Comparing the Effects of Diphenhydramine and Granisetron in Preventing Nausea and Vomiting and Pain after Laparoscopic Cholecystectomy: A Randomized Clinical Trial

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ABSTRACT

Objective: Considering that nausea and vomiting are very common after laparoscopic cholecystectomy surgery, it is important to take preventive measures. Also, no method has been able to completely prevent nausea and vomiting after surgery; In this study, the effects of two drugs granisetron (as a specific inhibitor of 5HT-3 receptor) and diphenhydramine (as an antihistamine) were evaluated.

Materials and Methods: In this one-blind clinical trial that was conducted in 2019 with the participation of patients who were candidates for elective laparoscopic cholecystectomy surgery (120 patients), the patients were randomly divided into two groups. Patients in the granisetron group received 3 mg of this drug 15 minutes before extubation, and patients in the diphenhydramine group received 50 mg of this drug intravenously 15 minutes before extubation. The intensity of pain, intensity of nausea and vomiting, occurrence of nausea and vomiting, dose of netoclopramide and opioid were compared between two groups.

Results: The average ± standard deviation of the severity of nausea and vomiting at all measured times in the granisetron group was insignificantly lower than the diphenhydramine group (P<0.05), also the need for metoclopramide was always lower in the granisetron group. It was less than the group receiving diphenhydramine (P<0.05); On the other hand, the pain intensity at all times in the group receiving granisetron was insignificantly lower than the group receiving diphenhydramine (P<0.05).

Conclusion: Granisetron slightly reduces nausea and vomiting, the need for metoclopramide, and pain intensity after laparoscopic cholecystectomy compared to diphenhydramine.

Keywords: Granisetron, Diphenhydramine, Nausea and Vomiting, Pain, Laparoscopic Cholecystectomy

INTRODUCTION

Nausea and vomiting after surgery is one of the most unpleasant complications after surgery and anesthesia[1], which can lead to other dangerous complications such as aspiration of stomach contents, opening of surgical sutures, esophageal rupture, subcutaneous emphysema, or pneumothorax[2].

The incidence rate of PONV in the normal population is 30-40%, which can even reach 75-80% in the high-risk population[3]. By using different techniques and methods as well as preventing the occurrence of this complication, this complication can be reduced to about 50% in high-risk patients[4]. These risks are more in laparoscopy patients, full stomach, eye trauma, head injury and cesarean section; Another effective factor in the occurrence of this complication is the experience of pain; Pain can increase the prevalence of PONV up to three times[5].

Until now, various methods and drugs have been used to treat or prevent nausea and vomiting after various surgeries, none of which has been 100% effective. On the other hand, some surgeries are associated with more nausea and vomiting than other surgeries[6,7]. Among these procedures, we can refer to laparoscopic head cystectomy. The prevalence of nausea and vomiting in laparoscopic cholecystectomy surgery is two to three times that of other surgeries; Therefore, special attention for this type of surgery should be considered to prevent the adverse side effects of nausea and vomiting after surgery[8]. Antagonists of the 5-hydroxytryptamine subtype three (5HT-3) receptor are among the effective drugs in the treatment of nausea and vomiting and have very few side effects and also lack the sedative, dysphoric, and extrapyramidal effects that are seen with other anti-nausea drugs[8,9].

Granisetron is a very specific 5HT-3 receptor inhibitor that binds strongly and irreversibly to 5HT-3 receptors and exerts its anti-nausea and anti-vomiting effects in this way[10].

Diphenhydramine is an antihistamine drug whose analgesic and antiemetic effects have already been proven. However, it is unknown whether the administration of diphenhydramine before surgery improves the quality of recovery after surgery[11,12]. Considering that nausea and vomiting are very common after laparoscopic cholecystectomy surgery, it is important to take preventive measures; Also, no method has been able to completely prevent nausea and vomiting after surgery; In this study, the effects of two drugs granisetron (as a specific inhibitor of 5HT-3 receptor) and diphenhydramine (as an antihistamine) were evaluated.

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MATERIALS AND METHODS

Study Design: This study is a randomized and blinded clinical trial that was conducted during 2019 (from the beginning to the end of the year) with the participation of patients who are candidates for elective laparoscopic cholecystectomy surgery referred to Imam Reza Hospital in Tabriz.

Sample Size and Sampling: The sample size was based on the results of a similar study[13] in which the severity of nausea and vomiting during the first 24 hours after surgery was 0.55±1.18 for granisetron and 1.23±0.97 for diphenhydramine and considering the power of the test equal to 90% and the confidence interval of 95% and using the average comparison formula between two independent groups, 55 people were estimated for each group and with a ten percent increase in the sample size (preventing the effects of sample loss) the volume The final sample reached 120 patients; According to the entry and exit criteria, patients were included in the present study as they were available.

Participant Criteria: Inclusion criteria include: age over 18 years, candidate for elective surgery, consent to participate in the research project, ASA class one and two, duration of anesthesia less than 120 minutes and maintenance of anesthesia during surgery with isoflurane gas. and the exclusion criteria included: pregnant and lactating women, patients with a history of uncontrolled blood pressure, patients with a history of endocrine or metabolic diseases, patients with a history of kidney and liver failure, patients with a history of cardiovascular diseases, obesity (index body mass above 40, history of lower respiratory system diseases, use of MAOIs, patients with glaucoma, patients with history of motion sickness, menstruating women, people who received anti-nausea drugs within 24 hours before surgery. Ondansetron or metoclopramide injection during surgery, patients undergoing chemotherapy and radiotherapy and patients taking ginger medicine on a daily basis.

Randomization and Blinding: In order to randomize and equalize the sample size in two groups, the random block of four methods was used, for this purpose, the letters G meaning granisetron and D meaning diphenhydramine were written on 4 lottery cards. Then the cards were placed side by side in the desk drawer. One of the members of the research team, who was responsible for determining the sequence of randomization, at the beginning of the study randomly drew one of the cards and based on which letter was written on the drawn card, 4-patients were assigned to the same group with they would get assigned cards and after completing these four samples according to the mentioned method, lottery cards would be drawn again. This randomization process was repeated until reaching the desired sample size in each group. Since only the person analyzing the results was unaware of the grouping of patients, this study was performed in a blinded manner.

Methods: In the operating room, routine anesthesia monitoring such as heart rate, non-invasive blood pressure, pulse oximetry, capnography and ECG were performed in all patients. After securing a secure intravenous line, normal saline infusion was started and patients in both groups received the same routine pretreatment and induction of anesthesia and maintenance. Pretreatment was done by fentanyl 1 μ/kg and midazolam 0.02 mg/kg. Subsequently, anesthesia was induced by propofol 3 mg/kg and atracurium 40-50 mg was used to facilitate intubation. Anesthesia was continued with isoflurane and oxygen. All patients were ventilated by mechanical ventilation by maintaining $EtCO_2$ in the range of 35-40 mm Hg.

Blood pressure, heart rate and baseline SpO_2 of the patients were recorded before the start of anesthesia and were measured and recorded every 5 minutes during anesthesia. Pneumoperitoneum was performed using closed needle technique and intra-abdominal pressure was maintained at 12-14 mmHg. After CO_2 injection, the patients were placed in reverse Trendelenburg position of 20 degrees.

Complications such as drop or increase in blood pressure, dysrhythmia, hypoxemia and bronchial spasm were recorded during the operation and treated immediately. In case of hemodynamic changes, this complication was treated by increasing the intravascular volume, vasopressor or atropine according to the case; It should be noted that the anesthesiologist was the same anesthetist for all patients and the same anesthesia method was used for all patients. Patients in the granisetron group received 3 mg of granisetron intravenously 15 minutes before extubation, and patients in the diphenhydramine group received 50 mg of diphenhydramine intravenously 15 minutes before extubation.

Then, the effects of relaxing drugs were removed with the help of two drugs, atropine and neostigmine, and the patients were intubated and transferred to recovery. Immediately after the operation and in the PACU and at intervals of 2, 4, 6, 12, 24 and 48 hours after the operation, PONV of the patients was evaluated using the Belleville instrument; Based on this tool, in this scale, score 0 means no nausea, 1 means nausea, 2 means retching, and 3 means vomiting. Also, by using Visual Analogue Scale (VAS), the numerical value of VAS was calculated for patients from 0 cm, which means the absence of PONV, and 10 cm, which means the maximum amount of PONV.

If needed, metoclopramide 5mg was used as treatment for nausea and vomiting. The total dose of metoclopramide was also recorded. Metoclopramide was prescribed when: PONV occurred once and the patient himself requested additional medication at the same time. PONV occurred more than once, or PONV with a VAS score of >5 (moderate to severe). Also, information such as age, height, weight, body mass index, duration of anesthesia, duration of surgery and ASA class were recorded for all patients.

Table 1: Comparison of demographic information of study participants

P Value	Study groups (N=120)		Variable
	Granisetron group (N=60)	Diphenhydramine group (N=60)	
0.478	39.18±7.21	38.98±7.11	Age
0.411	169.25 19.49	166.29±18.33	Height
0.514	71.80±7.41	70.14±7.79	Weight
0.603	26.49±3.11	26.12 3.19	Body mass index
0.552	89.59±12.29	88.88 12.49	Duration of surgery
0.398	120.19±11.39	121.45±11.99	Duration of anesthesia
0.303	48 people	46 people	I
	12 people	14 people	II
			Class ASA
Test used: T-test and chi-square			

Table 2: Comparison of nausea and vomiting and need for metoclopramide drug between two groups of participants in the study measured at different times

P Value	Study groups (N=120)				
	Granisetron group (N=60)	Diphenhydramine group (N=60)			
0.312	5.05±1.45	5.12± 1.49	Severity of nausea and vomiting (average)		During recovery
0.145	24 people	24 people	0	Belleville	
	8 people	7 people	1		
	16 people	20 people	2		
	12 people	9 people	3		
0.214	14 people	12 people	Yes	Need for metoclopramide	
	46 people	48 people	No		
0.489	4.18± 1.14	4.24± 1.16	Severity of nausea and vomiting (average)		Two hours after discharge from recovery
0.319	28 people	29 people	0	Belleville	
	8 people	9 people	1		
	14 people	14 people	2		
	10 persons	8 people	3		
0.411	11 people	9 people	Yes	Need for metoclopramide	
	29 people	31 people	No		
0.489	3.04± 0.29	3.11± 0.31	Severity of nausea and vomiting (average)		Four hours after discharge from recovery
0.665	34 people	33 people	0	Belleville Need for metoclopramide	
	6 people	5 people	1		
	13 people	15 people	2		
	7 people	7 people	3		
0.589	8 people	7 people	Yes		
	32 people	33 people	No		
0.396	1.14± 0.41	1.03± 0.36	Severity of nausea and vomiting (average)		Six hours after discharge from recovery
0.719	35 people	37 people	0	Belleville	
	8 people	7 people	1		
	6 people	6 people	2		
	1 person	0 people	3		
0.589	3person	2 people	Yes	Need for metoclopramide	
	57 people	58 people	No		
0.558	0.43± 0.21	0.39± 0.38	Severity of nausea and vomiting (average)		12 hours after discharge from recovery
0.669	50 people	47 people	0	Belleville	
	6 people	7 people	1		
	4 people	6 people	2		
	0 people	0 people	3		
0.589	0 people	1 person	Yes	Need for metoclopramide	
	60 people	59 people	No		
0.603	0.11± 0.10	0.13± 0.05	Severity of nausea and vomiting (average)		24 hours after discharge from recovery
0.711	55 people	57 people	0	Belleville	
	5 people	3 people	1		
	0 people	0 people	2		
	0 people	0 people	3		
0.999	0 people	0 people	Yes	Need for metoclopramide	
	60 people	60 people	No		
0.514	0.08± 0.19	0.11± 0.15	Severity of nausea and vomiting (average)		48 hours after discharge from recovery
0.619	91 people	53 people	0	Nausea	
	9 people	7 people	1		
	0 people	0 people	2		
	0 people	0 people	3		
0.999	0 people	0 people	Yes	Need for metoclopramide	
	60 people	60 people	No		
	Test used: ANOVA and chi-square				

Table 3: Comparison of pain intensity between two groups of participants in the study measured at different times

Intensity of pain	Study groups (N=120)		P Value
	Granisetron group (N=60)	Diphenhydramine group (N=60)	
Discharge from recovery	3.41± 1.59	3.48± 1.33	0.414
Two hours after discharge from Discovery	4.15± 1.36	4.23± 1.19	0.225
Four hours after discharge from Discovery	4.08± 1.33	4.15± 1.41	0.319
Six hours after discharge from Discovery	3.71± 1.11	3.85± 1.60	0.401
12 hours after discharge from recovery	3.41± 0.28	3.59± 0.42	0.514
24 hours after discharge from recovery	2.05± 0.33	2.15± 0.29	0.555
48 hours after discharge from recovery	1.22± 0.48	1.35± 0.39	0.459
Two hours after discharge from Discovery	1.01± 0.55	0.85± 0.35	0.396
Test used: T-test			

Statistical Analysis: The data obtained from the study using descriptive statistical methods (mean standard deviation and frequency-percentage) and t-test to compare the average for independent groups and to compare qualitative variables using the chi-square test using Statistical software SPSS.23 were examined and statistically analyzed; In this study, P value less than 0.05 was considered statistically significant.

Ethical Considerations: The code of ethics (IR.TBZMED.REC. 2019.431) was obtained from the ethics committee of Tabriz University of Medical Sciences and then registered in the clinical trial system of Iran (IRCT20150125020795N7); No fees were charged to the participants; An informed consent form was also signed by the participants.

RESULTS

In the mentioned period of time, 145 people underwent surgery in the operating room of Imam Reza Hospital, of which 120 people entered the study and were present until the end of the study. In other words, there was no sample loss in this study. The comparison of the average age and height, weight and body mass index, duration of anesthesia, duration of surgery and ASA class between the participants in the study indicated that there is no significant statistical difference between the two groups; It can be concluded that the allocation of participants to the intervention and control groups was random (Table 1).

The average ± standard deviation of the severity of nausea and vomiting in all the measured times indicated that this variable was always insignificantly lower in the granisetron group than in the group receiving diphenhydramine ($P<0.05$), as well as the severity of nausea and vomiting in both groups, it was associated with a decrease over time; On the other hand, according to the obtained results, it was found that the need for metoclopramide drug between the two groups was also without statistically significant difference ($P<0.05$), so that the number of people who needed metoclopramide injection in the group receiving granisetron was always less than The group received diphenhydramine (Table 2).

Examining the intensity of pain between the two groups indicated that the intensity of pain at all times in the group receiving granisetron was insignificantly lower than the group receiving diphenhydramine ($P<0.05$). The comparison of pain intensity between the two groups of participants in the rejection study is presented in table 3.

DISCUSSION

Nausea and vomiting after laparoscopic surgery is known as one of the most common side effects of this type of surgery and in some studies it has been reported that more than 90% of patients who undergo laparoscopic surgery experience nausea and vomiting. experience within 24 hours after surgery; Since nausea and vomiting after surgery can be associated with various complications, therefore, early prevention and treatment of this complication can be effective in the early recovery of these patients[6,11]. Many studies have used different methods to prevent this complication. have worked; Single-drug and multi-drug treatments[14-17].

Examining the results of the present study indicated that granisetron and diphenhydramine have similar effects in the prevention and treatment of nausea and vomiting after laparoscopic cholecystectomy surgery; Of course, it should be mentioned that the effects of granisetron are slightly greater than Diphenhydramine; Granisetron exerts its anti-emetic effects by antagonizing serotonin receptors at the end of the vagus nerve (vagus nerve) and its central receptors in the vomiting center, thus preventing nausea and vomiting by inhibiting the vomiting reflex and the anti-allergic effect of diphenhydramine is due to competition with histamine for binding to H1 receptors. Its anti-vomiting and anti-vertigo effect can be related to its anti-muscarinic effect; Therefore, this drug can be used with optimal preventive purposes in the prevention of PONV[18,19].

The antitussive effect of diphenhydramine is due to the direct effect on the cough center in the medulla. This drug affects the H1 receptors of the brain and causes hypnotic effects; This drug leads to the control of nausea and vomiting with its antagonistic effects on H1 receptors[20]. The amount of metoclopramide needed to treat nausea and vomiting after laparoscopic cholecystectomy in the present study was almost the same in both groups, however, the effects of granisetron were slightly better than diphenhydramine. The results of several studies[21-24], such as Pour-Rashidi 's study, have shown that the effects of granisetron are better than Diphenhydramine; In all these studies, it has been stated that the effects of granisetron are longer than diphenhydramine and this drug can be used for long-term control of nausea and vomiting; However, according to the range of side effects of these two drugs, the side effects of diphenhydramine are less than granisetron, and it seems that the use of diphenhydramine is more rational than granisetron, considering the similar effects of these two drugs in the present study[25]. One of the limitations of our study was maintaining anesthesia with isoflurane gas, this drug leads to nausea and vomiting; On the other hand, this study was conducted in a single center and may differ from the results of multicenter studies; Therefore, according to the limitations of this study, it is recommended to conduct more studies by removing the limitations of this study.

CONCLUSION AND RECOMMENDATIONS

.3Granisetron slightly reduces nausea and vomiting, need for metoclopramide, and pain intensity after laparoscopic cholecystectomy compared to diphenhydramine. Also, considering that none of these two drugs could lead to a 100% reduction in

nausea and vomiting after surgery, it is recommended that future studies be conducted as a combination of several drugs to prevent PONV.

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REFERENCES

1. Bastani P, Hajebrahimi S, Mallah F, et al. Long-term outcome of synthetic mesh use in Iranian women with genital prolapse. Urol J 2020;17(1):73-7.
2. Bameshki A, Namaiee MH, Jangjoo A, et al. Effect of oral ginger on prevention of nausea and vomiting after laparoscopic cholecystectomy: a double-blind, randomized, placebo-controlled trial. Electron physician 2018;10(2):6354-62.
3. Awad K, Ahmed H, Abushouk AI, et al. Dexamethasone combined with other antiemetics versus single antiemetics for prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy: an updated systematic review and meta-analysis. Int J Surg 2016;36(Pt A):152-63.
4. Saboktakin L, Bilan N, Behbahan AG, et al. Relationship between resistin levels and sepsis among children under 12 years of age: a case control study. Front Pediatr 2019;7:355
5. Isazadehfar K, Entezariasl M, Shahbazzadegan B, et al. The comparative study of ondansetron and metoclopramide effects in reducing nausea and vomiting after laparoscopic cholecystectomy. Acta Med Iran 2017;55(4):254-8.
6. Mehrotra S. Postoperative anaesthetic concerns in children: Postoperative pain, emergence delirium and postoperative nausea and vomiting. *Indian J* Anaesth 2019;63(9):763-70.
7. Hashemzadeh K, Dehdilani M, Gol MK. Study of the effects of simple exercise with or without physiotherapy on prevention of deep vein thrombosis among postmenopausal women requiring coronary artery bypass graft surgery. Int J Womens Health Reprod Sci 2021;9(1):69-74.
8. Gol MK, Dadashzadeh M, Anvari HM. Design and implementation of a checklist for prediction of anesthesia-induced nausea and vomiting in candidate patients for mastectomy. Int J Womens Health Reprod Sci 2020;8(1):90-4.
9. Eghdam-Zamiri R, Khanbabayi Gol M. Effects of ginger capsule on treatment of nausea and vomiting in patients receiving cisplatin undergoing mastectomy: a randomized clinical trial. Iran J Obstet Gynecol Infertil 2020;22(11):15-21.
10. Saboktakin L, Rafeey M, Kousha A, et al. Study on prevalence of Helicobacterpylori infection in adolescents with failure to thrive to compare with control group. Life Sci J 2012;9(4):1425-31
11. Firouzian A, Kiasari AZ, Godazandeh G, et al. The effect of intravenous dextrose administration for prevention of post-operative nausea and vomiting after laparoscopic cholecystectomy: A double-blind, randomised controlled trial. Indian J Anaesth 2017;61(10):803-10.
12. Khodaveisi Z, Borzou S, Mohammadi Y, et al. The Effect of Inhalation of Ginger Extract on Postoperative Nausea, Retching and Vomiting after Laparoscopic Cholecystectomy: A Randomized Clinical Trial. J Health Care 2019;21(2):126-34.
13. Albooghobeish M, Ghomeishi A, Adarvishi S, et al. The effect of preoperative zintoma capsule on postoperative nausea and vomiting after laparoscopic cholecystectomy. Anesth Pain Med 2018;8(5):e67132
14. Turgut HC, Arslan M. An overview of treatment options for postoperative nausea and vomiting after laparoscopic surgical procedures. Anaesth Pain Intensive Care 2016;20(2):193-200.
15. Wu M, Yang L, Zeng X, et al. Safety and feasibility of early oral hydration in the postanesthesia care unit after laparoscopic cholecystectomy: a prospective, randomized, and controlled study. J Perianesth Nurs 2019;34(2):425-30.
16. Tahir S, Mir AA, Hameed A. Comparison of palonosetron with granisetron for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic abdominal surgery. Anesth Essays Res 2018;12(3):63-43.
17. Gustafsson S, Strömqvist M, Ekelund J, et al. Factors influencing early postoperative recovery after laparoscopic cholecystectomy. J Perianesth Nurs 2020;35(1):80-4.
18. Sridharan K, Sivaramakrishnan G. Drugs for preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: Network meta-analysis of randomized clinical trials and trial sequential analysis. Int J Surg 2019;69:1-12.
19. Salazar-Parra M, Guzman-Ramirez BG, Pintor-Belmontes KJ, et al. Gender differences in postoperative pain, nausea and vomiting after elective laparoscopic cholecystectomy. World J Surg 2020;44(12):4070-6.
20. Sahin SY, Iyigun E, Can MF. Effect of acupressure application to the P6 acupoint before laparoscopic cholecystectomy on postoperative nausea-vomiting: A randomized controlled clinical study. Int J Nurs Stud 2018;87:40-8.
21. Salajegheh S, Kuhestani S, Kermani MS, et al. Comparison of Ondansetron and Granisetron Effects for Prevention of Nausea and Vomiting Following Strabismus Surgery. Open Access Maced J Med Sci 2019;7(19):3195-200.
22. Pourfakhr P, Aghabagheri M, Mahmoudabadi HZ, et al. Prophylactic Administration of Diphenhydramine/Acetaminophen and Ondansetron Reduced Postoperative Nausea and Vomiting and Pain Following Laparoscopic Sleeve Gastrectomy: A Randomized Controlled Trial. Obes Surg 2021;31(10):4371-5.
23. Pour-Rashidi A, Mardani M, Etezadi F, et al. The Effect of Intraoperative Diphenhydramine/Morphine on Acute Pain and Opioid Consumption after Spine Surgery. Arch Anesth Critical Care 2022;8(1):36-40.
24. Emir S, Erturgut P, Vidinlisan S. Comparison of granisetron plus dexamethasone versus an antiemetic cocktail containing midazolam and diphenhydramine for chemotherapy induced nausea and vomiting in children. Indian J Med Paediatr Oncol 2013;34(4):270-3.
25. Sharma S, Chaudhary RK, Gupta L, et al. Prevention of Post-Operative Nausea and Vomiting Using Granisetron and Ondansetron in Laparoscopic Surgeries in a Comparative Clinical Study. Indian J Public Health Res Dev 2017;8(1):198-203.