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Comparing the impacts of ephedrine, ketamine, ondansetron, and atropine on postoperative nausea and vomiting in patients with lower limb–fracture repair surgery: A randomized clinical trial

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ABSTRACT

Objective: To compare the impacts of ephedrine, ketamine, ondansetron, and atropine on postoperative nausea and vomiting among patients with lower limb fracture repair surgery under spinal anesthesia.

Methods: This randomized, double-blind trial was conducted at Valiasr Hospital, Arak, Iran. Participants were allocated *via* balanced block randomization into four groups: ephedrine, ketamine, ondansetron, and atropine. Nausea frequency (episode count) and severity (visual analogue scale [VAS]) were assessed at recovery and 2, 4, 6, 12, and 24 hours postoperatively. Severe nausea (VAS>3) was treated with intravenous metoclopramide (10 mg), with total 24-hour doses recorded. Sedation levels (Ramsay Sedation Scale) and medication side effects (*e.g.*, confusion, hallucinations) were evaluated at recovery and 1, 2, and 4 hours post-surgery. Data were analyzed using SPSS (v. 20.0), with $P<0.05$ considered significant.

Results: A total of 128 patients were included. No significant difference was observed among the groups concerning vomiting score and nausea frequency ($P>0.05$). Nausea severity in the ondansetron and ephedrine groups was significantly less than the other two groups ($P=0.001$) and nausea severity in the ondansetron group was significantly less than the ephedrine group ($P=0.01$). The Ramsay sedation score in the ketamine group was also significantly higher than the other groups at recovery and one hour after surgery ($P=0.001$).

Conclusions: Ondansetron and ephedrine are effective in significantly reducing postoperative nausea severity and ondansetron acts better. Therefore, these medications can be recommended for postoperative nausea and vomiting management.

KEYWORDS: Nausea; Vomiting; Spinal anesthesia; Lower limb fracture; Ephedrine; Ketamine; Ondansetron; Atropine

Trial registration: Iranian Registry of Clinical Trials (IRCT20230713058769N1)

Summary

Question: What is the difference in impacts of ephedrine, ketamine, ondansetron, and atropine on postoperative nausea and vomiting among patients with lower limb fracture repair surgery under spinal anesthesia?

Findings: The vomiting score and nausea frequency were not statistically different among groups, but nausea in the ondansetron and ephedrine groups was more severe than than the other two groups, although nausea severity in the ondansetron group was less than the ephedrine group. Ramsay sedation score in the ketamine group was significantly higher than the other groups.

Meaning: Ephedrine, ketamine, ondansetron, and atropine had similar effects on vomiting score. Nevertheless, ondansetron acts better than other medications, based on the type of surgery and patients conditions, these medications are recommended for postoperative nausea and vomiting management.

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1. Introduction

Postoperative nausea and vomiting (PONV) are among the most common post-anesthesia complaints of patients and are usually associated with postoperative pain[1,2]. One of their underlying causes is the impact of anesthetic agents on the vomiting center in the medulla. They may occur up to 24 hours after surgery in 20%-30% of patients[1,3,4]. PONV may lead to different complications such as airway obstruction, pneumonia, aspiration, or surgical wound opening[2,5]. They may also cause dehydration, electrolyte disturbances, hypertension, bleeding from skin flaps, and delay in hospital discharge[2,4].

There are different medications which can be used independently or in adjacent to other methods for PONV management[5]. Metoclopramide, ondansetron, dexmedetomidine, dexamethasone, midazolam, ephedrineantihistamines, butyrophenones, and other 5HT3 antagonists are medication for these adverse effects[2,6-8]. Metoclopramide, antihistamines, and butyrophenones have different side effects such as oversedation, hypotension, xerostomia, extrapyramidal symptoms, and tachycardia, and hence, their routine use has been restricted[9,10] and studies to find safer and more effective medications are still in progress.

Ketamine is an anesthetic agent that blocks *N*-methyl-*D*-aspartate (NMDA) receptors and thereby, reduces the sensitivity of the central nervous system to pain. NMDA receptors are ligand-gated ion channels that allow the transmission of neural signals among neurons in the brain and spinal cord[11]. For the transmission of neural signals, the gates of these channels are opened through the connection of glycine and glutamate to these receptors, which activates these channels. Chemical compounds that occupy and deactivate NMDA receptors are called NMDA antagonists[11,12].

Ondansetron is a 5HT3 receptor antagonist for the prevention of nausea and vomiting after surgery and chemotherapy[13,14]. Specific 5HT3 receptor antagonists have strong antiemetic effects through inhibiting 5HT3 receptors in the center of vomiting[15]. Ondansetron has a half-life of 4-9 hours and can be administered once daily either orally or intravenously[1].

Atropine can also reduce nausea and vomiting through exerting vagolytic effects on peripheral receptors. Intravenous atropine is widely used during surgeries under general or spinal anesthesia to prevent nausea, vomiting, and bodily secretions. A study showed that atropine and ondansetron significantly reduce PONV prevalence and atropine is as effective as ondansetron in reducing PONV and patient stay in the recovery room after strabismus surgery[16].

Ephedrine is a selective sympathomimetic agent for hypotension management, which is administered through different routes, including continuous infusion, single doses, or intramuscular injection. A study on women with cesarean section under spinal anesthesia found that the prophylactic use of ephedrine 5 mg/kg administered at the time of spinal anesthesia induction reduced blood pressure and thereby, reduced severity of PONV[17].

Although various studies have evaluated the impacts of ephedrine, ketamine, ondansetron, and atropine, we did not find any comparative study into their impacts on PONV. Moreover, the results of some studies into their impacts are contradictory. Therefore, we decided to undertake the present study to compare the impacts of ephedrine, ketamine, ondansetron, and atropine on

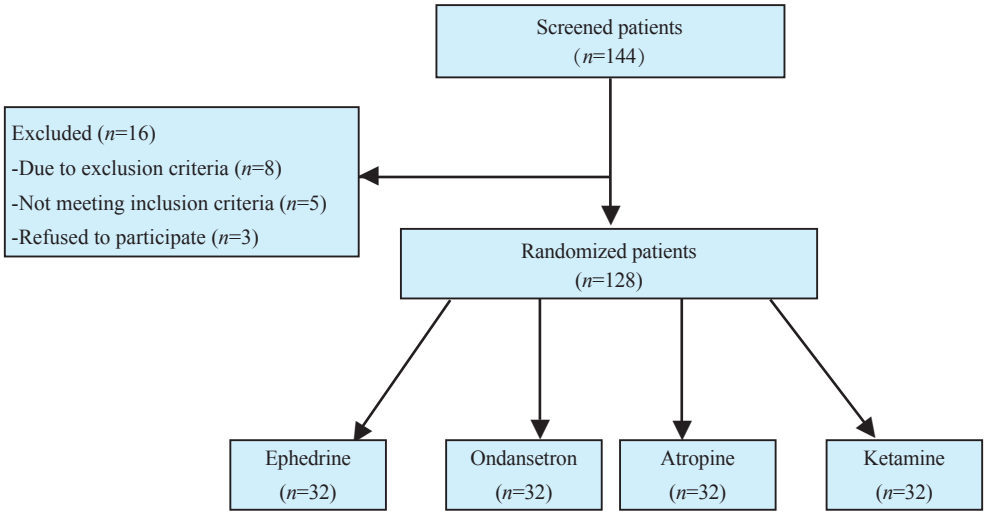

Figure 1. The study flowchart.

PONV among patients with lower limb-fracture repair surgery under spinal anesthesia to determine the safest and most effective medication for PONV prevention.

2. Patients and methods

2.1. Study design and setting

This double-blind clinical trial was undertaken on 128 patients with lower limb fracture repair surgery under spinal anesthesia. Participants were selected from Valiasr hospital, Arak, Iran. Sample size calculation was done based on the results of recent studies with regard to study power 80%, and confidence interval 95%. Balanced block randomization was employed to allocate participants to four groups with equally 32 patients, namely ephedrine, ketamine, ondansetron, and atropine groups (Figure 1). A statistical analyst generated the allocation sequence using an online platform (www.sealedenvelope.com) and concealed it using opaque envelopes.

Inclusion criteria included informed consent for participation in study and age between 18-75 years, class Ⅰ or Ⅱ physical status based on the classification system of the American Society of Anesthesiologists and lower limb fracture repair under spinal anesthesia. Exclusion criteria were anesthesia method failure and voluntary withdrawal from the study as well as history of drug abuse or cigarette smoking, history of allergy to pollens or study medications, history of neuromuscular disorders, cardiomyopathy, coagulopathy, and chronic diseases.

2.2. Intervention

All participants were hospitalized at least one day before surgery and did not receive anything per month from eight hours before surgery. At the time of entrance to the operating room, an intravenous line was established, Ringer's solution was administered at a rate of 10 mL/kg, and heart rate, mean arterial blood pressure, and arterial oxygen saturation were measured and documented. Before the induction of spinal anesthesia, participants in the ephedrine, ketamine, ondansetron, and atropine groups respectively received ephedrine 5 mg (Sterop Co., Belgium), ketamine 0.3 mg/kg (Exir Co., Iran), ondansetron 8 mg (Alborz Daru Co., Iran), and atropine 100 μg (Caspian Tamin Co., Iran). The volume of the medications was increased to 5 mL using distilled water and the medications were administered intravenously. Then, spinal anesthesia was induced under sterile conditions using bupivacaine 15 mg (Caspian Tamin, Co., Iran) and through a Quincke spinal needle 25 inserted in sitting position in the space between the third and the fourth lumbar vertebrae. Participants were placed in supine position immediately after anesthesia induction and their heart rate, mean arterial blood pressure, and arterial oxygen saturation were measured and documented every fifteen minutes in the first hour and every thirty minutes during the rest of the surgery and recovery. Patients who developed persistent hypotension (*i.e.*, a decline of more than 20% in mean arterial blood pressure) despite routine treatments (such as Ringer's solution) received ephedrine 10 mg. Moreover, patients who developed bradycardia (*i.e.*, a heart rate of less than 50 beats per minute) received atropine 0.5 mg. These patients were excluded from the study.

2.3. Measurements

The frequency of nausea episodes was counted and its severity was assessed using a visual analogue scale at recovery and 2, 4, 6, 12, and 24 hours after surgery. The visual analogue scale was a ten-centimeter ruler with zero (No nausea) at one end and 10 (Severest nausea) at the other end. Participants were asked to rate their nausea by placing a sign on the ruler. The distance between zero and the sign was measured and documented as nausea severity[18]. Vomiting was also measured using a five-point scale from zero (No vomiting) to 4 (Frequent uncontrollable vomiting)[19]. Patients with a nausea severity of 3 or more received intravenous metoclopramide 10 mg and the total administered dose of metoclopramide during the first 24 hours after surgery was documented. The potential side effects of the medications, including confusion and hallucination, were also documented and sedation level was measured at recovery and 1, 2, and 4 hours after surgery using the Ramsay Sedation Scale.

2.4. Statistical analysis

The data were analyzed using the SPSS software (v. 20.0). The frequency, mean, and standard deviation measures of descriptive statistics were used for data presentation. Between-group comparisons were made using the *Chi*-square and the one-way analysis of variance. The repeated measures analysis of variance was also conducted for within-group comparisons.

2.5. Ethical statement

Ethical approval for the study was gained from the Ethics Committee of Arak University of Medical Sciences, Arak, Iran by code IR.ARAKMU.REC.1402.087 at 2023.06.07 and the study was registered in the Iranian Registry of Clinical Trials by IRCT20230713058769N1 code 2023.07.09 (trialsearch.who.int/Trial2.aspx?TrialID=IRCT20230713058769N1). Participant

privacy was protected and informed consent was obtained from all participants.

3. Results

Study participants were 81 male (63.3%) and 47 female (36.7%) patients with lower limb fracture repair surgery under spinal anesthesia. The mean and the range of participants' age were 33.89 ±8.87 and 20-56 years, respectively. There were no significant differences among the groups concerning participants' age, gender, the total administered dose of metoclopramide and the side effects (Table 1), and vomiting score (Table 2) (P>0.05).

There was at least one significant difference among the four groups concerning nausea severity at all measurement time points (P=0.001). Nausea severity in the ondansetron and ephedrine groups was significantly less than the other two groups (P<0.05) and nausea severity in the ondansetron group was significantly less than the ephedrine group (P=0.01). The results of the repeated measures analysis of variance also indicated that nausea severity in the ondansetron group was significantly less than all other groups (P=0.001) (Table 2). However, no significant difference was found among the four groups concerning nausea frequency (P>0.05) (Table 3).

There was at least one significant difference among the four groups in terms of the Ramsay sedation score (P=0.001). Further analysis

Table 1. Patient characteristics.

Variables	Ephedrine (n=32)	Ondansetron (n=32)	Atropine (n=32)	Ketamine (n=32)	P
Age, years, mean±SD	33.8±9.0	33.8±7.8	33.9±3.4	34.8±0.8	0.875
Sex, n, %					
Female	11 (34)	12 (37)	12 (37)	12 (37)	0.992
Male	21 (66)	20 (63)	20 (63)	20 (63)	
Vertigo, n, %	0	0	0	1 (3)	0.390
Hallucination, n, %	0	3 (9)	3 (9)	3 (9)	
Metoclopramide consumption, n, %	3 (9)	2 (6)	7 (22)	6 (19)	0.222

Table 2. Mean vomiting and nausea severity scores.

Time point	Ephedrine (n=32)	Ondansetron (n=32)	Atropine (n=32)	Ketamine (n=32)	P
Vomiting					
0 hour after surgery	0.41±0.50	0.31±0.47	0.50±0.51	0.47±0.51	0.450
2 hours after surgery	0.47±0.51	0.38±0.49	0.56±0.50	0.53±0.51	0.460
4 hours after surgery	0.53±0.51	0.44±0.50	0.63±0.49	0.59±0.80	0.457
6 hours after surgery	0.59±0.50	0.50±0.51	0.72±0.46	0.69±0.47	0.267
12 hours after surgery	0.66±0.48	0.56±0.50	0.84±0.51	0.81±0.54	0.090
24 hours after surgery	0.75±0.62	0.66±0.60	1.00±0.51	0.97±0.59	0.060
Nausea severity					
0 hours after surgery	0.19±0.40	0.09±0.29	0.75±0.44	0.81±0.40	<0.001
2 hours after surgery	0.44±0.50	0.28±0.46	1.03±0.40	1.03 ±0.47	<0.001
4 hours after surgery	0.62±0.55	0.50±0.51	1.28±0.46	1.25±0.51	<0.001
6 hours after surgery	0.97±0.40	0.91±0.59	1.59±0.50	1.62±0.49	<0.001
12 hours after surgery	1.44±0.50	1.87±0.59	1.81±0.60	1.72±0.58	<0.001
24 hours after surgery	1.75±0.62	1.25±0.72	1.91±0.59	1.90±0.59	<0.001

Table 3. Mean Ramsay Sedation Scale scores.

Time point	Ephedrine (n=32)	Ondansetron (n=32)	Atropine (n=32)	Ketamine (n=32)	P
0 hour after surgery	2.00±0.00	2.00±0.00	2.00±0.00	2.22±0.42	0.001
1 hour after surgery	2.00±0.00	2.00±0.00	2.00±0.00	2.02±0.43	0.001
2 hour after surgery	2.00±0.00	2.00±0.00	2.00±0.00	2.03±0.18	0.395
4 hour after surgery	2.00±0.00	2.00±0.00	2.00±0.00	2.06±0.24	0.108

Table 4. Nausea frequency according to recovery status.

Time point	Ephedrine (*n*=32)	Ondansetron (*n*=32)	Atropine (*n*=32)	Ketamine (*n*=32)	*P*
0 hour after surgery					
Yes	0	0	0	0	0.999
No	32 (100.0)	32 (100.0)	32 (100.0)	32 (100.0)	
2 hours after surgery					
Yes	0	0	0	0	0.999
No	32 (100.0)	32 (100.0)	32 (100.0)	32 (100.0)	
4 hours after surgery					
Yes	0	0	0	0	0.999
No	32 (100.0)	32 (100.0)	32 (100.0)	32 (100.0)	
6 hours after surgery					
Yes	0	0	0	0	0.999
No	32 (100.0)	32 (100.0)	32 (100.0)	32 (100.0)	
12 hours after surgery					
Yes	0	0	3 (9.4)	2 (6.3)	0.132
No	32 (100.0)	32 (100.0)	29 (90.6)	30 (93.7)	
24 hours after surgery					
Yes	3 (9.4)	2 (6.2)	4 (12.5)	4 (12.5)	0.815
No	29 (90.6)	30 (93.8)	28 (87.5)	28 (87.5)	

showed that the Ramsay sedation score in the ketamine group was significantly higher than the other groups ($P<0.05$), while there was no significant difference among the ephedrine, ondansetron, and atropine groups respecting this score ($P>0.05$) (Table 4).

4. Discussion

This study aimed to find the safest and most effective medication for the prevention of PONV. Our results showed ephedrine, nausea severity in the ondansetron and ephedrine groups was significantly less than other groups and nausea severity in the ondansetron group was significantly less than the ephedrine group. Moreover, the Ramsay sedation score in the ketamine group was significantly higher than other groups. Although, a study showed that subanesthetic doses of ketamine could be used in adjacent to opioids to better manage pain and PONV[20]. Given the significant role of NMDA receptors in developing tolerance to opioids, their inhibition using ketamine can reduce opioid tolerance[21].

Our findings indicated the significant positive impact of ephedrine on PONV. Similarly, a study showed that the administration of ephedrine 5 mg before changing position from lithotomy to supine position was effective in maintaining hemodynamic stability and reducing blood pressure, bradycardia, and PONV among patients with percutaneous nephrolithotomy under spinal anesthesia. In addition, it may help maintain hemodynamic stability and reduce nausea and vomiting[22]. A comparative study into the impacts of dexamethasone, ketamine, and dexmedetomidine on PONV among women with cesarean section under spinal anesthesia found that all these medications were effective in reducing PONV. Although dexmedetomidine was the most effective medication for PONV reduction, its use was associated with greater decline in blood pressure and heart rate. That study recommended dexmedetomidine to reduce PONV among women with cesarean section under spinal anesthesia[23]. Another study reported the effectiveness of prophylactic ephedrine administration in preventing hypotension[24].

This study also revealed the significant positive impact of ondansetron on nausea severity. Ondansetron is a 5HT3 receptor antagonist approved for the prevention of the nausea and vomiting associated with surgeries and chemotherapy. Specific 5HT3 receptor antagonists have strong antiemetic characteristics and exert their impacts through inhibiting central 5HT3 receptors in the center of vomiting[15]. A comparative study on patients with strabismus surgery found no significant difference between the impacts of ondansetron and atropine on PONV, while both of them significantly shortened the length of stay in the recovery room and enhanced nurse satisfaction[16]. Another comparative study into the impacts of intravenous granisetron and ondansetron administered before spinal anesthesia found that 40 μg/kg granisetron was more effective than 100 μg/kg of ondansetron in reducing PONV after cesarean section[25]. While another study showed the superior effect of granisetron than ondansetron in PONV in the late postoperative period with lower cinsequences[26].

Our study findings revealed ondansetron as the most effective medication in reducing PONV. In agreement with our findings, a study showed that intrathecal atropine prevented PONV induced by intrathecal morphine among patients with lower limb surgeries without altering hemodynamic stability[27]. Moreover, our findings

showed the insignificant impact of ketamine on PONV. This agrees with the findings of a study on fifty non-smoking women with lumbar spinal surgery that showed that subanesthetic doses of ketamine increased PONV and reduced the need for fentany administration[20].

This study concludes that only ondansetron and ephedrine are effective in significantly reducing PONV among patients with lower limb-fracture repair surgery under spinal anesthesia and ondansetron acts better. Moreover, only ketamine is effective in improving sedation among these patients. Ephedrine, ketamine, ondansetron, and atropine used for PONV management have trivial side effects. Therefore, ondansetron and ephedrine could be used to reduce PONV among patients with surgeries under spinal anesthesia.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

All authors worked on manuscript preparation and final approval of manuscript. HM, MH: data collection and data analysis. HM, EM, and MPK: study concept and design, management, data collection. MH, EM, HM; analysis and interpretation of data, critical revision of the manuscript for important intellectual content. MPK, EM, MH: statistical analysis and interpretation of data.

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