Effect of Pretreatment with Diphenhydramine on Recovery Complications in Minor Ear, Nose and Throat Surgeries: A Randomized Clinical Trial

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ABSTRACT

Objective: Pain after surgery is one of the risk factors of postoperative nausea and vomiting (PONV) and increased recovery complications due to the mechanisms it causes. Histamine blockers with their effects (sedation, reduction of pain and anxiety) may lead to reduction of recovery complications; Therefore, the present study was conducted with the aim of the effect of pretreatment with diphenhydramine on recovery complications in minor ear, nose, and throat surgeries.

Materials and Methods: 100 patients' candidates for minor ENT surgeries were included in this double-blind randomized clinical trial study as available sampling. Ten minutes before the induction of anesthesia, 2 cc of diphenhydramine (25 mg) were injected into the patients of the intervention group and 2 cc of normal saline were injected into the patients of the control group; Pain intensity and PONV in recovery and 2, 4, 8, 10, 12, 24 hours after discharge from recovery were compared between two groups using Independent-Samples T-Test.

Results: In recovery, the incidence of nausea and vomiting (p=0.02) and the need for ondansetron in the diphenhydramine group were significantly lower than the control group (p=0.05). On the other hand, the incidence of nausea and vomiting in the 24-hour evaluation was significantly lower in the diphenhydramine group than in the control group; The average total injected ondansetron during 24 hours in the intervention group (4.41±0.17) was significantly (P=0.031) lower than the control group (9.37±1.41).

Conclusion: Prophylactic injection of diphenhydramine leads to reduction of recovery complications (short term) after anesthesia in limited ENT surgeries.

Keywords: Diphenhydramine, Nausea and Vomiting, Pain, Recovery, ENT

INTRODUCTION

There are various risk factors related to PONV, which can be mentioned as risk factors related to the patient, anesthesia and surgery[1,2]. The risk factors related to the patient include female gender, previous history of PONV, motion sickness and the risk factors related to anesthesia include the use of inhalation anesthesia during surgery, the use of narcotics during and after surgery, and the use of nitrous oxide[3]. With surgery, we can refer to the type of surgery and the duration of the surgery[4].

Nausea and vomiting after surgery is a stress for the patient, surgeon and anesthesiologist, and causes distress and confusion in the patient, delay in the discharge of patients from recovery and additional care and treatment measures and increases the cost of the patient and the treatment system[5]. The results of the studies have shown that patients are willing to spend a lot of money for the prevention and treatment of this condition or even prefer to be in pain instead of experiencing nausea and vomiting[6,7].

Another neurophysiological response to surgery that increases length of stay in recovery and delays discharge is pain, which may have an overall detrimental effect on the quality of improvement in recovery[8]. Pain after surgery is one of the main focuses of attention and its prevention is a challenge as an indicator of health care quality. Postoperative pain and PONV are separate outcomes, but it is well known that pain leads to anxiety and this can be associated with nausea[9,10]. Therefore, it is important to choose the anesthesia method and drugs that can reduce the complications of recovery in outpatient surgeries, because unrelieved pain can cause mental vulnerability and nausea and vomiting can lead to dehydration with long-term hospitalization[11,12].

Diphenhydramine is an antihistamine drug that is commonly used before surgery to reduce nausea and vomiting after surgery[13]. In addition, histamine blocking agents can reduce pain, improve sleep, and reduce anxiety. But it is still not clear whether diphenhydramine can improve the quality of recovery after outpatient surgery or not[14,15].

Because diphenhydramine also has sedative effects, which may increase the length of hospitalization and the time until the patient's discharge, which is undesirable in outpatients; Therefore, the present study was conducted with the aim of determining the effect of pretreatment with diphenhydramine on recovery complications in minor ear, nose, and throat surgeries.

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MATERIALS AND METHODS

Study Design: The current study is a randomized, double-blind, parallel-group clinical trial that was conducted during 2019 (from the beginning to the end of the year) in Imam Reza Hospital (Tabriz University of Medical Sciences) with the participation of 100 patients who are candidates for limited surgeries. Ear, throat and nose were included in the study, it was done.

Estimation of Sample Size and Sampling: With unknown population size and using the following formula, the sample size in this study was 95 patients, and in order to increase the validity of the results, 100 patients were included in this study using available sampling method.

Inclusion and Exclusion Criteria: Inclusion criteria include: age over 18 years, duration of anesthesia less than 120 minutes, alert and oriented patients, patients with ASA class I, II, patient consent to participate in the study and candidates for small ear surgeries and were pharynx and nose, and the exclusion criteria included: suffering from uncontrolled diabetes - porphyria - acute asthma attack - liver diseases, scleroderma or underlying gastrointestinal disease, taking anti-nausea drugs and vomiting during 24 hours before surgery.

Patients with middle ear disease, history of pelvic surgery, history of nausea and vomiting in the last 24 hours, pregnant and lactating women, history of allergy to diphenhydramine.

Randomization and Blinding: patients were divided completely randomly using www.random.org and Gaussian command; With the help of this site, the patients were divided into two intervention groups (diphenhydramine injection) and control (normal saline injection).

In this study, the second anesthesiologist was in the course of the study; The first anesthesiologist was the person who was in charge of anesthesia and the injection of drugs and was not blinded during the study, but the second anesthesiologist who checked the results of the study was unaware of the type of drug injected for the patients and was blinded during the study.

Also, the person analyzing the data (he was not a member of the research group) was not aware of the type of patient grouping and was blind; Therefore, this study was conducted in a double-blind manner.

Procedure: All patients were given an induction by an anesthesia method, which included 0.04 mg of midazolam per kilogram of body weight, 2 micrograms of fentanyl per kilogram of body weight, 1 mg per kilogram of body weight. Lidocaine, in case of egg and soy allergy, 1-2 mg per kg of body weight of propofol and 0.5 mg of atracurium per kg of body weight were used.

Maintenance was done by TIVA method with propofol and remifentanil in the form of pump infusion. The control group received 2 cc of intravenous normal saline ten minutes before the induction of anesthesia, and the diphenhydramine group received 25 mg of diphenhydramine diluted with normal saline to a volume of 2 cc normal saline before the induction of anesthesia. It should be noted that in this study, only the patients of one ear, nose and throat surgeon were used, so that the results of different surgical methods, different surgical techniques and the type of surgeon have no effect on the final results of the study. In this survey, demographic information, duration of surgery, duration of anesthesia and post-surgery information such as pain, nausea and vomiting during recovery and at time intervals of 2, 4, 8, 10, 12, 24 hours were recorded. During recovery, patients' pain was relieved with 30 mg of ketorolac and, if requested again, with pethidine, and in case of nausea and vomiting (minimum score of 2 based on Belleville criteria), they received 4 mg of ondansetron intravenously.

The severity of nausea and vomiting was measured using the Belleville scale. In this scale, 0 means no nausea, 1 means nausea, 2 means retching, and 3 means vomiting. Pain assessment was measured using the VAS scale. where 0 (no pain), 1-3 mild pain, 4-7 moderate pain and 8-10 severe pain.

Ethical Considerations: Informed consent was signed by all study participants the night before surgery; The informed consent form had explanations in simple language regarding the intervention process, advantages and disadvantages of the study, ethical code of the study (IR.TBZMED.REC.1398.1292) and registration code in the Iranian clinical trial system (IRCT20150217021121N4).

Statistical Analysis: In general: the data obtained from the study by means of descriptive statistical methods (mean, standard deviation, frequency and percentage) and Independent-Samples T-Test to compare quantitative data and non-normality of data distribution to It was evaluated by the Kolmogorov-Smirnov test. The data was analyzed by SPSS 20 software. In this study, P-Value less than 0.05 was considered significant.

RESULTS

During the mentioned period of time, 165 patients were candidates for minor otolaryngology surgery, 100 of them entered the study and after being assigned to two intervention and control groups, they received the intervention and after follow-up, their results were compared; The current study started with 100 patients and ended with 100 patients.

The gender of the patients included 60 (60%) males and 40 (40%) females. The dominant gender in both groups was male (p = 0.072). In this study, in terms of physical condition and ASA class, 88% had class I, 12% had class II (p=0.067). Average weight and age in the two groups of patients studied were the same and had no significant difference (p=0.317) (p=0.125). The duration of the surgery in the control group was 100 minutes, and this average was 90 minutes for the diphenhydramine group, and there was no statistically significant difference from each other. Also, in the examination of the patients in terms of the duration of anesthesia, the control group was 110 minutes, and for the diphenhydramine group, it was 110 minutes. It was 105 minutes and the difference were not significant (p=0.06) (Table 1).

The length of stay in recovery was slightly longer in the diphenhydramine group, but this increase was significant (p=0.07).

Table 1: Comparison of basic and demographic information of study participants

Variables		Groups (N=100)		P value
		Intervention (N=50)	Control (N=50)	
Sex	Female	19(38%)	21(42%)	0.072*
	Male	31(62%)	29(58%)	
ASA	I	46(92%)	42(84%)	0.067*
	II	4(8%)	8(12%)	
Age		41.29±5.25	36.14±6.12	0.125**
Weight		78.63±7.17	75.29±8.15	0.317 **
Anesthesia Duration(min)		105.89±14.41	110.96±12.12	0.081 **
Surgery Duration(Min)		95.98±12.18	100.29±12.41	0.07 **

Recovery Duration(min)	32.14±2.27	28.77±2.10	0.051 **

*: Chi Square **: T Test

During recovery, the incidence of nausea and vomiting in the diphenhydramine group was significantly lower than the control group (p=0.02). Also, we observed the highest need for ondansetron in the control group, which was a significant difference (p=0.05). Also, the incidence of nausea and vomiting in the 24-hour evaluation was lower in the diphenhydramine group than in the control group, and this difference was not significant (Table 2).

Table 2: Comparison of evaluation of nausea and vomiting of patients in recovery according to Belleville criteria

Variables	Witness	Diphenhydramine	P Value
Absence of nausea	30/50 60%	40/50 80%	0.026
Presence of nausea	12/50 24%	7/50 14%	
Yelling	2/50 4%	2/50 4%	
Vomiting	3/50 6%	1/50 2%	
Need for ondansetron	10/50 20%	2/50 4%	0.05

In the assessment of pain during recovery, 82% of the diphenhydramine group had no pain or mild pain, and the number of people who had moderate pain and severe pain (17people-34%) was more in the control group, but no significant difference was observed between the two groups (p=0.76).

Also, in recovery, the need for Ketorolac was more in the control group (18 people) than in the intervention group (9 people) and a significant difference was observed between them (p=0.05). In this study, if the pain was not controlled by Ketorolac, pethidine was used, and in both groups (4 people in the control group and one person in the intervention group), a smaller number of patients needed pethidine, and there was no significant difference between the groups (p=0.68) and this reduces the effects of pethidine on nausea and vomiting in the results of our study.

Also, in the assessment of pain in 24 hours, the number of people with moderate and severe pain was less in the diphenhydramine group (the total number of moderate and severe pain was 3 people in the intervention group and 5 people in the control group), but this decrease was not significant (Table 3).

The average total injected ondansetron during 24 hours in the intervention group (4.41±0.17) was significantly (P=0.031) lower than the control group (9.37±1.41).

DISCUSSION

Cost constraints in recent health care demand to evaluate outcomes such as long stay in recovery, unanticipated admission to intensive care units, readmission after discharge, quality of recovery, patient expectations and costs of care. In these evaluations, the concern about the quality of post-operative service provision has caused the serious focus of anesthesiologists in this field so that they can have a more realistic approach to the influencing factors in the anesthesia period by being aware of the concerns and views of the patients[16-18].

In this study, we evaluated the quality of recovery in the use of 25 mg of diphenhydramine before induction of anesthesia in patients undergoing

Table 3: Evaluation results of nausea and vomiting of patients up to 24 hours after discharge from recovery according to Belleville criteria

	2hours			4hours			8 hours		
	Witness	Diphenhydramine	P Value	Witness	Diphenhydramine	P Value	Witness	Diphenhydramine	P Value
Absence of nausea (0)	38 76%	45 90%	0.057	40 80%	46 92%	0.77	42 84%	47 94%	0.83
presence of nausea (1)	8 16%	3 6%		9 18%	2 4%		7 14%	2 4%	
yelling (2)	4 8%	2 4%		1 2%	2 4%		1 2%	1 2%	
Vomiting (3)	0 0%	0 0%		0 0%	0 0%		0 0%	0 0%	
	10Hours			12Hours			24Hours		
	Witness	Diphenhydramine	P Value	Witness	Diphenhydramine	P Value	Witness	Diphenhydramine	P Value
Absence of nausea (0)	45 90%	47 94%	0.78	46 92%	48 96%	0.46	47 94%	50 100%	0.79
presence of nausea (1)	5 10%	3 6%		4 8%	2 4%		3 6%	0 0%	
yelling (2)	0 0%	0 0%		0 0%	0 0%		0 0%	0 0%	
Vomiting (3)	0 0%	0 0%		0 0%	0 0%		0 0%	0 0%	

outpatient otolaryngology surgery, so that we can take an important step in completing previous similar studies[19-21] in case of improvement in the quality of recovery. to have other parts of the world and with its widespread use, to provide the cause of faster improvement of recovery complications and consequently reduce the duration of hospitalization and reduce the costs imposed on the family and society.

In this study, the technique of induction and maintenance of anesthesia and the use of analgesics during surgery were similar for all patients. The patients had no statistically significant difference in terms of demographic characteristics, i.e. age, sex, weight, ASA status, duration of anesthesia and surgery (Tables 1, 2 and 3). It has been shown in the studies[22-25] that the long duration of the surgery causes an increase in nausea and vomiting after the operation, and the incidence of nausea and vomiting is from 2.8% in patients with an operation duration of at least 30 minutes to 27% in patients with an operation duration between It increases from 151 to 180 minutes.

It has also been reported in studies that the duration of anesthesia increases the risk of nausea and vomiting by 59% for every 30 minutes of increase in time, which is probably caused by the accumulation of nausea-causing agents of the anesthetic drug.

In this study, the length of stay in recovery in the diphenhydramine group was almost equal to the control group, and no significant difference was observed between the two groups. (Table 3) Therefore, it can be concluded that a low dose of diphenhydramine does not lead to a long stay in recovery. In the diphenhydramine group, the level of agitation and anxiety was significantly lower than the control group (Table 3), which may be due to the sedative properties of diphenhydramine. In the study of Rainer[20] and Kay[21], the effect of diphenhydramine on the H1 receptor, which causes sedation and sleep, has been mentioned. Other studies have also mentioned the use of diphenhydramine as a sedative and hypnotic in dentistry, ophthalmology and endoscopy, and our study was in line with these studies.

In the present study, a significant difference was observed between the two groups in terms of nausea and vomiting in recovery (p=0.02), and the diphenhydramine group had less nausea and vomiting than the control group. This reduction can be related to the anti-muscarinic effect of diphenhydramine[26].

In these patients, the need for ondansetron was less in the diphenhydramine group, which was significant (p=0.05). In the 24-hour evaluation, the amount of nausea and vomiting in the control group decreased and there was no significant difference between the two groups which may be related to the therapeutic effect of ondansetron in recovery. In the study of Köseoglu[25] and his colleagues, ondansetron was superior to diphenhydramine in controlling vomiting caused by chemotherapy drugs. In the study of Kizilchik et al.[26], the combination of dimenhydramine-dexamethasone along with anesthetic drugs can reduce nausea and unpleasant vomiting after the operation. In Oliveira's study[12], the use of diphenhydramine before laparoscopic cholecystectomy surgery prevents nausea and vomiting after surgery and in Yu et al.'s study[27], the preventive administration of 30 mg of diphenhydramine intravenously in induction of anesthesia is effective. It reduced the incidence, severity of pain and PONV in treated patients, which were in line with our study.

Finally, comparing the pain parameters of the patients, the present study showed that the patients in the diphenhydramine group compared to the control group had an improvement in pain during recovery and 24-hour evaluation but this reduction was not significant. People in the diphenhydramine group received lower doses of ketorolac, and the use of narcotics was less in these patients. These findings are in accordance with the results published by Arslan et al.[28] in 2016. Also, in Santiago's study[29], the analgesic effects of diphenhydramine are mentioned. They have stated that postoperative patients are resistant to treatment with oral, intravenous and epidural drugs for pain relief. In these patients, a dose of 25 mg of diphenhydramine IV or orally every 6 to 8 hours can relieve pain and Bloom's study in 2004[30] indicated that antihistamines may facilitate the binding of opioid substances to receptors. Opioid or by releasing cyclic GMP can act as a central pain reliever.

Single-centeredness and non-separation of the type of surgery were the weaknesses and limitations of this study; It is recommended that other studies be conducted with the aim of reducing the limitations of this study.

CONCLUSION AND RECOMMENDATIONS

Diphenhydramine has been associated with improved acute postoperative analgesia, reduced incidence of PONV and postoperative agitation, and decreased narcotic use leading to improved quality of recovery after outpatient otolaryngology surgery compared to patients receiving saline. Also, considering that diphenhydramine could not lead to zero side effects during recovery. It is recommended that future studies be conducted by comparing this drug with other antihistamine drugs in order to choose the best drug to prevent these side effects.

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