The influence of dexamethasone and ketolgan on postoperative nausea and vomiting and estimation of risk factors in women undergoing gynecologic laparoscopic surgeries

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Key words: *gynecologic laparoscopic surgery; nausea; vomiting.*

Summary. *The aim of this study was to determine the effect of dexamethasone and ketolgan on postoperative nausea and vomiting and to evaluate risk factors for postoperative nausea and vomiting.*

Material and methods. A prospective, double-blind, randomized clinical study was carried out. One hundred fifty-three ASA I–II women undergoing laparoscopic gynecologic operations were randomized into three groups: dexamethasone group (n=51), ketolgan group (n=51), and control group (n=51). Patients in the dexamethasone group were given 4 mg of dexamethasone intravenously before the induction of general anesthesia, the ketolgan group received 30-mg ketolgan intravenously, and control group did not receive any medication. The incidence and severity of postoperative nausea and vomiting were registered 24 hours after the surgery.

Results. The incidence of postoperative nausea and vomiting in the dexamethasone group was 13.8%; in the ketolgan group, 37.3%, and in the control group, 58.9% (P=0.026). Patients with a history of migraine suffered from postoperative nausea and vomiting in 70.3% of cases and migraine-free patients in 25.8% of cases (P=0.015). Opioids for postoperative analgesia increased the incidence of postoperative nausea and vomiting as compared with nonsteroidal anti-inflammatory drugs (P=0.00002).

Conclusions. Preoperative medication with dexamethasone significantly reduces the incidence of postoperative nausea and vomiting. Avoidance of opioids for postoperative analgesia reduces the incidence of postoperative nausea and vomiting. Migraine and motion sickness are independent risk factors for postoperative nausea and vomiting.

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common complications in the early postoperative period associated with surgery performed under general anesthesia. Despite its high prevalence, the control of PONV remains a difficult task (1–3). Many patients recognize PONV as one of the most unpleasant experiences associated with surgery. Most of them admit to fear PONV even more than pain or other postoperative complications. Literature data show that the incidence of PONV is approximately 25–30% with specific surgeries having much higher incidence of up to 70%–80% (1). It is documented that gynecologic surgery (3–5), especially laparoscopic surgery, related to increased intra-abdominal pressure is often followed by PONV (2). Moreover, the incidence of PONV is 2- to 4-fold higher in female population (2). Even though PONV usually is not a life-threatening postoperative complication (6), it increases the risk of other complications, such as wound dehiscence, electrolyte imbalance, increased intraocular pressure, increased intracranial pressure, aspiration, esophageal rupture, and loss of vision due to retinal detachment (2, 6). Moreover, PONV may cause a prolonged hospital stay, which consequently increases treatment costs (1). Unfortunately, there are no accurate Lithuanian statistical data about the incidence of PONV and its risk factors. Despite the relevance of the problem, PONV prophylaxis is not routinely applied. The aim of our study was to determine the effect of premedication with dexamethasone and ketolgan on the incidence of PONV and to evaluate risk factors for PONV.

Material and methods

One hundred fifty-three women classified as ASA physical status I–II, undergoing laparoscopic gynecologic surgery were enrolled in our pro-

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spective, randomized, double-blind, comparative study. The study was carried out in the Clinic of Anesthesiology, the Hospital of Kaunas University of Medicine. The study was approved by the Bioethics Center of Kaunas University of Medicine according to the protocol No. BC-MF-116. Written consent was obtained from all the study patients before they were randomly assigned to one of three groups: dexamethasone (group 1, n=51); ketolgan (group 2, n=51); and control (group 3, n=51). Patients in the group 1 received 4 mg of dexamethasone intravenously, patients in the group 2 received 30 mg of ketolgan intravenously, and patients in the group 3 did not get any medication before the induction of anesthesia. Induction and maintenance of general anesthesia was performed according to the standardized protocol. Induction was as follows: fentanyl, 2 μg/kg; thiopental, 5 mg/kg; and rocuronium, 0.6 mg/kg. Maintenance of anesthesia was as follows: fentanyl boluses under clinical requirement and 1.3% end-tidal sevoflurane. Mechanical lung ventilation was performed with air-oxygen mixture (FiO_2, 0.35).

The questionnaire about PONV and its risk factors was filled in postoperatively by the patients. The intensity of vomiting and nausea was evaluated using the following 3-point scale: 0, no nausea and vomiting; 1, nausea; and 2, vomiting. Risk factors for PONV, such as female gender, nonsmoking, history of PONV, migraine, ASA physical status, use of opioids, were registered. All the study groups were coded; therefore, neither study patients nor investigators knew group dependence.

Data were analyzed using the SPSS 13.0 software. The Kruskal and Wallis test was used for the analysis of parametric data. Nonparametric χ^2 test was used for the analysis of nominal qualitative data. The Mann-Whitney *U* test was used for qualitative ranking data. Data were expressed as mean values (SD) or number (percentage). A *P* value of <0.05 was considered statistically significant.

Results

Demographic data of the study population are presented in Table 1. There were no significant differences between the study groups with respect to age, weight, height, ASA status, and body mass index (BMI).

There were no statistically significant differences between the study groups with respect to the type of laparoscopic gynecologic surgery and length of the procedure. The findings are showed in Table 2.

Six (11.8%) patients in the dexamethasone group (n=51) reported nausea and 1 (2%) patient reported vomiting. There were 12 (23.5%) patients that suffered from nausea and 7 (13.7%) patients that reported vomiting after the surgery in the ketolgan group (n=51). The incidence of nausea and vomiting in the control group (n=51) was 37.3% (n=19) and 21.6% (n=11), respectively. The frequency of PONV was significantly lower in both the dexamethasone and ketolgan groups as compared with the control group (*P*=0.026). The in-

Table 1. Demographic characteristics of the study population

Variable	Dexamethasone group	Ketolgan group	Control group	*P*
Age, mean (SD), years	39 (9)	40 (11)	42 (15)	0.1
Weight, mean (SD), kg	68 (10)	70 (9)	69 (2)	0.84
Body mass index, mean (SD), kg/m^2	24 (4)	24 (6)	25 (5)	0.84
ASA I, n (%)	28 (55)	30 (59)	29 (57)	1
ASA II, n (%)	23 (45)	21 (41)	22 (43)	0.95

Table 2. Types of gynecologic laparoscopic surgery

Surgery	Dexamethasone group	Ketolgan group	Control group	*P*
Chromosalpingoscopy, n	9	8	8	0.94
Ovarian cystectomy, n	20	22	25	0.86
Adnexectomy, n	12	14	10	0.82
Laparoscopic assisted vaginal hysterectomy, n	10	7	8	0.88
Length of surgery, mean (SD), min	45 (25)	52 (18)	47 (20)	0.81

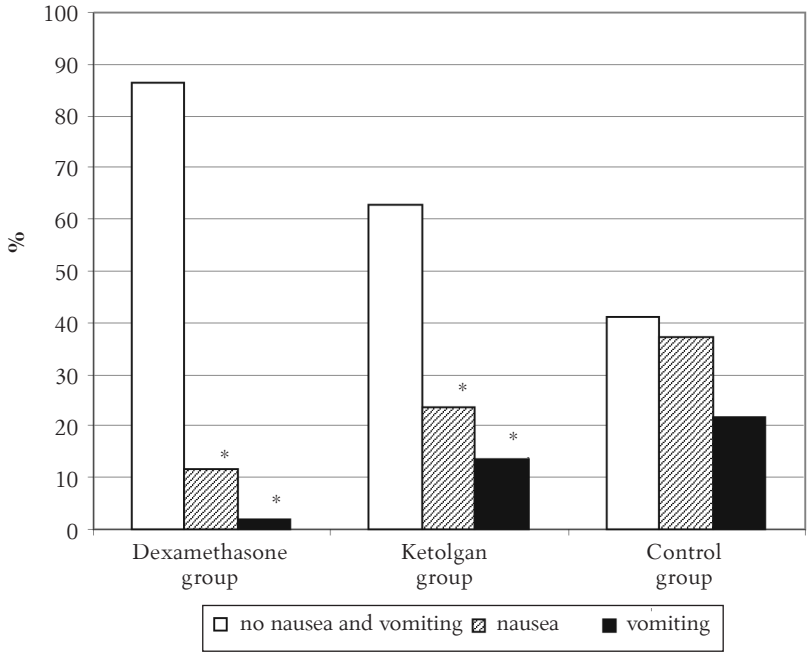

Fig. 1. The incidence of nausea and vomiting in the groups
*P=0.026, statistically significant difference comparing the incidence of postoperative nausea and vomiting among the groups.

cidence of PONV in the study groups is presented in Fig. 1.

Of the 153 study women, 43 (28.1%) had a history of PONV. Thirteen (30.2%) cases of nausea and 7 (16.3%) cases of vomiting were documented among these patients. The incidence of nausea and vomiting among study patients without a history of PONV (n=110) was 21.8% (n=24) and 10.9% (n=12), respectively. Our study showed that a history of PONV was not a statistically significant risk factor (P=0.115).

Of the 153 patients enrolled, 37 (24%) had a history of migraine. The incidence of nausea and vomiting among these patients was 59.5% (n=22) and 10.8% (n=4), respectively. On the contrary, the incidence of PONV in patients without a history of migraine (n=116) was lower: 15 (12.9%) episodes of nausea and 15 (12.9%) episodes of vomiting were registered. Migraine was a statistically significant independent risk factor for PONV (P=0.015). The impact of migraine on the incidence of PONV is showed in Fig. 2.

There were 10 (27%) patients who had migraine in the dexamethasone group (n=51); 2 of them (20%) reported nausea and 1 (10%) vomited after the surgery. Eleven (30%) patients in the ketolgan group (n=51) suffered from migraine; 7 of them experienced nausea (63.6%) and 2 (18.2%) reported vomiting. The incidence of migraine in control group was 43% (n=16). Thirteen (81.3%)

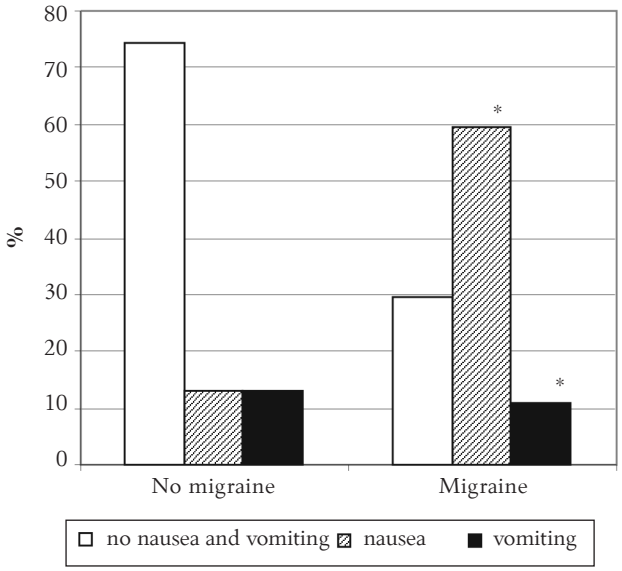

Fig. 2. The influence of migraine on the frequency of postoperative nausea and vomiting
*P=0.015, statistically significant difference comparing with those without migraine.

patients in the control group experienced nausea and 1 (6.3%) vomited. The frequency of PONV among patients suffering from migraine was significantly lower in the dexamethasone group as compared with both the ketolgan and control groups (P=0.017) (Fig. 3).

There were 41 smokers (26.8%) and 112 (73.2%) nonsmokers in the study. Postoperative nausea was registered in 11 (26.8%) smokers and 25 (22.3%)

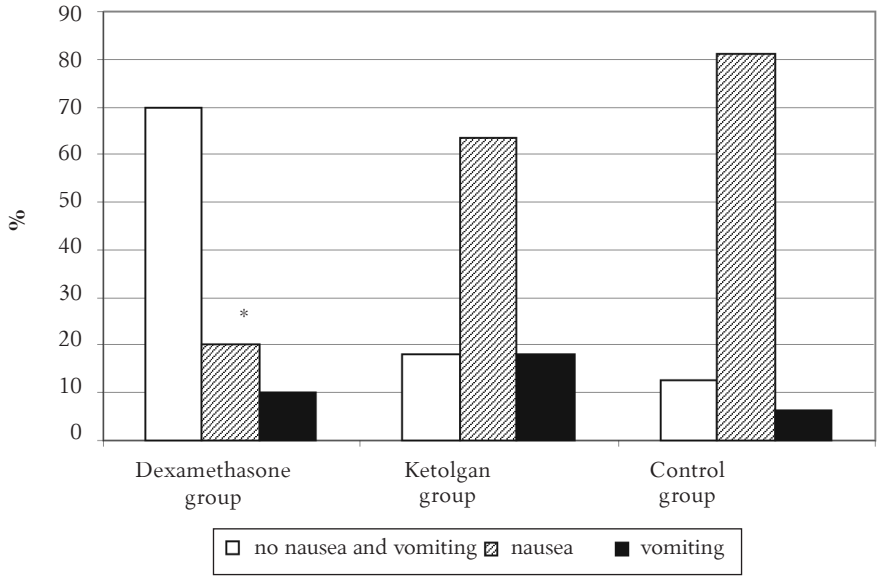

Fig. 3. The influence of dexamethasone (4 mg) and ketolgan (30 mg) on the frequency of postoperative nausea and vomiting in women with a history of migraine
*P=0.017, statistically significant difference comparing with the ketolgan and control groups.

nonsmokers. Vomiting was reported by 3 (7.3%) nonsmoking patients and 16 (14.3%) smokers. The findings of our study showed no significant difference in the incidence of PONV comparing nonsmokers and smokers (P=0.468).

We compared the incidence of PONV in patients who received nonsteroidal anti-inflammatory drugs for postoperative analgesia with patients who received opioids. Of the 112 patients who received nonsteroidal anti-inflammatory drugs (NSAIDs), 20 (17.9%) experienced nausea, 9 (8%) vomited, and 83 (74.1%) patients did not report any complaints. On the contrary, 17 (41.5%) of those who received opioids (n=41) for postoperative analgesia experienced nausea and 10 patients (24.4%) vomited. Our study results showed that opioids for postoperative analgesia statistically significantly increased the incidence of PONV as compared with

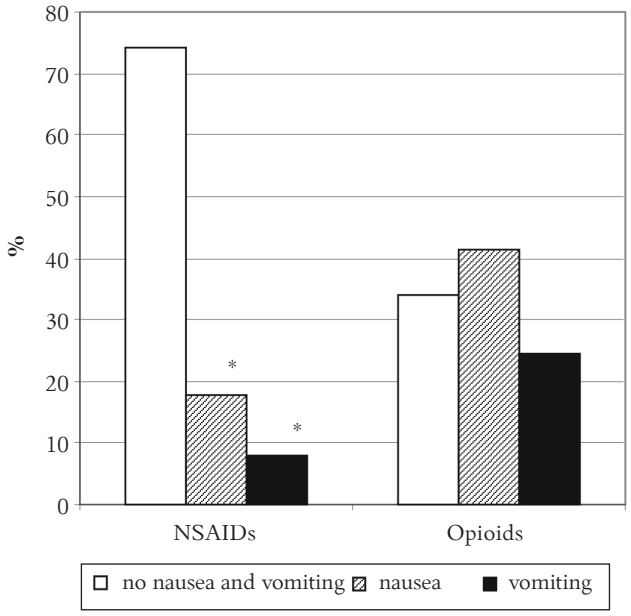

Fig. 4. The influence of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) on the frequency of postoperative nausea and vomiting
P=0.00002, statistically significant difference comparing with those who received opioids for the management of postoperative pain.

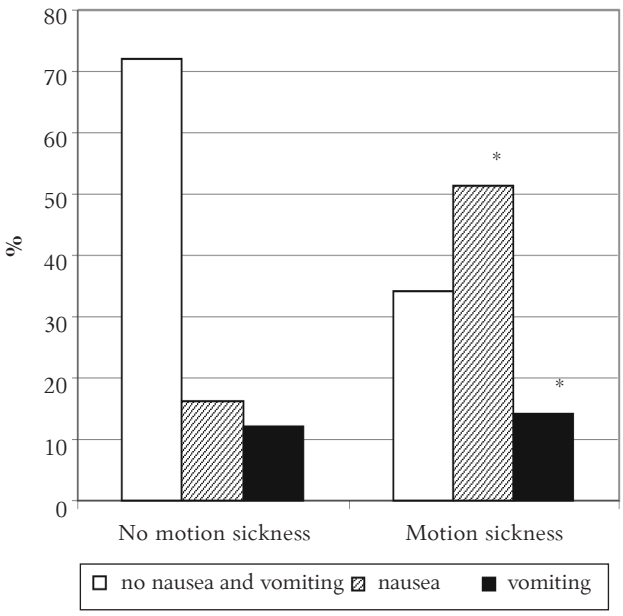

Fig. 5. The influence of motion sickness on the frequency of postoperative nausea and vomiting
*P=0.0002, statistically significant difference comparing with those who did not have a history of motion sickness.

NSAIDs (P=0.00002). The frequency of PONV using NSAIDs and opioids is presented in Fig. 4.

Of the 153 women enrolled in the study, 35 (23%) reported a history of motion sickness. The incidence of postoperative nausea and vomiting was significantly higher among patients who had motion sickness. Eighteen (51.4%) patients suffered from nausea and 5 (14.3%) women vomited, while those who did not have motion sickness (n=118) experienced PONV rarely: 19 (16.1%) women experienced nausea and 14 (11.9%) vomited. Motion sickness was a statistically significant risk factor for PONV (P=0.0002). The results are shown in Fig. 5.

Discussion

PONV may lead to prolonged hospital stay and increased treatment costs. Moreover, PONV has an impact on satisfaction of patients receiving anesthesia (1, 2); therefore, it is very important to reduce or eliminate this early postoperative complication. The routine use of PONV prophylaxis is inexpedient and expensive. It is necessary to have sufficient knowledge regarding the risk factors for PONV and to optimize the use of prophylactic regimens.

Dexamethasone has been used as an antiemetic in patients undergoing highly emetogenic chemotherapy since 1981. However, the mechanism of its action remains unclear (3, 4). Numerous glucocorticoid receptors are found in the nucleus of the solitary tract, raphe nucleus, and the area postrema. These nuclei are known to have a significant neuronal activity in the regulation of the nausea and vomiting reflex (4, 5). Corticosteroids are thought to reduce the levels of 5-hydroxytryptophan in nerve tissue by depleting its precursor tryptophan (6) and in such a way to inhibit the reflex of nausea and vomiting. According to the literature, 5-mg and 2.5-mg doses of dexamethasone are equally effective as 10 mg, and all of these doses lead to significant reductions in the incidence of postoperative emesis as compared with 1.25 mg of dexamethasone (7). We have chosen a 4-mg dose of dexamethasone expecting an optimal antiemetic effect. Our study showed that 4 mg of dexamethasone administered intravenously before the induction of anesthesia significantly reduced the incidence of postoperative nausea and vomiting.

Currently available 5-HT3 antagonists (e.g., ondansetron, granisetron) are effective antiemetics, but their cost limits their widespread clinical application (8, 9). Other antiemetics, such as antihistamines (e.g., hydroxyzine), anticholinergics (e.g., scopolamine), and dopamine receptor antagonists (e.g., droperidol, metoclopramide), have undesirable side effects that include excessive sedation, tachycardia, dry mouth, dysphoria, and possible extrapyramidal symptoms (8, 9). A single dose of dexamethasone demonstrated a significant antiemetic effect without evident adverse events (9). Moreover, studies have showed that the onset of dexamethasone antiemetic effect is approximately 2 h after administration, and its biological half-life is 36 to 72 h, so delayed emesis (up to 24 h) is better controlled with dexamethasone than using other antiemetics (10, 11).

PONV is a polyetiologic event. At least 7 types of neurotransmitters are documented or believed to be involved in PONV, namely serotonin, dopamine, muscarine, acetylcholine, neurokinin-1, histamine, and opioids (12). Nausea and vomiting might also be induced by stimulation of vestibulocochlear, glossopharyngeal, or vagus nerves. The most important risk factors for PONV pointed out in the literature include a history of motion sickness (1, 2, 8, 9, 11, 13), prolonged surgical procedure (13), intraoperative and postoperative use of opioids (1, 10–14), postoperative pain (8, 9), migraine (12, 15), and nonsmoking (12). In fact, large prospective studies have shown that differences in the incidence of PONV are mainly caused by patient- and anesthesia- related risk factors but not the surgery itself (10, 15).

A history of PONV is considered as other risk factor for PONV (2, 9, 12, 16). However, it was not statistically significant in our study. There are several factors that might have affected our results. Some of the women enrolled in the study had a surgery 5, 10, or 15 years ago. In the past, intravenous or inhaled anesthetics of older generation were used for general anesthesia. Inhaled anesthetics, such as halothane, are more likely to cause PONV than isoflurane or sevoflurane, even though these are also associated with increased risk of PONV (16). The risk of PONV can also be increased by intravenous anesthetics; however, innovative anesthetics, such as propofol, rarely induce PONV (16). Aforementioned reasons make it difficult to assess a history of PONV as a risk factor for the recurrence of PONV.

Migraine is the second reason of headache worldwide. It affects approximately 15% of female population (17). Pathogenesis of migraine attacks is not fully elucidated; however, there are three possible theories considered: neurogenic inflammation, extracranial dilation, and decreased sup-

pression of central pain transmitters. Triggers that might provoke migraine include emotional stress, lifestyle changes, insomnia, or prolonged sleep (17). Nausea and vomiting are known as the leading symptoms of migraine (17), while surgery is a great stress; therefore, it is obvious that patients with a history of migraine are at increased risk of PONV and require special attention. Our study showed that the incidence of PONV in women who had a history of migraine was 5 times higher as compared with migraine-free patients. Moreover, the incidence of PONV in women with a history of migraine in the dexamethasone group was significantly lower as compared with both the ketolgan and control groups.

Some authors have reported that nonsmoking might be one of the risk factors for PONV (12). Our study did not support this hypothesis. The incidence of nausea and vomiting in early postoperative period was almost equal among nonsmokers and smokers (34.1% and 36.6%, respectively). Despite the fact that the questionnaire was taken anonymously, some of the respondents might have concealed their harmful habit, which could have affected the results. A history of motion sickness is also considered as an individual risk factor for PONV (1, 2, 8, 9, 11, 13). Nausea and vomiting may be provoked by moving the patient after the surgery or turning in the bed on the other side. Our results confirm that a history of motion sickness is an independent risk factor for PONV.

The use of opioids for postoperative pain management increases the risk of PONV (18). Nausea occurs in approximately 25% of patients after administration of opioids. Some authors suggest avoiding the administration of opioids in early postoperative period if possible (18, 19). Mechanisms for nausea may include direct stimulation of chemoreceptor trigger zone (CTZ), reduced gastrointestinal motility, or enhanced vestibular sensitivity (19). The risk of PONV in patients undergoing gynecologic laparoscopic surgery is high because of the following reasons: female gender, general anesthesia, increased intra-abdominal pressure. Administration of opioids increases this risk even more. We administered 30 mg of ketolgan during the induction of anesthesia for group 2 patients targeting to reduce the need of opioids in early postoperative period and thus to avoid opioid-related PONV. Unfortunately, some patients received opioids postoperatively despite the administration of ketolgan during induction of anesthesia. Opioids were given to 12 (23.52%) and 20 (39.2%) patients in the ketolgan and control groups, respectively. However, the incidence of PONV in the ketolgan group was 2 times lower than in the control group. Avoidance of opioid administration postoperatively could reduce the risk of opioid-related PONV. Only sufficient knowledge of the risk factors for PONV can enable us to predict this unpleasant postoperative event and apply adequate prophylaxis to avoid it (20).

Conclusions

1. Prophylaxis with 4 mg of dexamethasone during the induction of anesthesia statistically significantly reduced the incidence of postoperative nausea and vomiting in women undergoing gynecologic laparoscopic surgery.

2. Administration of 30 mg of ketolgan intravenously during the induction of anesthesia and avoidance of opioids postoperatively significantly reduced the risk of postoperative nausea and vomiting.

3. Migraine and motion sickness are independent individual risk factors for postoperative nausea and vomiting; therefore, additional prophylaxis is required.

Deksametazono ir ketolgano įtaka pykinimo ir vėmimo dažnumui po laparoskopinių ginekologinių operacijų bei rizikos veiksnių įvertinimas

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Raktažodžiai: ginekologinė laparoskopinė operacija, pykinimas, vėmimas.

Santrauka. Tyrimo tikslas. Nustatyti pooperacinio pykinimo ir vėmimo dažnumą, skiriant ligoniams deksametazoną ir ketolganą, bei įvertinti pooperacinio pykinimo ir vėmimo galimus rizikos veiksnius.

Tyrimo metodai. Atliktas perspektyvusis, dvigubai aklas atsitiktinių imčių klinikinis tyrimas. Ištirtos 153 ASA I–II klasės moterys, kurioms atliktos ginekologinės laparoskopinės operacijos. Tiriamosios atsitiktiniu būdu suskirstytos į tris grupes: deksametazono (n=51), ketolgano (n=51) bei kontrolinę (n=51) grupę. Nustatytas pooperacinio pykinimo ir vėmimo pasireiškimas per 24 val. po operacijos bei galimi rizikos veiksniai.

Rezultatai. Deksametazono grupėje pooperacinis pykinimas ir vėmimas pasireiškė 13,8 proc. ligonių, ketolgano grupėje – 37,3 proc., o kontrolinėje – 58,9 proc. (p=0,026). Moterims, sergančioms migrena, pooperacinis pykinimas ir vėmimas užregistruotas 70,3 proc., tuo tarpu nesergančioms – 25,8 proc. atvejų (p=0,015). Lyginant pooperacinį skausmo malšinimą nesteroidiniais vaistais nuo uždegimo ir opioidais, pastarieji turėjo įtakos dažnesniam pooperaciniam pykinimui ir vėmimui (p=0,00002).

Išvados. Profilaktika deksametazonu kliniškai reikšmingai sumažina pooperacinio pykinimo ir vėmimo dažnumą. Vartojant nesteroidinius vaistus nuo uždegimo, galima išvengti opioidų vartojimo pooperaciniu laikotarpiu ir reikšmingai sumažinti pooperacinio pykinimo ir vėmimo pasireiškimą. Migrena ir supimo negalavimai yra pooperacinio pykinimo ir vėmimo nepriklausomi rizikos veiksniai.

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