) and age affected this level; patients who were in their seventh decade of life had no complaints (59.4%). There was no significant difference in the mean arterial blood pressure, the mean heart rate, and the mean arterial oxygen saturation between the three groups. The level of pain was considerably different in the study groups ($p = 0.000$), and the 8 mg ondansetron group had the lowest pain.
Conclusion: Ondansetron can reduce the injection pain of Etomidate, and the greatest effect is related to the 8 mg dose of Ondansetron.

Introduction

A variety of drugs are used to induce anesthesia by intravenous (IV) injection; however, some side effects of these drugs reduce their use [1]. Postoperative nausea and vomiting (PONV) are the two most common complications of anesthesia. PONV results in the patient hospital stay and delayed recovery of patients [2].

Etomidate is a special drug used for the induction of general anesthesia and sedation and is usually used as an IV injection in the clinic. Nausea and vomiting are some other side effects of this drug [3]. Etomidate is a suitable alternative to propofol and barbiturates due to the rapid induction of IV anesthesia, especially in patients with compromised myocardial contractility [4]. During IV injection, etomidate damages the vascular endothelium and causes pain as it is prepared from propylene glycol [1]. Rapid recovery occurs from a single IV dose, and there is little possibility of persisting debilitating effects. Etomidate is basically not used as a painkiller, and resulting nausea and vomiting are more common than prescribed events of thiopental and propofol [5]. Pain is an unpleasant sensation caused by harmful stimuli sensed by neuronal receptors of pain receptor neurons [6]. Pain receptors are free neuronal terminals that are present in different areas of the body, such as close to the surface of

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the skin, muscles, vessels, and other regions of the body [6]. A feeling of pain can be a sign of various diseases and can also trigger one's restlessness and the onset of psychological stress [7].

Extensive destruction of the 5-hydroxytryptamine OR 5-HT3 receptor in the human body underpinned the research on ondansetron, a serotonin 5-HT3 receptor antagonist that blocks sodium channels, and its anesthetic effect upon subcutaneous injection is 15 times that of lidocaine [8], which has recently been used for sedation and PONV; however, the results have not always been consistent and similar. Ondansetron was patented in 1984, and its drug use was confirmed in 1990 [9]. It is sold under the brand name Zofran, a drug used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery [9]. It is also used for the treatment of gastroenteritis and can be applied orally or by intramuscular or IV injection. Ondansetron is a highly specific antagonist of the serotonin 5-HT3 receptor that has negligible affinity for dopamine receptors [10]. 5-HT3 receptors are present both in the peripheral and central nervous systems (PNS & CNS) at the end of the vagus nerve terminals and in the area of chemical receptors at the end of the medulla in the CNS [10]. Serotonin is secreted by enterochromaffin cells in the small intestine in response to chemotherapeutic agents and can stimulate the sensory part of the vagus nerve to trigger the vomiting reflex. As a serotonin receptor antagonist, endostatin is supposed to inhibit the binding of serotonin to the sensory part of the vagus nerve and prevent the onset of vomiting [10].

Etomidate is widely used for general anesthesia and is irreplaceable for heart patients due to its vascular stability; therefore, it is used increasingly in hospitals in Isfahan city. It cannot be discontinued despite its side effects, such as pain, nausea, and vomiting; hence, there is a need for a drug to reduce its side effects. According to recent studies, ondansetron can effectively reduce pain, nausea, and vomiting caused by etomidate injection. This drug is being extensively used owing to its low side effects and has been used at different doses in studies, but researchers have not yet achieved a single dose of the drug to treat the complications of etomidate. This study, therefore, aimed to compare the effect of two frequently used doses of ondansetron on reducing the side effects of etomidate injection to achieve a suitable and single dose of ondansetron for the least side effects of etomidate injection.

Methods

In this study, 60 patients were examined in a double-blind clinical trial. First, demographic information and the history of diabetes, hypertension, smoking, drug use, and alcohol addiction, as well as the use of psychiatric drugs, were obtained by examining patients' records. Patients were then randomly divided into three groups. After entering the operating room, patients underwent surgical care and monitoring such as electrocardiogram, blood pressure, and pulse oximetry. Then, venipuncture was done with Branol No. 20 from their dorsal hand veins, and a normal saline solution was injected at a rate of 300 ml/h. Ondansetron and placebo were coated in previously coded 4 ml syringes. Ondansetron was packaged in 4 cc ampoules, half of which contained 8 mg and the other half containing 4 mg of ondansetron (Elixir Pharmaceutical Co.). After the administration of 100% oxygen, syringes containing ondansetron and placebo were injected intravenously within 2 min. Patients underwent ondansetron and placebo IV injection 2 min before the induction of anesthesia. Then, all patients received etomidate intravenously in 10 ml ampoules containing 20 mg of etomidate (Abu-Reihan Pharmaceutical Co.; the onset of action: 30-60 sec, peak effect: 1 min, and duration of effect: 3-5 min). Although the half-life of this drug is 75 min, the duration of the etomidate effect in a normal dose is 5-10 min due to the redistribution of this drug from plasma to other tissues of the body.

Data were collected using a checklist. Pain score was measured and recorded using the FPRS (Faces Pain Rating Scale), which was rated from 0 to 10. According to this scale, scores of zero and 10, respectively, indicate a happy face with no pain and a crying face with the most severe pain. The pain was measured after the etomidate injection. All patient data, including demographic factors and preclinical symptoms, were recorded in a researcher-made checklist and entered into SPSS software (Version 26). Data were analyzed using Chi-square, Wilcoxon, and analysis of variance (ANOVA) tests at a 5% error level.

Results

In the present study, out of 60 patients studied the participants consisted of 27 men (45%) and 33 women (55%), with minimum and maximum ages of 27 and 75 years, respectively, and a mean age of 56.48 ± 13.82 years. (Figure 1). The weight of patients averaged 85.72 ± 8.70 kg, with minimum and maximum values of 63 and 100 kg, respectively. The shortest and the highest statures of patients were 159 cm and 190 cm, respectively, with a mean of 171.37 ± 8.96 cm. The patient's body mass index (BMI) was evaluated from the lowest (23.71) to the highest (34.89) values, with a mean of 29.23 ± 2.67 on the overweight scale. (Table 1)

Demographic indicators based on the studied groups included mean heights in the placebo group (51.90 ± 13.46), ondansetron 4 mg group (54.45 ± 13.31), and ondansetron 8 mg group (63.10 ± 12.73). The weight averaged 78.65 ± 8.36, 85.90 ± 5.72, and 92.60 ± 5.47 kg in placebo, ondansetron 4 mg, and ondansetron 8 mg groups, respectively. Mean heights in placebo,

ondansetron 4 mg, and ondansetron 8 mg groups were 168.10 ± 7.28), 168.60 ± 6.84, and 177.40 ± 9.61 cm, respectively. BMI averaged 27.85 ± 2.79, 30.25 ± 1.74, and 29.58 ± 2.86 in placebo, ondansetron 4 mg, and ondansetron 8 mg groups, respectively. The age, weight, height, and BMI of patients were significantly different in the study groups (Table 1). There was no significant difference between the genders of patients in the study groups ($p > 0.05$); in other words, gender distribution was the same in the groups (Table 1), when prescribing high doses of this drug.

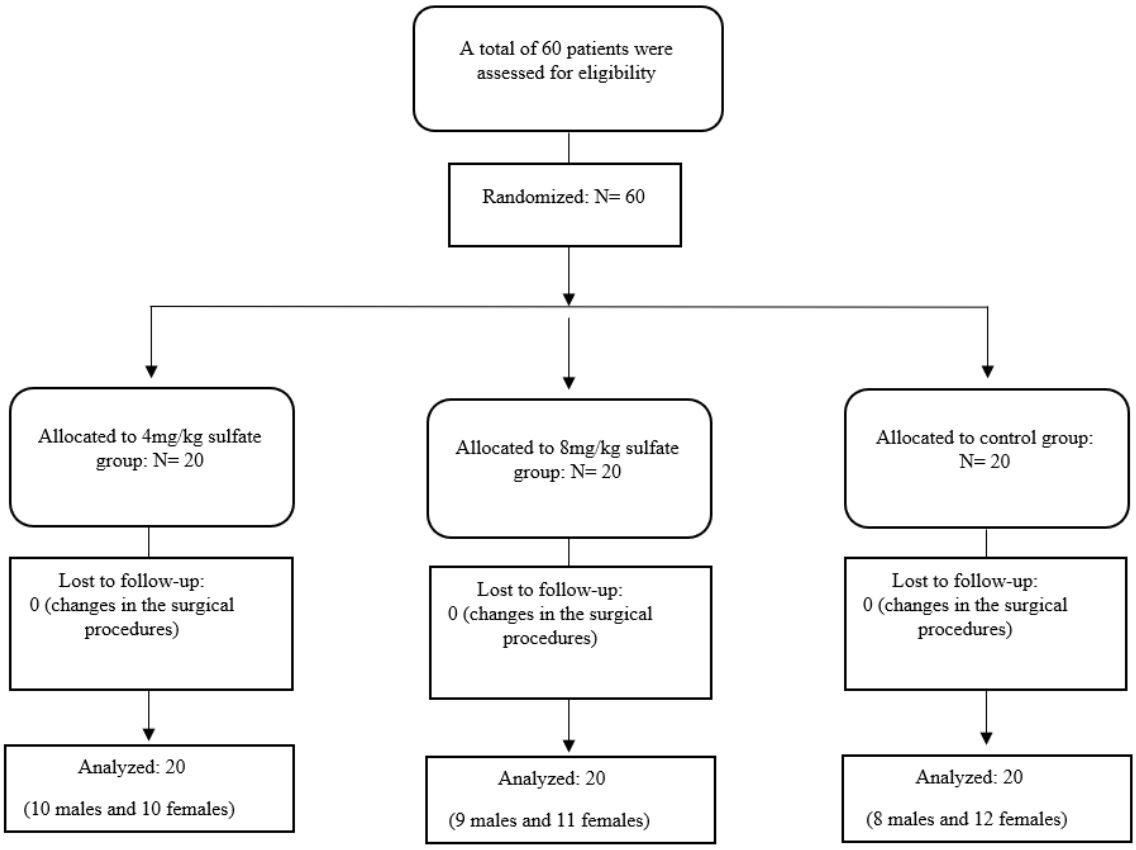

Figure 1- CONSORT flow diagram

Table 1- Comparison of patients' demographic characteristics based on the studied groups

	Group	**N**	**Mean**	**SD**	**Sig.**
Age	Placebo	20	51.90	13.46	0.024
	4 mg	20	54.45	13.31	
	8 mg	20	63.10	12.73	
Weight	Placebo	20	78.65	8.36	0.000
	4 mg	20	85.90	5.72	
	8 mg	20	92.60	5.47	
Stature	Placebo	20	168.10	7.28	0.001
	4 mg	20	168.60	6.84	
	8 mg	20	177.40	9.61	
BMI	Placebo	20	27.85	2.79	0.012
	4 mg	20	30.25	1.74	
	8 mg	20	29.58	2.86	
		Frequency	%	Sig.	
Male	Placebo	9	45	0.168	
	4 mg	6	30		
	8 mg	12	60		
Female	Placebo	11	55		
	4 mg	14	70		

	8 mg	8	40

Mean systolic blood pressures before injection and 5, 10, 25, 40, and 55 min after injection were significantly higher in the ondansetron 8 mg group than in the other groups. Diastolic blood pressures before injection, after injection, and 5, 10, 25, 40, 55, and 70 min after injection were significantly higher in the ondansetron 8 mg group than in the other groups. Mean arterial blood pressures at 25, 40, 55, and 70 min after injection were significantly higher in the ondansetron 8 mg group than in the other groups. Mean heart rates were not different at the studied times in the three groups, and similar heart rates were recorded for patients in all three groups. Mean arterial oxygen saturation (O_2 sat) rates at 10, 25, 40, and 55 min after injection were significantly higher in the ondansetron 8 mg group than in the other groups. Pre-injection mean arterial O_2 saturation was much higher in the ondansetron 4 mg group than in the other groups (Table 2).

Table 2- Mean systolic, diastolic, and arterial blood pressures, heart rate, and O_2 sat in the three groups at the studied times

	Variable	Mean ± SD			Sig.
		Placebo	Ondansetron 4 mg	Ondansetron 8 mg	
Systolic blood pressure	Baseline	8.82±126.2	14.54±123	6.48±130	0.118
	Before injection	10.24±131.5	15.15±123.5	6.506±134.3	0.010
	After injection	11.52±124.6	15.9±126.2	70.052±132.6	0.094
	After 5 min	7.16±122	16.22±126.9	14.76±138.6	0.001
	After 10 min	11.01±119.9	14.63±128.4	13.84±136.3	0.001
	After 25 min	12.23±118.2	36.95±115.5	15.73±134.4	0.035
	After 40 min	13.58±115.1	16.26±123.2	17.54±134.5	0.001
	After 55 min	15.98±114.2	13.31±125.9	22.4±135.2	0.002
	After 70 min	27.27±124.7	13.31±124.4	18.57±132.3	0.388
Diastolic blood pressure	Baseline	4.84±74.5	4.52±75.7	5.98±78.30	0.067
	Before injection	7.63±74.30	5.2±76	5.66±79.90	0.019
	After injection	9.03±72.8	7.88±71	3.53±81.90	0.000
	After 5 min	7.11±77.40	7.41±74.50	5.07±87.90	0.003
	After 10 min	3.61±78.30	8.52±74	4.51±87.20	0.000
	After 25 min	6.931±77.40	8.87±73.80	5.55±82.8	0.001
	After 40 min	8.04±74.80	9.87±72.90	7.54±83.60	0.000
	After 55 min	7.28±76.60	9.71±74	6.311±84.40	0.001
	After 70 min	5.54±72.50	6.96±73.90	6.99±82.10	0.000
Arterial blood pressure	Baseline	7.83±78.7	8.28±78.5	5.33±81.60	0.232
	Before injection	4.32±81	8.67±81.30	4.63±82.30	0.787
	After injection	4.98±83.30	83.50±79.30	5.01±83.50	0.082
	After 5 min	3.54±84.20	9.16±80.40	5.74±84.80	0.080.
	After 10 min	6.75±81	9.55±78.60	5.39±84	0.080
	After 25 min	7.8±91.30	10.1±77.30	4.83±84.70	0.017
	After 40 min	4.37±80.70	8.01±78.70	2.73±84.10	0.011
	After 55 min	4.77±80.90	7.48±77.20	3.44±85.40	0.000
	After 70 min	5.69±78.30	5.58±78.70	2.61±84.50	0.000
Heart rate	Baseline	3.40±96.30	22.59±91.65	3.57±94.80	0.535
	Before injection	5.09±94.30	22.52±91.30	23.678±87.70	0.553
	After injection	8.38±90.20	22.84±88.75	7.38±91.60	0.829
	After 5 min	9.91±84.80	20.88±84.25	7.08±91.10	0.235
	After 10 min	7.71±82.90	21.09±83.50	5.11±89.90	0.191
	After 25 min	7.03±81.50	20.82±82.80	5.35±89.40	0.131
	After 40 min	6.89±79.30	20.964±83.35	7.34±86	0.291
	After 55 min	6.73±79.40	21.17±84.35	6.92±86.10	0.273
	After 70 min	4.96±79.70	21.21±81.45	7.69±84.50	0.519
Mean arterial O_2 saturation (O_2 sat)	Baseline	0.41±98.8	0.47±99.7	3.21±98.30	0.068
	Before injection	0.0±98	0.47±98.7	0.5±98.4	0.000
	After injection	0.41±97.8	0.76±98.2	0.3±97.9	0.055
	After 5 min	0.5±97.6	0.8±97.7	041±97.8	0.572
	After 10 min	068±97.8	.071±97.1	0.47±97.7	0.014
	After 25 min	0.51±97.5	0.96±96.9	0.47±97.7	0.001
	After 40 min	0.68±97.4	0.649±97	0.50±97.6	0.011

After 55 min	0.82±97.6	1.12±97	0.76±97.8	0.021
After 70 min	0.50±97.6	1.19±96.8	1.13±97.3	0.044

The duration of surgery was significantly different between the three groups (p = 0.001), with a shorter duration of surgery in the ondansetron 8 mg group than that of the other two groups. Patients in the ondansetron 8 mg group were more satisfied than the other groups, and a significant difference was observed between the three groups (p = 0.000) (Table 3).

Mean FPRS scores were lower in the ondansetron 8 mg group than in the other groups at all times, and the highest FPRS score was observed in the placebo group. The three groups were significantly different in all the studied times (p = 0.000) (Table 4).

Table 3- Mean duration of surgery and patient satisfaction in the three groups

		Mean ± SD			Sig.
		Placebo	Ondansetron 4 mg	Ondansetron 8 mg	
Duration of surgery		2.3±0.47	2.55±0.35	2.1±0.21	0.001
Patient satisfaction	0	(82.6%)19	(82.6%)19	(82.6%)19	0.000
	(26.4%)6	(4.3%)1	(4.3)%1	(4.3)%1	
	(100%)14	0	0	0	
Mean ± SD		0.47±2.70	041±1.80	0.22±10.5	

Table 4- Mean FPRS scores in the three groups at the studied times

Variable	Mean ± SD			Sig.
	Placebo	Ondansetron 4 mg	Ondansetron 8 mg	
Baseline	1.5±5.2	1.64±3.2	1.16±1.90	0.000
Before injection	1.2±5.7	1.7±3.2	1.01±1.1	0.000
After injection	1.55±5.90	1.43±3.20	1.12±1	0.000
After 5 min	1.48±6.1	1.36±3.2	1.11±1.2	0.000
After 10 min	1.25±5.9	1.21±2.7	1.45±1	0.000
After 25 min	1.45±5.7	1.36±2.8	0.94±0.5	0.000
After 40 min	1.23±5.4	1.14±2.6	0.94±0.40	0.000
After 55 min	1.31±5.40	1.14±2.60	0.93±0.30	0.000
After 70 min	1.38±5.30	1.05±2.50	0.92±0.3	0.000

Discussion

Pain is a phenomenon consisting of a series of biological, psychological, and social signs, an indicator of the quality of life and mental health, a sign of an underlying disorder, and a symptom of the disease. Pain is a predictable consequence of acute diseases, injury, and surgery that usually resolves with recovery [11]. The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [12-13].

Etomidate is a hypnotic anesthetic that provides sedation by GABA (gamma-aminobutyric acid) receptors in the CNS [14-15]. This drug is applied in several clinical uses [16-18]. Immediate onset of action, short duration of action, and subtle effects of etomidate on body hemodynamics are some of the favorable effects of this drug, making its wide use in anesthesia and sedation [19-20]. Potential side effects of the drug include nausea and vomiting, myoclonus, pain at the injection site, and temporary suppression of the adrenocortical axis.

Nowadays, pain at the injection site is reduced using several methods, including slow injection of the drug [21], warming/cooling of the drug [22], dilution of the drug, using special solutions, and conjugate use of the drug [23].

Endonestrone is the important neurotransmitter serotonin (5-hydroxy-tryptamine) in the CNS, which is derived from tryptophan and is found in the gastrointestinal tract, platelets, and the CNS [24]. This mediator is known as a happiness hormone and includes several cognitive/non-cognitive behaviors such as humor and mood [25], sex [26], appetite and sleep [27], memory [28-29], feeling and anxiety [30], body temperature [31], movement [32-33], muscle contraction behavior, the function of the cardiovascular and endocrine systems [34], and water absorption [35]. Approximately 80% of the total serotonin in the human body is present in intestinal enterochromaffin cells [34], and the rest is synthesized in serotonergic neurons in the CNS [24,34].

Although the analgesic properties of this drug have been investigated in numerous studies, no specific mechanism has been found for this property. Some

researchers believe that this drug helps gastric evacuation and has the potential property to increase the absorption of other analgesic drugs, in addition to its anti-nausea properties [36].

In the present study, etomidate injection pain was similar in the studied men and women, but less pain was observed in older people, especially those in the seventh decade of life.

The examination of the relationship between height, weight, and BMI of patients revealed that the height and weight of patients were the factors affecting the level of pain, so the pain was less prevalent in taller and higher-weight patients than the other ones. As announced by the American Dental Association (ADA), pain disorders are diagnosed twice as often in women as in men, and the fourth and fifth decades of life are the most common ages of affection, which may be because pain tolerance decreases with age [37]. This discrepancy between the results of the present study and the presented theory may be because the level of pain was studied with drug injection in the present study, but the ADA announced the level of pain in the elderly at all stages of life. Aghdaei et al. [38] observed no significant difference in the rate of pain reduction after analgesic injection in the sex of patients. They also stated that age was not a factor in patients' pain reduction. The present results are significantly related to Aghdaei et al. in terms of no associations between patients' gender and pain level, but the two studies are not consistent in terms of no associations between patients' ages and pain reduction. This difference may result from the difference in the method of investigation in the two studies.

According to the results of this study, the mean diastolic blood pressure increased in patients immediately after ondansetron injection, and ondansetron 8 mg produced the greatest effect. The increase in diastolic blood pressure continued for up to 70 min after injection, and blood pressure was significantly higher in the two experimental groups than in the placebo group. The highest increase in diastolic blood pressure belonged to the ondansetron 8 mg group. The same was true for systolic blood pressure and mean arterial blood pressure, in which blood pressure increased with the injection of ondansetron, especially 8 mg. Mean systolic blood pressures before injection and 5, 10, 25, 40, and 55 min after injection were significantly higher in the ondansetron 8 mg group than the other groups. Mean arterial blood pressures at 25, 40, 55, and 70 min after injection were significantly higher in the ondansetron 8 mg group than in the other groups. The increased blood pressure in the studied patients could be attributed to the high BMI. In line with the present study, Azimaraghi et al. [39] found that IV injection of ondansetron reduced etomidate injection pain, and ondansetron 8 mg was more effective than 4 mg. Malekianzadeh et al. reported that ondansetron injection (4 mg) did not affect patients' blood pressure, which is inconsistent with our result [40]. This discrepancy may arise from assessing the effect of IV ondansetron in preventing hypotension after spinal anesthesia in elective cesarean section patients. It is noteworthy that mean levels of systolic, diastolic, and arterial blood pressures increased in their study in the ondansetron 4 mg group compared to the control group, but it was not statistically significant. Atikahmed et al. (2020) claimed that ondansetron injection reduced the pain caused by etomidate injection [41]. Therefore, the results of the present study correspond to those of Azimaraghi et al., Malekianzadeh et al., and Atikahmed et al.

Mean heart rates at the studied times were not different in the three groups, and patients in all three groups had similar heart rates. Mean O_2 sat values at 10, 25, 40, and 55 min after injection were significantly higher in the ondansetron 8 mg group than in the other groups. Before the injection, the mean O_2 sat was much higher in the ondansetron 4 mg group than those in the other groups. The mean duration of surgery was significantly different in the three groups, with the highest and the lowest treatment times recorded for the ondansetron 4 mg and 8 mg groups, respectively. Patients in the ondansetron 8 mg group were more satisfied than those in the other groups. According to FPRS scores, the amount of pain was much lower in the ondansetron groups at the studied times than in the placebo group, and the highest pain reduction was observed in the ondansetron 8 mg group at all the examined times. Aghajani et al. [1] reported that ondansetron injection before etomidate significantly reduced the etomidate injection pain. In a study conducted by the anesthesia department of Farabi Hospital in Tehran [42], it was found that pain intensity was significantly lower in patients who received medication than in those without medication. Banavasi et al. [43] also claimed that the mean pain was lower in lignocaine-injected people than in those who were injected with ondansetron.

In our study, the results obtained regarding the reduction of pain in ondansetron-treated patients compared to the other patients are in line with previous studies. Moreover, the effect of using ondansetron 4 mg to reduce the side effects of etomidate has been examined in many studies. For example, Khorasanizadeh et al. presented evidence that the use of ondansetron 4 mg had a positive and high effect on the reduction of complications, especially the etomidate injection pain, in patients [44]. Likewise, Napolitano et al. reported a positive effect of ondansetron 4 mg on pain reduction in patients undergoing etomidate [45]. Kaushal et al. also found that ondansetron 4 mg was the most effective drug to reduce the complications of etomidate injection pain in patients under general anesthesia for cardiac bypass [46]. In their study, the effects of three drugs, midazolam, ranitidine, and ondansetron, were examined on pain

reduction following etomidate injections. Rathore et al. reported similar results to the present study and previous studies, suggesting that ondansetron was one of the most effective analgesics for etomidate injection pain [47]. Therefore, our results and those of previous studies demonstrate that the use of ondansetron 4 mg effectively reduces the etomidate injection pain. Thus, ondansetron 4 mg can be used to reduce the pain of etomidate, considering the possibility of drug complications and the twice-daily dose of ondansetron 8 mg.

Based on the results of the present study and those reported in previous studies, it can be concluded that ondansetron injection effectively reduces pain following etomidate injection and greatly reduces the amount of pain in patients, thereby increasing patient satisfaction with the duration and type of treatment. Accordingly, the use of ondansetron 8 mg can be considered an effective treatment to reduce patients' pain.

Conclusion

Ondansetron injection effectively reduces the pain of etomidate injections, with ondansetron 8 mg having the greatest effect. However, one of the potentially dangerous side effects of ondansetron, i.e., prolonging QT, is recommended to be considered by anesthesiologists as well as intensive care and pain specialists when prescribing high doses of this drug.

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Ethical considerations

The participants were assured of the confidentiality of their data, and they were informed that the measures and methods employed in hemorrhagic surgery are designed to save lives via preserving the vital organ's functions. The purpose of the study was to lower bleeding during surgery and prevent complications caused by bleeding, as well as the need for blood transfusion.

All patients signed an informed written consent. The research committee of Isfahan University of Medical Sciences and the ethics committee approved the study design (ethics code: IR.MUI.MED.REC.1399.443, Iranian Registry of Clinical Trials (IRCT) code: IRCT20160307026950N38).

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