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Original Article

Dexmedetomidine versus Propofol in reducing postoperative nausea and vomiting in gynecologic laparoscopic surgery

Mansour Choubsaz[1], Mansour Rezaei[2] , Aida Lahoorpour[1]*, Rasoul Mahdavi Jafari[1]

1. Department of Anesthesiology, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran.
2. Department of Biostatistics, Fertility and Infertility Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

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***Corresponding Author**: Department of Anesthesiology, Imam Reza hospital, Sayyad-e-Shirazi Blvd, Kermanshah, Iran. Tel: +98 9186189162
Email: montedramo@gmail.com

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Abstract

Introduction: Post-Operative Nausea and Vomiting (PONV) occurs in 20%-30% of patients, and is the second most common complaints after pain. This unpleasant complication can lead to rare but serious medical complications such as aspiration of gastric contents, suture dehiscence, esophageal rupture, subcutaneous emphysema, or pneumothorax. Annual PONV-related health care costs reach several hundred million dollars. Many interventions have been done to control PONV, but complications of drug interactions limit the use of drugs. For example, Dropridol has been placed on the Black Box Warning because of the risk of cardiac arrhythmias.

Methods: This clinical trial recruited 80 patients with American Society of Anesthesiologist (ASA) class I or II who were scheduled for elective gynecologic laparoscopic surgery. They were randomly divided into two groups: Propofol and Dexmedetomidine. The data was collected by the first nurse in PACUs and the second nurse in post-surgery ward, including age, weight, smoking history, nausea, vomiting and severity of vomiting. Patients and observers were blinded to the prescribed hypnotic drugs. The severity of nausea was assessed by visual analogue scale (ranging 0 to 10) in 0-2, 2-6 and 6-24 hours. The state of nausea was also recorded.

Results: The incidence of nausea and the severity of vomiting significantly decreased in the dexmedetomidine group compared to the Propofol group (PV=0.001).

Conclusion: The results showed that Dexmedetomidine can reduce the incidence of nausea and severity of vomiting compared to Propofol.

Introduction

Post-operative nausea and vomiting (PONV) is the second most common complication occurring in 20%-30% of patients. It is a very unpleasant experience for the patient, and some describe it worse than pain. PONV can lead to rare but serious medical complications such as aspiration of gastric contents, suture dehiscence, esophageal rupture, subcutaneous emphysema, or pneumothorax. Therefore, PONV control is important for anesthesiologists (due to aspiration risk) and surgeons (due to other mentioned complications). Annual PONV-related health care costs reach several hundred million dollars. Many interventions have been done to control PONV, but complications of drug interactions limit the use of drugs. For example, Droperidol has been placed on the Black Box Warning because of the risk of cardiac arrhythmias (1). With regard to the prevalence, being unpleasant, and related complications, the need for PONV control is evident for anesthesiologists, post-anesthetic care units (PACUs) and post-operative care. Laparoscopic Surgery (LS) is one of the most popular surgical procedures with such benefits as reducing postoperative pain and shortening the length of hospitalization and rapid recovery of the patient. One of the major problems with LS includes cardiopulmonary effects, systemic absorption of CO2 and gas. Vagal stimulation due to pneumoperitoneum, in addition to risk factors related to surgery, may cause PONV. Despite the many improvements over the past years to minimize the post-anesthetic harmful effects, PONV is still the second most unexpected consequence of surgery for patients. PONV is one of the most common causes of post-anesthetic patient dissatisfaction, with an incidence of over 63% in laparoscopic cholecystectomy surgery.

Vomiting can cause stress wounds, as well as electrolyte imbalance and bleeding (2). Early PONV refers to nausea and vomiting during the first 2 hours after surgery. There are many drugs and methods for preventing and treating PONV. However, there is no consensus on one or several treatments (1, 3).

Several risk factors have been identified for PONV. Factors such as female sex, previous history of PONV or history of motion sickness, non-smoking status, certain agents used in perioperative period (volatile anesthetics, N2O, opioids, ketamine, parasympathomimetic drugs (neostigmine>2.5mg), long duration of surgery, intra-abdominal surgery (gynecologic surgeries and LS) are

among these risk factors (3). The use of perioperative opioids is the major PONV risk factor, not to mention pain which itself is a significant risk factor for PONV (2). Four obvious risk factors that independently predict PONV include female sex, postoperative opioid treatment, previous history or motion sickness and non-smoking, each of which increases the risk of PONV by 20% (4).

According to Apfel's categorization, the simplified risk score of Post-Discharge Nausea and Vomiting (PDNV) in adults is explained as when there are 0, 1, 2, 3, 4, and 5 risk factors, the risk of PONV is 10%, 20%, 30%, 50%, 60%, and 80%, respectively (Figure 1).

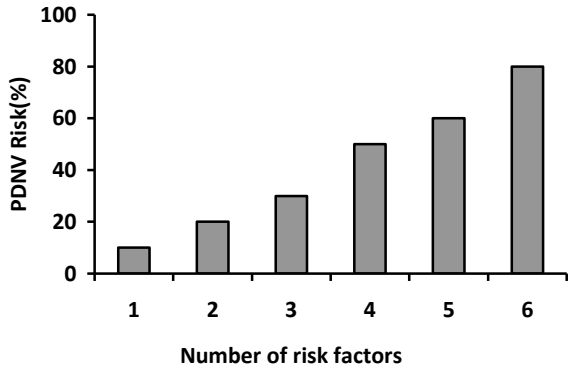

Figure 1. PONV risk factors and their risk scores

PONV can be specifically reduced by reducing the major risk factors, for example through the following measures:

1. Replacing general anesthesia (GA) with regional anesthesia (RA).
2. Administering propofol infusion.
3. Avoiding N2O.
4. Avoiding inhalation anesthetics.
5. Restriction on perioperative use of opioids.
6. Adequate hydration.

In both adults and children, the use of RA instead of GA reduces PONV by 9 times (5).

Although Apfel defined some of the risk factors associated with PONV, some other risk factors have not yet been defined. Risk factors can be divided into three groups: related to the anesthetic technique, type of surgery, and the patient. Patient-related risk factors are female sex (adults), non-smoking, PONV history, motion sickness, and genetic background. The factors associated with anesthesia technique include the use of volatile anesthetics, N2O, a high dose of neostigmine, and the use of opioids during and after the surgery. Surgical factors include long duration of surgery and various types of surgery (6).

In terms of physiological mechanism, central and peripheral signals of nausea and vomiting are received by different receptors, which are the primary goal of nausea and vomiting medications. Chemoreceptor Trigger Zone (CTZ) is located in the area postrema on the floor of the fourth ventricle of brain and identifies harmful chemicals such as anesthetic gases and opioids. Other nausea-inducing substances are found in body fluids including blood and CSF. The 5HT3, M1, H1, D2, NK1, and opioid receptors are in the CTZ. Toxins or medications that impulse in the CTZ as an afferent center reach Nucleus Tractus Solitarius (NTS) in the brain stem, and finally, activate vomiting center in the lateral reticular formation in the medulla oblongata and initiate vomiting (Figure 2).

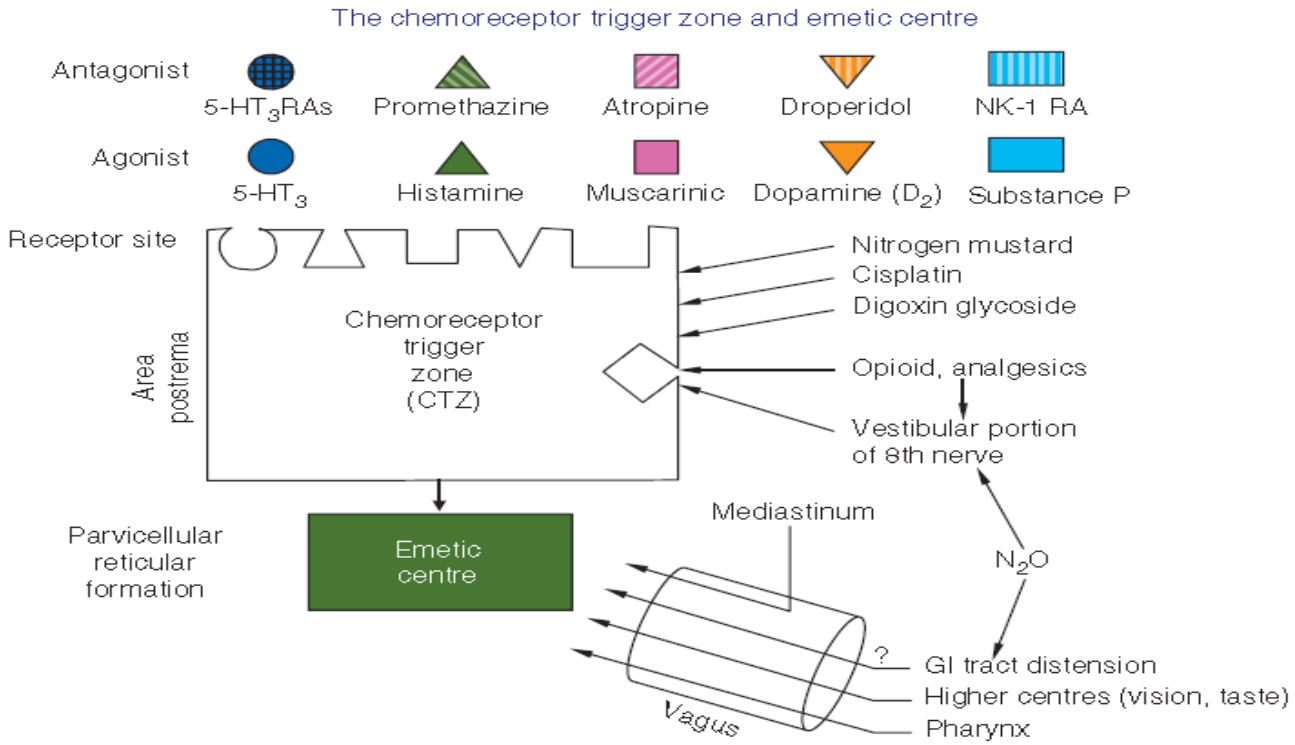

Figure 2. The mechanism of CTZ and the emetic center

Serotonin is the key neurotransmitter in the gastrointestinal (GI) tract and binds to 5HT3 receptors in the GI tract and activates the vagal channels and vagal impulses in the CTZ, leading to nausea and vomiting. These receptors are the targets of 5HT3 receptors blocking drugs (1, 7). The aim of this study was to compare the effect of dexmedetomidine (DEX) with propofol on decreasing the incidence of PONV in gynecologic laparoscopic (GL) surgery. This study was able to clarify some uncertainties about the role of DEX compared with propofol in reducing nausea and vomiting. There are different medication regimens for PONV such as anticholinergics (most commonly scopolamine), antihistamines such as cyclosin, dimenhydrinate, diphenhydramine, hydroxyzine, meclizine and promethazine, D2 receptor antagonists including phenothiazines (chlorpromazine, fluphenazine), benzamides (domperidone, metoclopramide) and butyrophenones (droperidol, haloperidol), serotonin receptor antagonists such as ondansetron, granisetron, tropisetron, dolasetron, ramosetron, opioid receptor antagonists, corticosteroids, neurokinin (NK) receptors antagonists. Propofol is primarily an anesthetic with hypnotic and opioid properties. However, its clinical use has gradually increased due to its antiemetic properties. Although its antiemetic properties are fully known, a serotonin antagonistic effect and/or glutamate and aspartate secretion blocking effect (CNS secretion amino acids) potentially explains the antiemetic properties of propofol (1, 3) (Table 1).

Table 1. Side effects of the class of commonly used drugs

Drug Class	Side-effects
Serotonin Antagonists	headache, diarrhoea, constipation, arrhythmia
Neurokinin inhibitors	Dizziness, headache, diarrhoea, weakness
Steroids Antihistamines	Dizziness, mood changes, nervousness confusion, drying of mucosal membranes, Sedation, urinary retention
Butyrophenones	prolonged QT interval (at dose≥0.1 mg/kg) Hypotension, tachycardia, extra-pyramidal symptoms
Benzodiazepines	sedation, disorientation

DEX is a stereoisomer medetomidine, approved by FDA in 1999 for short-term use in humans (<24h) for analgesia and sedation in the ICU. Physiology of α2 receptors: Adrenergic receptors are essentially divided into α and β receptors. It is believed that the activity of adrenergic receptors of α or β are under the influence of and stimulated by secretions from some tissues and the inhibition from some secretions from other tissues. Later a subclass of α receptors was detected that regulated the release of neurotransmitters. It is concluded that these receptors are presynaptic. However, the receptor classification based on their location is surprising because α2 receptors have been found at postsynaptic and extrasynaptic spaces, too. DEX is increasingly used as an adjuvant medication during anesthesia due to its benefits such as delaying the release of catecholamines. It results in hemodynamic stability, saves on the use of anesthetic drugs and opioids, and improves the quality of recovery. The mechanism of reducing PONV by DEX through less use of anesthetic medications and opioids. Reduction in sympathetic tone leads to a reduction in PONV (3, 8, 9).

Patients after GL surgery are at a relatively high risk and the PONV incidence may be higher than 80%. The incidence of PONV may be prolonged in the recovery room, resulting in an increase in nursing workload and increased pain, discomfort, and dissatisfaction of patients. Despite the many prevention strategies in high-risk patients, the effect of PONV prophylaxis is far from optimal (10). DEX has no effect on GABA (γ-aminobutyric acid) (11).

DEX has a highly selective α2-A agonist property and binding to the membrane glycoprotein receptor (G-P) acts on the GABA without effect (4).

The use of DEX during anesthesia dramatically reduces the use of opioids and inhalational anesthetics, provides appropriate recovery, and reduces pain without altering hemodynamics, thus, may decrease PONV (12).

A new systematic study reported that 36% (range: 18%-45%) of patients with GA experience PONV, which reaches 80% in high-risk patients (13).

A meta-analysis on the evaluation of the effect of DEX on the prevention of nausea and vomiting had findings including:

1. DEX is superior to placebo in preventing nausea and vomiting in patients with or without high-risk factors.
2. The beneficial effect of DEX on nausea and vomiting may be detected by intravenous injection.
3. The most commonly used dosage of injections in studies was 0.5μg/kg bolus which prevents nausea and the injection of 1μg/kg bolus affecting vomiting.
4. DEX during an operation reduces the use of analgesic drugs. The beneficial effect of DEX may be due to the direct antiemetic effect of α 2 agonists.

In addition, vomiting and nausea may be explained by high concentrations of catecholamines, and justified by the diminishing sympathetic tone by DEX.

DEX may induce noradrenergic activity by binding to the inhibiting presynaptic adrenoceptors in locus ceruleus, an inhibition that may result in antiemetic effects.

DEX reduces sympathetic tone by reducing neuroendocrine and hemodynamic responses and decreases the need for sedation and analgesia with opioids (12).

Reducing perioperative anxiety is important in reducing PONV. Benzodiazepines are recommended in many small studies as a way to reduce anxiety. Other interventions such as a friendly, sympathetic and positive relationship with the patient can reduce the incidence of PONV. Administration of dexamethasone before surgery reduces PONV. Aprepitant is the first neurokinin-1 receptor antagonist, administered before anesthesia,

which reduces nausea and vomiting up to 48h after surgery. Hydrating the patient with oral carbohydrates, including smooth fluids up to 2h before surgery also leads to a reduction in PONV. Similarly, giving enough fluid is part of the multiple treatment regimens of PONV. However, whether longer surgeries are directly causal is difficult to prove, since higher doses of opioids and longer exposure to inhalation anesthetics (MAC-hours) are likely to occur and known risk factors of PONV. Anesthetic gases, including N2O (dose dependent), increase the risk of PONV. The use of RA reduces PONV compared with GA. TIVA reduces PONV compared to anesthetic gases and N2O. Propofol has direct antiemetic effects and has been used after operation to treat PONV at doses of 10-20 mg administered at a dose of 10-20 mg. The minimum effective concentration of propofol in PONV is 300ng/ml. However, the administration of opioids during and after surgery is a major risk factor for PONV. Short-acting opioids do not increase PONV when used as part of TIVA but, if applied after surgery they increase the risk of PONV. Pain increases PONV itself. There are several analgesic substitutes for opioids that have been administered IV in recent years. NSAIDs reduce PONV compared to neostigmine (6).

During GA, vomiting occurs in 30% and nausea in 50%, and PONV reaches 80% in high-risk patients. If PONV is not treated in the PACU, the length of hospitalization and re-admissions as well as hospital costs increases (7). Despite the many improvements over the past years to minimize the post-anesthetic harmful effects, PONV is still patients' most unexpected outcome of surgery (6).

Materials and Methods

After approval by the Research Deputy and the Ethics Committee, this randomized, double-blind clinical trial recruited 80 women aged 18 to 50 years with American Society of Anesthesiologist (ASA) class I or II who were scheduled for elective GL surgery and willing to participate in the study. They were randomly divided into case and control groups. Inclusion criteria were female sex, gynecologic surgery candidate, NPO for eight hours, and consent to participate in the study. Exclusion criteria were an allergy to the drugs used in the study, use of antiemetic drugs, duration of operation more than two hours, and the patient's unwillingness. Patients were assigned to either propofol (P) or dexmedetomidine (D) groups with permutated block randomization. All patients received 500-cc Ringer serum before induction of anesthesia and were under cardiopulmonary monitoring with pulse oximetry, non-invasive blood pressure measurements, capnography, and electrocardiography. All patients were preoxygenated and all of them were administered with 0.1 to 0.2 µg of sufentanil /kg bw. Anesthesia induction was administered by an anesthesiology resident to all patients with 1.5 mg propofol /kg bw. After the induction of hypnosis, 0.5 mg /kg bw of atracurium was administered for muscle relaxation. The patient was intubated and treated with mechanical ventilation with 50% oxygen and 50% air. Then through permutated block randomization, they were randomly assigned to two groups to continue their anesthesia either with 50 to 150 µg /kg bw per minute of propofol infusion in the group (P) or 7 µg /kg bw per minute of DEX infusion in the group (D) during the surgery.

After surgery and after the disappearance of hypnosis effect, and the return of muscular activity, the patient was reversed with neostigmine and atropine, and the tracheal tube was removed and after ensuring the safety of transfer, the patient was transferred to the recovery. In the recovery, patients were assessed for the incidence of nausea and vomiting, the severity of vomiting, and injection of antiemetic drugs at 0, 2, and 6 hours after surgery by a trained nurse using a visual analogous scale who was blinded to the type of induction and administered drugs. If vomiting occurred within 24 hours after surgery in gynecology ward, a nurse recorded it in a specific form in patients' file. This objective tool is a 10cm ruler with clear beginning and end, and a specified range on which the patient indicated their health status. Zero represented the best status and 10 represented the worst. Vomiting with a degree higher than 7 was classified as severe, between 5 to 7 as moderate, and less than 5 as mild (8). Data were analyzed by SPSS V.16 software. U-Mann-Withney test was used to compare pain severity in the two groups, independent t-test to compare the duration of pain, and chi-square test to compare the complications.

Findings

The results of this study showed that the two groups did not have statistically significant differences in terms of the underlying variables including height, weight, age, duration of surgery, duration of anesthesia and education (Table 2).

Eighteen of the subjects had nausea, and six vomited. The highest incidence of vomiting was reported at 0-2 h after surgery. All those who had nausea and vomiting were nonsmokers. The number of people who had nausea was 12 in the propofol group and 6 in the DEX group. The highest incidence of nausea was reported at 0-2 h after surgery (Table 3).

Table 2. Comparison of mean and percentage of patients in the two groups

Variables	Propofol	DEX	P-value
Age	30/5±6.6	31.68±7.7	0.360
BMI	25.6	26	0.3
Height	166.3	164.6	0.4
Duration of surgery	65±10	62±10	0.580
Duration of anesthesia	2H±20 min	2H±20 min	1.0
high school diploma and lower	80%	83.4%	0.664

Table 3. Comparison of incidence of nausea and vomiting in the two groups

Variables		Propofol	DEX	Total
Nausea	Yes	12 (30.0)	6 (15.0)	18 (22.0)
	No	28 (70.0)	34 (85.0)	62 (77.0)
Vomit	Yes	36 (90.0)	38 (95.0)	74 (92.5)
	No	4 (10.0)	2 (5.0)	6 (7.5)
Total		40 (100.0)	40 (100.0)	80 (100.0)

The highest incidence of vomiting was observed at 0-2 hours after the surgery, which was in the propofol group. Vomiting was more severe in the propofol group. The mean duration of the surgery, weight, and age were almost the same in both groups, while the mean vomiting severity was higher in the propofol group than that of the DEX group.

In this study, 12 of 40 subjects who received propofol had nausea, of whom 50% (6) had nausea in the first 2 hours, and only 4 had vomiting, whose vomiting was also more severe in the propofol group. Only 6 of 40 subjects in the DEX group had nausea. All of them had nausea within the first 2 hours and only 2 had vomiting within the first 2 hours. The 30% nausea in the propofol group was greater than the 15% in the DEX group (15%) receiving propofol (p.v = 0.001). The severity of vomiting in 4 patients receiving propofol was VAS=$\frac{4}{10}$, VAS=$\frac{1}{10}$, VAS=$\frac{6}{10}$, and VAS=$\frac{8}{10}$; while it was VAS=$\frac{2}{10}$ and VAS=$\frac{3}{10}$ in the DEX group. In the group receiving DEX, nausea and vomiting were significantly reduced at 0-2 h and 4-6 h compared to the group receiving propofol. The severity of vomiting at 0-2, 2-6, and 6-24 hours in the propofol group was greater than that of the DEX group. Nausea and vomiting were controlled by antiemetic drugs in the patients.

Discussion

Recently, researchers have focused on the effect of DEX on PONV, though conflicting results are observed in the literature. GL surgery is a common high-risk PONV surgery in the operation room. In addition, over the past decades, PONV has remained a major issue as a result of its complex mechanisms. This study showed that DEX, in addition to reducing nausea, significantly reduced vomiting severity more than propofol. GL surgery places patients at a relatively high risk of PONV, whose rate may exceed 80%. The incidence of PONV may be prolonged in the recovery room, resulting in an increase in nursing workload and increased pain, discomfort, and dissatisfaction of patients. Despite the many preventive strategies in high-risk patients, the effect of PONV prophylaxis is far from optimal (10). The mechanism of reducing PONV by DEX includes using less anesthetic medications and opioids, which reduces PONV. Reduction in sympathetic tone leads to a reduction in PONV. A meta-analysis showed that DEX infusion may reduce the prevalence of PONV, which may also be due to reduced opioid use (4).

Various studies have compared the effects of the antiemetic property of propofol in combination with other drugs or alone in GL surgeries. Kim et al. showed that the effect of administering a low dose of propofol (0.5-1 mg/kg infusion over 15 min) before the end of anesthesia was better than placebo in LS with vaginal hysterectomy to prevent PONV. Instead, Scaderi et al. showed that the effect of administration of 0.1 mg/kg bolus of propofol followed by 0.1 mg/kg/h propofol infusion was similar to placebo in preventing PONV in GL surgery (3). A study compared the effect of remifentanil and DEX on pain intensity, analgesic need and PONV in PACU in patients undergoing GL surgery. The study also determined that DEX would reduce PONV for 24 hours after surgery. The antiemetic effect of DEX might be due to the antagonistic effect of α2, although its biological effect is still unknown (2). Arian et al. compared the effects of DEX and morphine during surgery in patients in a hospital and found similar results in terms of pain scores (11). In a study with a prolonged recovery period, the opioid-free method with DEX, lidocaine propofol can be an alternative technique for laparoscopic cholecystectomy in selected patients, especially in patients high risk for PONV (8). A study showed that DEX infusion was better than administration of propofol and fentanyl during elective spinal surgery, and improved hemodynamic control during and after surgery. It also reduced postoperative pain and PONV in a better way. It also reduced the risk of respiratory depression and hypoxia associated with opioids (14). Comparing propofol with sedation dose, of 0.5 µg/kg DEX provides statistically lower levels of analgesia and sedation and need for opioids. DEX at a dose of 1µg/kg is sometimes accompanied with hypotension, bradycardia, confusion, PONV, and delayed discharge. These side effects may limit the effects of its useful dose (15). The findings of this study can determine the effects of DEX on nausea and vomiting, and furthermore, be a basis for comparing the effect of this medication and other similar medications. In future studies, a larger sample size is required to monitor complications more closely. The findings of this study can be used to treat nausea and vomiting.

Conclusion

This study showed that DEX, in addition to reducing nausea, has significantly reduced vomiting severity more than propofol. The effects of DEX on them is not certain yet, and due to the low prevalence of these complications, there is a need for a larger statistical population.

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