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Evaluation of the Prophylactic Effect of Preoperative Ondansetron on Postoperative Delirium in Older Adults Undergoing Orthopedic Surgery: A Double-Blind Randomized Controlled Clinical Trial

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Abstract

Objective: This study aimed to investigate the prophylactic effect of preoperative ondansetron on the occurrence of postoperative delirium (POD) in older adults who are undergoing orthopedic surgery.

Materials and Methods: One hundred included patients with American Society of Anesthesiologists (ASA) classification of I and II were randomly divided into two groups: Group A (n=50) and Group B (n=50), who were preoperatively received 2 mL intravenous ondansetron or placebo (saline solution), respectively. Delirium, nausea, itching, and shivering were analyzed between the two groups at 30 minutes, 1, 6, 8, and 24 hours postoperatively.

Results: There was no significant difference in terms of sex, age, and ASA class of the patients in the two studied groups. Preoperative ondansetron administration has no impact on POD and itching frequency. In addition, no significant relationship between sex and the occurrence of delirium was observed in the ondansetron group. The frequency of shivering at 30 minutes and nausea at 6 and 8 hours in the postoperative period was significantly decreased in the A group compared with the control group.

Conclusion: Ondansetron can still be considered the first line of prevention of postoperative nausea, but does not affect POD, shivering, and itching. However, the study data are not sufficient to draw robust conclusions, and further randomized controlled trials with larger sample sizes are required to validate our results.

Keywords: Nausea, older adults, ondansetron, postoperative delirium, pruritis, shivering

Introduction

Delirium is a common acute cognitive and attentional disorder that is life-threatening and an inevitable clinical state in older adults (1,2). Postoperative delirium (POD) is a common problem in surgical interventions (3,4). This complication usually occurs within five days, especially during the first 24-48 hours postoperatively (5). The incidence rate of delirium in total joint arthroplasty and hip fracture surgery has been reported to range from 5% to 14% and 12% to 56%, respectively (6). It has been known that advanced age, frailty, pre-existing cognitive impairment, intra-operative blood loss, sleep disruption after surgery, the type of surgery, and poorly controlled pain post-surgery, are the main risk factors involved in development of POD (3,7). POD results in longer hospital stays, which is accompanied by higher hospital costs, increased rates of post-hospital institutionalization, poorer functional recovery, cognitive decline, and increased morbidity and mortality (8). Intervention for prevention and treatment of delirium is the two

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main methods of POD management (3). It has been emphasized that overactivity of the serotonergic system and underactivity of the cholinergic system are prominent among the critical factors in delirium occurrence (9,10). Recently, the majority of investigations concerning the prevention or management of POD have primarily concentrated on the serotonergic system. Ondansetron, a selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, blocks the action of serotonin (8). In this regard, some experimental trials have indicated that postoperative administration of ondansetron resulted in a decreased occurrence and duration of delirium in the postoperative period, specifically on the 30th day after surgery (11,12). To the best of our knowledge, there is no study evaluating the effect of preoperative ondansetron administration on POD prevention. This study aimed to investigate whether preoperative ondansetron administration aids in POD prevention in patients undergoing surgery with spinal anesthesia due to femoral or hip fractures.

Materials and Methods

Patients and Design

This double-blind randomized controlled clinical trial was registered in the Iranian registry of clinical trials with registration number IRCT20170515033986N1 (registration date: 16.11.2020). This study was conducted in Urmia, Iran, between November 2020 and June 2021. The patients over 60 years old with ASA class I and II, who were candidates for hip and proximal femoral fracture surgery, were enrolled in the study. All participants had a new onset fracture and surgeries were performed within 24-48 hours after, following the institute's protocol for early intervention, aimed at minimizing complications associated with hip fractures.

As frailty affects delirium, the evaluation of frailty was conducted exclusively for patients categorized as robust according to their FRAIL score. Also, a thorough method for assessing cognitive status was implemented prior to enrollment. A comprehensive cognitive assessment was completed by all participants using standardized tools to ensure that the inclusion criteria were met and that no pre-existing cognitive impairments were present. A combination of clinical interviews and validated cognitive screening tools-specifically, the Mini-Mental State Examination and the Montreal Cognitive Assessment -was utilized to evaluate cognitive function. Additionally, the exclusion criteria specifically included any current or past history of neurological disorders, such as dementia, Parkinson's disease, and Alzheimer's disease. This was done to ensure that the study population consisted of individuals with intact cognitive function, thereby allowing for an accurate assessment of the effects of preoperative ondansetron on POD without confounding factors related to cognitive decline.

Other exclusion criteria were a history of alcohol abuse, receiving antidepressant and sedative drugs, hearing, vision, and speech disorders, and surgery duration of more than 3-hours. The sample size required for the study was determined using the following formula. Based on the frequency of delirium in the study of Papadopoulos et al. (11) (15.68% in the ondansetron group and 41.81% in the placebo group) and taking into account the experimental power of 80% and 95% confidence interval, the sample size of 44 people in each group was determined. Considering a 10% chance of dropping out, the final sample size was 50 people in each group.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \left[P_1(1-P_1) + P_2(1-P_2)\right]}{(P_1 - P_2)^2}$$

After obtaining the approval of the Ethics Committee of Urmia University of Medical Sciences (approval number: IRCT20170515033986N1, date: 30.05.2018) and patients' informed consent, randomization was performed using Random Allocation Software version 1.0.0 to generate two groups of 50 patients each. Only a single nurse anesthetist possessed knowledge of the two categories and dispensed the 2 mL syringe that contained either the medication or the placebo to the anesthesiologist. After standard hemodynamic monitoring and before spinal anesthesia, the A group received 8 mg (2 mL) of intravenous ondansetron, and the B group received 2 mL of intravenous normal saline (placebo). The participant, anesthesiologist, care provider, investigator, and outcome assessor were blinded to the study groups.

Spinal anesthesia was performed by injecting 10 mg of bupivacaine 0.5%, and 30 micrograms of fentanyl in the L3-L4 or L4-L5 intervertebral space. Delirium, nausea, itching, and shivering were evaluated at 30 minutes, 1st, 6th, 8th, and 24th hours postoperatively by the same in-charge anesthesiologist to enhance the reliability of the findings. Delirium was assessed based on a 4-point scale following (13), 0: normal, 1: a restless patient with mild confusion and good cooperation, 2: the patient has memory impairment and is unaware of the place and time but cooperates well, 3: the patient is unaware of the time and does not cooperate , with a possibility of danger due to excessive movements, and 4: the patient is entirely unaware of the place, time, and person, and is very aggressive and delusional.

Statistics

Quantitative data are presented as mean ± standard deviation, and qualitative data are reported as frequency and percentage. A chi-square test (if necessary, Fisher's exact test) was used to compare the frequency of the variables between the two groups. Quantitative data were analyzed using an independent sample t-test. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL); $p<0.05$ was considered statistically significant.

Results

A total of 122 hip and anterior femoral fracture patients were admitted to the project between November 2020 and June 2021. Twenty-two patients were excluded from the study: 14 refused to participate, one patient had Parkinson's disease, one patient had Alzheimer's disease, and six patients had a history of drug or alcohol abuse. The remaining 100 patients were randomly divided into two groups (Group A, n=50; Group B, n=50) (Figure 1). As shown in Table 1, there was no significant disparity in terms of age and sex between the two groups. Also, the distribution of ASA classifications and comorbidities in the two groups is shown in Table 1. There were no significant differences in the proportion of ASA I and II patients or in the specific comorbidities that classified patients as ASA II. The results of our study showed the frequency of POD decreased in group A compared with group B, but this decrease was not statistically significant at any time in the study (Table 2). The prevalence of delirium was the same in both sexes, and the effect of ondansetron on delirium was not sex-dependent (Table 3).

The Fisher's exact test showed that the frequency of postoperative itching dose not significantly different between the two groups at any time in the study. As shown in Table 4, the frequency of nausea at 6- and 8-hours post-surgery significantly decreased in Group A compared to Group B. In addition, our results showed a significant decrease in shivering frequency at 30 minutes after surgery in Group A compared with Group B.

Discussion

The global population is getting older, leading to a higher need for orthopedic surgeries (6). POD is common among older patients undergoing elective surgery, especially orthopedic surgery (1, 3, 6), which results in longer hospitalizations and increased morbidity and mortality (8). Prevention, timely diagnosis, and appropriate treatment can improve the recognition and risk stratification of delirium and mitigate its unwanted side effects (7). Delirium has now gained recognition as a severe challenge for both patients and medical professionals due to the emergence of discussions in recent years surrounding the specific type of medication that can effectively mitigate the occurrence of delirium (14). Several classes of drugs, such as

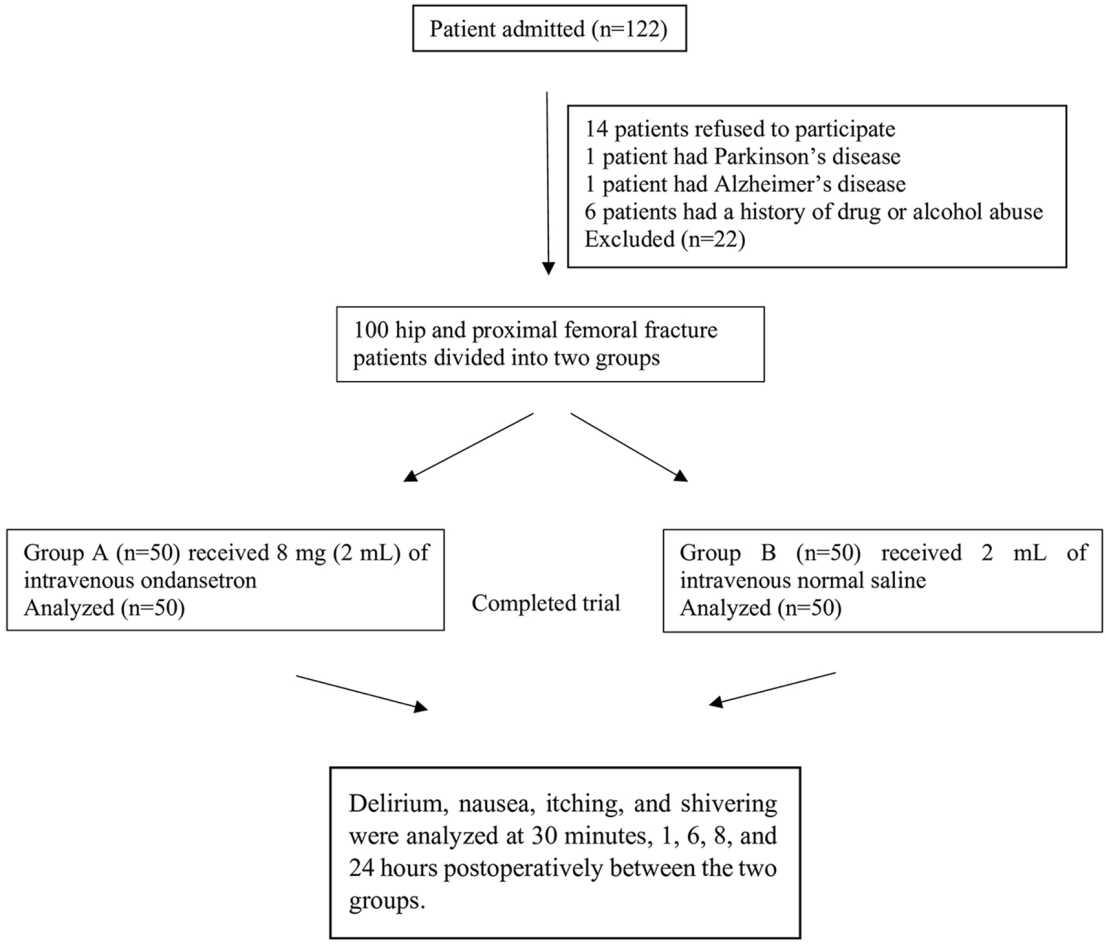

Figure 1. A flow chart of the study

2-receptor agonists, atypical antipsychotics, sleep-regulatory drugs, and 5-HT3 receptor antagonists, have garnered significant interest regarding their potential in preventing or managing delirium (8,11,12,15). However, it remains a topic of ongoing discussion in achieving agreement on this issue, and there is a lack of convincing evidence to support the effectiveness of any particular approach in preventing or treating delirium. The pathophysiology of delirium is related to increased serotonergic activity (8). Ondansetron is a selective serotonin 5HT-3 antagonist, mainly used for postoperative nausea and vomiting control (13). Some experimental trials focused on the effect of postoperative ondansetron administration on the prevention and treatment of POD. However, the results of these studies are controversial (11,12). A retrospective study by Shin et al. (16) was conducted to demonstrate the effect of 5-HT3 receptor antagonists on the occurrence of POD in older adults who underwent hip fracture surgery. In contrast to our study, another study used ramosetron and palonosetron intraoperatively and found that a 5-HT3 receptor antagonist may be a preventive strategy for POD (16). Papadopoulos et al. (11) showed that postoperative ondansetron administration for five days in patients undergoing surgical procedures for femoral or hip fractures resulted in a reduced incidence and duration of delirium. A meta-analysis stated that among the candidate pharmacological interventions for the treatment of delirium in critically ill adults, only the alpha2 agonist dexmedetomidine reduces the duration of delirium, while ondansetron does not affect the treatment of delirium (17). To the best of our knowledge, our study evaluated for the first time the effect of ondansetron administration in the preoperative period on POD management in older patients undergoing orthopedic surgery. Our data, inconsistent with other studies, confirmed that ondansetron can still be considered as the first line of prevention of postoperative nausea and vomiting. We also found that preoperative ondansetron administration has no impact on POD, shivering, and itching frequency in patients undergoing surgery for hip and anterior femoral fracture with spinal anesthesia. This

Table 1. Patient's demographic characteristics

Variable	Group A (ondansetron) (n=50)	Group B (placebo) (n=50)	p
Sex (male/female)	(23/27)	(27/23)	0.42
Age (mean ± SD)	73.66±13.50	72.02±10.28	0.49
ASA (I/II)	(14/36)	(11/39)	0.49
Comorbidities (ASA II)			
Hypertension	20	25	0.45
Diabetes mellitus	8	5	0.36
Coronary artery disease	5	8	0.55
Asthma	0	2	0.49
Hypothyroidism	6	4	0.51

SD: Standard deviation, ASA: American Society of Anesthesiologists

Table 2. Postoperative delirium incidence in groups A and B

Post-operative time	Group A (ondansetron) (n=50) delirium positive patients n (%)	Group B (placebo) (n=50) delirium positivepatients n (%)	p
30 min.	0	0	-
1 h	0	0	-
6 h	9 (18%)	12 (24%)	0.46
8 h	10 (20%)	17 (34%)	0.11
24 h	9 (18%)	10 (20%)	0.79

min.: Minute, h: Hour

Table 3. Distribution of postoperative delirium among different sex

Post-op. time	Group A (ondansetron) delirium positive n (%)		Group A (ondansetron) delirium negative n (%)			Group B (placebo) delirium positive n (%)		Group B (placebo) delirium negative n (%)		
	Male	Female	Male	Female	p	Male	Female	Male	Female	p
30 min.	0	0	27 (54)	23 (47)		0	0	23 (47)	27 (54)	
2 h	0	0	27 (54)	23 (47)	-	0	0	23 (47)	27 (54)	-
6 h	4 (33.3)	8 (66.7)	23 (60.5)	15 (39.5)	0.1	4 (44.4)	5 (55.6)	19 (46.3)	22 (53.7)	0.92
8 h	9 (52.9)	8 (47.1)	18 (54.5)	15 (45.5)	0.91	4 (40)	6 (60)	19 (47.5)	21 (52.5)	0.67
24 h	7 (70)	3 (30)	20 (50)	20 (50)	0.26	3 (33.3)	6 (66.7)	20 (48.8)	21 (51.2)	0.4

min.: Minunte, h: Hour

Table 4. Frequency of complications in groups A and B

Post-op. time	Itching			Vomiting			Shivering		
	A (ondansetron) (n=50)	B (placebo) (n=50)	p	A (ondansetron) (n=50)	B (placebo) (n=50)	p	A (ondansetron) (n=50)	B (placebo) (n=50)	p
30 min.	1 (2%)	0	0.5	4 (8%)	4 (8%)	1	7 (14%)	16 (32%)	0.03
1 h	0	0	-	4 (8%)	7 (14%)	0.33	5 (10%)	9 (18%)	0.24
6 h	0	1 (2%)	0.5	3 (6%)	16 (32%)	0.01	1 (2%)	2 (4%)	0.58
8 h	0	2 (4%)	0.15	1 (2%)	8 (16%)	0.01	2 (4%)	1 (2%)	0.55
24 h	0	0	-	1 (2%)	2 (4%)	0.58	0	0	1

min.: Minute, h: Hour

contradiction in results between different studies may be due to the type of surgery and anesthesia, the type of preoperative risk factors, and the time and dose of ondansetron administration (18-20). After intravenous administration, ondansetron undergoes metabolism and is subsequently eliminated through the urinary system. The elimination half-life of ondansetron following an intravenous dose of 8 mg is likely to be around 3-6 hours; it could extend to 6-8 hours among the older population (21). In Papadopoulos' study, ondansetron was administered daily for five days postoperatively, while in our study a single dose of ondansetron was administered preoperatively. The administration of several doses of ondansetron before the surgery may have a favorable effect on POD management. Furthermore, the anesthetic procedure is different between 2 studies;

Since there is no worldwide guideline with standardized concepts for POD management, delirium management should consist of a multi-professional consisting of pharmacological, and non-pharmacological approaches (2,22,23). The critical care guidelines first recommend the use of non-pharmacological strategies in both the prevention and management of delirium. One of the types of non-pharmacological plans is individual assessment to identify preoperative delirium risk factors and their underlying causes and to remove them if possible. The factors that are frequently linked to POD include advanced age, pre-existing deficits in the central nervous system, psychiatric illness, alcohol misuse, emergency surgical procedures, and the presence of multiple comorbidities (13), whereas other factors are controversial. The relationship between sex and POD occurrence in various clinical settings has been proven. Some studies reported that men have a higher risk of developing POD after hip and femoral neck fracture (24,25); other studies, consistent with our research, have failed to find a relationship between sex and the POD incidence (26,27).

Frailty and delirium are closely associated, particularly in older adults undergoing surgical procedures. Frailty, characterized by decreased physiological reserve and increased vulnerability to stressors, significantly heightens the risk of POD. The FRAIL scale is a widely recognized tool used for assessing frailty in older adults. Individuals classified as frail (scores of 3 or more) or prefrail (scores of 1-2) had approximately 2.7 times the odds of developing in-hospital delirium compared to those deemed robust (score of 0) after adjusting for various factors such as age and cognitive status (28). Therefore, higher scores, which indicate prefrailty or frailty, were not included in the study due to their correlation with an increased risk of deliriumto eliminate its effect.

Furthermore, a meta-analysis by Hua et al. (29) indicated that the ASA classification was identified as an independent risk factor for POD, with an odds ratio of 2,343, suggesting that patients classified as ASA III or higher, are at a greater risk compared to those classified as ASA I or II.

To mitigate this factor and reduce variability, we included only ASA I and II patients in our study. The distribution of ASA I and II patients was balanced between the two groups, with 14 ASA I and 36 ASA II patients in the ondansetron group and 11 ASA I and 39 ASA II patients in the placebo group. However, limiting the study population to lower-risk patients narrows the scope of generalizability, as the results may not fully represent higher-risk populations. Future studies should include patients across all ASA classifications to better understand the impact of ondansetron on delirium prevention. To mitigate this confounding factor, we included patients classified as ASA I and II in our study, with a balanced distribution of 14 ASA I and 36 ASA II patients in the ondansetron group and 11 ASA I and 39 ASA II patients in the placebo group. This approach reduced variability and ensured comparability between groups, thereby strengthening internal validity.

Study Limitations

This study has some limitations, and the current data are insufficient to draw robust conclusions. First, this study did not assess all the possible risk factors associated with POD other than the factors mentioned in the methods section. Identifying these potential risk factors and the underlying cause(s) can be effective in using the best pharmacological strategies to remove them and finally prevent or treat POD.

Second, the study protocol involved administering only a single dose of preoperative ondansetron, because early surgery was performed for participants undergoing hip fracture surgery. Future studies are recommended to explore the use of varying doses at different intervals prior to surgery.

Third, while our study included only ASA I and II patients to minimize the impact of coexisting comorbidities, this selection limits the generalizability of our findings. The exclusion of older adults with ASA III and IV classifications, who are at a higher risk of POD, restricts the ability to fully evaluate ondansetron's effect across a broader risk profile. Furthermore, we did not analyze the presence of concomitant comorbidities. Although the distribution of these comorbidities was balanced between the two groups, their potential influence on the risk of POD cannot be entirely ruled out. The presence of concomitant comorbidities, even within the ASA II group, may have contributed to the observed outcomes, including the ineffectiveness of ondansetron in preventing POD. Future studies should consider a more diverse patient population, including those with a broader range of comorbidities, to better understand the role of ondansetron in preventing POD.

Fourth, our results are from a small study, and further randomized controlled trials with larger sample sizes are required to validate our results. Additionally, nausea, itching, and shivering were assessed as presence or absence instead of evaluating their intensity, which may have limited our ability to detect more subtle differences between the groups.

Conclusion

In conclusion, we found that preoperative ondansetron administration has no effect on POD, shivering, and itching frequency in patients undergoing surgery for hip and anterior femoral fractures under spinal anesthesia.

Ethics

Ethics Committee Approval: After obtaining the approval of the Ethics Committee of Urmia University of Medical Sciences (approval number: IRCT20170515033986N1, date: 30.05.2018).

Informed Consent: Informed consent, which was approved by the ethics committee, was obtained from all participants before participating in the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: R.A.B., Concept: N.K., Design: N.K., Data Collection or Processing: R.A.B., Analysis or Interpretation: A.S., Literature Search: A.S., Writing: T.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Erisman M, Klugheit M. Interventions for preventing delirium in older people in institutional long-term care. Esential Reviews in Geriatric Psychiatry. 2022:147-151.
2. Grover S, Avasthi A. Clinical practice guidelines for management of delirium in elderly. Indian J Psychiatry. 2018;60:329-340.
3. Shim JJ, Leung JM. An update on delirium in the postoperative setting: prevention, diagnosis and management. Best Pract Res Clin Anaesthesiol. 2012;26:327-343.
4. Wu J, Yin Y, Jin M, Li B. The risk factors for postoperative delirium in adult patients after hip fracture surgery: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2021;36:3-14.
5. Guo Y, Jia P, Zhang J, Wang X, Jiang H, Jiang W. Prevalence and risk factors of postoperative delirium in elderly hip fracture patients. J Int Med Res. 2016;44:317-327.
6. Hong H, Zhang DZ, Li M, Wang G, Zhu SN, Zhang Y, Wang DX, Sessler DI. Impact of dexmedetomidine supplemented analgesia on delirium in patients recovering from orthopedic surgery: a randomized controlled trial. BMC Anesthesiol. 2021;21:223.
7. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. JAMA. 2017;318:1161-1174.
8. Haque N, Naqvi RM, Dasgupta M. Efficacy of ondansetron in the prevention or treatment of post-operative delirium-a systematic review. Can Geriatr J. 2019;22:1-6.
9. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. J Gerontol A Biol Sci Med Sci. 2008;63:764-772.
10. Egberts A, Fekkes D, Wijnbeld EH, van der Ploeg MA, van Saase JL, Ziere G, van der Cammen TJ, Mattace-Raso FU. Disturbed serotonergic neurotransmission and oxidative stress in elderly patients with delirium. Dement Geriatr Cogn Dis Extra. 2015;5:450-458.
11. Papadopoulos G, Pouangare M, Papathanakos G, Arnaoutoglou E, Petrou A, Tzimas P. The effect of ondansetron on postoperative delirium and cognitive function in aged orthopedic patients. Minerva Anestesiol. 2013;80:444-451.
12. Lirk P, Hollmann MW. Ondansetron: a new therapeutic option to attenuate postoperative cognitive dysfunction and delirium? Minerva Anestesiol. 2013;80:407-409.
13. Tagarakis GI, Voucharas C, Tsolaki F, Daskalopoulos ME, Papaliagkas V, Parisis C, Gogaki E, Tsagalas I, Sataitidis I, Tsolaki M, Tsilimingas NB. Ondasetron versus haloperidol for the treatment of postcardiotomy delirium: a

prospective, randomized, double-blinded study. J Cardiothorac Surg. 2012;7:25.

14. Liu Y, Li XJ, Liang Y, Kang Y. Pharmacological Prevention of postoperative delirium: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2019;2019:9607129.
15. Gosch M, Nicholas J. Pharmacologic prevention of postoperative delirium. Z Gerontol Geriatr. 2014;47:105-109.
16. Shin HJ, Park JI, Lee S, Hwang JW, Na HS. Intraoperative 5-HT3 receptor antagonists decrease the prevalence of postoperative delirium in older adults undergoing hip fracture surgery: a single-center retrospective study. J Anesth. 2023;37:379-386.
17. Burry L, Hutton B, Williamson DR, Mehta S, Adhikari NK, Cheng W, Ely EW, Egerod I, Fergusson DA, Rose L. Pharmacological interventions for the treatment of delirium in critically ill adults. Cochrane Database Syst Rev. 2019;9:CD011749.
18. Urban MK, Sasaki M, Schmucker AM, Magid SK. Postoperative delirium after major orthopedic surgery. World J Orthop. 2020;11:90-106.
19. Weinstein SM, Poultsides L, Baaklini LR, Mörwald EE, Cozowicz C, Saleh JN, Arrington MB, Poeran J, Zubizarreta N, Memtsoudis SG. Postoperative delirium in total knee and hip arthroplasty patients: a study of perioperative modifiable risk factors. Br J Anaesth. 2018;120:999-1008.
20. Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, Mehta RL, Wang M, Yeung J, Jackson T, Melody T, Jin S, Yao Y, Wu J, Chen J, Smith FG, Lian Q. RAGA study investigators. effect of regional vs general anesthesia on incidence of postoperative delirium in older patients undergoing hip fracture surgery: The RAGA randomized Trial. JAMA. 2022;327:50-58.
21. Huddart R, Altman RB, Klein TE. PharmGKB summary: ondansetron and tropisetron pathways, pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics. 2019;29:91-97.
22. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. Neurotherapeutics. 2012;9:158-175.
23. Abraha I, Trotta F, Rimland JM, Cruz-Jentoft A, Lozano-Montoya I, Soiza RL, Pierini V, Dessì Fulgheri P, Lattanzio F, O'Mahony D, Cherubini A. Efficacy of non-pharmacological interventions to prevent and treat delirium in older patients: a systematic overview. The SENATOR project ONTOP Series. PLoS One. 2015;10:e0123090.
24. Edlund A, Lundström M, Brännström B, Bucht G, Gustafson Y. Delirium before and after operation for femoral neck fracture. J Am Geriatr Soc. 2001;49:1335-1340.
25. Oh ES, Sieber FE, Leoutsakos JM, Inouye SK, Lee HB. Sex differences in hip fracture surgery: preoperative risk factors for delirium and postoperative outcomes. J Am Geriatr Soc. 2016;64:1616-1621.
26. Andersson EM, Gustafson L, Hallberg IR. Acute confusional state in elderly orthopaedic patients: factors of importance for detection in nursing care. Int J Geriatr Psychiatry. 2001;16:7-17.
27. Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, Strauss E, Siu AL. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003;58:76-81.
28. Mahanna-Gabrielli E, Zhang K, Sieber FE, Lin HM, Liu X, Sewell M, Deiner SG, Boockvar KS. Frailty is associated with postoperative delirium but not with postoperative cognitive decline in older noncardiac surgery patients. Anesth Analg. 2020;130:1516-1523.
29. Hua Y, Yuan Y, Wang X, Liu L, Zhu J, Li D, Tu P. Risk prediction models for postoperative delirium in elderly patients with hip fracture: a systematic review. Front Med (Lausanne). 2023;10:1226473.