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POSTOPERATIVE NAUSEA AND VOMITING IN OPIOID-FREE ANESTHESIA VERSUS OPIOID BASED ANESTHESIA IN LAPAROSCOPIC CHOLECYSTECTOMY

Marija Toleska[1], Aleksandar Dimitrovski[1], Natasha Toleska Dimitrovska[2]

[1] University Clinical Center "Mother Teresa" Skopje, University Clinic of TOARILUC, Department of Anesthesiology, Reanimation and Intensive Care – KARIL, Medical Faculty - Skopje, University ″Ss. Cyril and Methodius″ Skopje, Republic of Macedonia

[2] University Clinical Center "Mother Teresa" Skopje, University Clinic for Thoracic and Vascular Surgery, Medical Faculty - Skopje, University ″Ss. Cyril and Methodius″ Skopje, Republic of Macedonia

Corresponding author: Marija Toleska, MD, MSc, PhD. University Clinical Center "Mother Teresa" Skopje, University Clinic of TOARILUC, Department of Anesthesia, Reanimation and Intensive Care – KARIL, Medical Faculty - Skopje, University ″Ss.Cyril and Methodius″ - Skopje, "Vodnjanska" Str. No.:17, 1000 Skopje, Republic of Macedonia; E-mail: marija_toleska@yahoo.com

ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is a usual complication in patients undergoing laparoscopic cholecystectomy. Minimized opioid use due to surgery has been shown to have a better effect on patient recovery after surgery. In this study we evaluate the effect of opioid free anesthesia for postoperative nausea and vomiting in laparoscopic cholecystectomy.

Materials and methods: 80 patients aged 20-65 years old were included in this randomized, clinical and prospective trial. The patients belonged to the ASA classifications 1 and 2 and were scheduled for laparoscopic cholecystectomy. Patients were classified into two groups: group 1 (fentanyl group- FG), which included 40 patients who received opioid anesthesia, and group 2 (opioid free anesthesia group-OFAG) which included 40 patients who received opioid free anesthesia. In patients from group 1 (fentanyl group - FG) introduction to general anesthesia consisted of giving midazolam at 0.04 mg/kg, fentanyl at 0.002 mg/kg, 2 mg/kg of propofol and 0.6 mg/kg of rocuronium bromide. These patients received fractionated bolus doses of fentanyl during surgery. Prior to general anesthesia these patients did not receive dexamethasone. The patients from group 2 (opioid free anesthesia group - OFAG) received dexamethasone at 0.1 mg/kg and 1 g of paracetamol before introduction to anesthesia as a pre-emptive analgesia. Introduction to anesthesia consisted of giving midazolam at 0.04 mg/kg, lidocaine at 1 mg/kg, propofol at 2 mg/kg, ketamine at 0.5 mg/kg, and 0.6 mg/kg of rocuronium bromide. Immediately after intubation, continuous intravenous infusion with lidocaine at 2 mg/kg/h and magnesium sulfate at 1.5 g/h was given. In this group, fentanyl was not given either during the introduction of anesthesia or during the intraoperative period. Immediately after extraction of the gallbladder patients from group 2 (OFAG) received 2.5 g of metamizole intravenously. PONV were recorded in the postoperative period of 24 hours after surgery.

Results: There was no significant difference with respect to age, weight, sex, duration of surgery, and anesthesia time. PONV at different time intervals were statistically not significant at all postoperative time points – 1 hr, 4 hr, 8 hr, 12 hr and 24 hr after surgery in fentanyl group compared to opioid free anesthesia group. Even not statistically significant, PONV have occurred more often in patients who received opioid anesthesia.

Conclusion: Postoperative nausea and vomiting occurs more often in patients who received opioids during laparoscopic cholecystectomy compared to patients who received opioid free anesthesia, but without statistical significance.

Keywords: laparoscopic cholecystectomy, opioid free anesthesia, opioid based anesthesia, postoperative nausea and vomiting

INTRODUCTION

Postoperative nausea and vomiting (PONV) are some of the most common complications after anesthesia, often reducing patient satisfaction and prolonging the recovery and discharge from hospital. It is defined as nausea or vomiting that occurs during the first 24 to 48 hours after surgery. Approximately 12-38% of patients report having PONV after surgery [1]. In high risk patients, this number is much higher, reaching up to 70-80% [2]. PONV can directly cause airway obstruction and aspiration of gastric contents, aspiration pneumonia, esophageal rupture, dehydration, electrolyte imbalance, wound dehiscence, and increased intracranial pressure [3]. The physiology of PONV is complex and not entirely clear. The pathophysiology of vomiting involves structures that are located along the extended brain and are not centralized in the anatomically defined "vomiting center." These structures include chemoreceptor trigger zone (CTZ) and nucleus tract solitarius (NTS). CTZ as an afferent center receives afferent impulses from the vagal nerve from the gastrointestinal tract, and may also be stimulated by emetogenic toxins, metabolites, and drugs circulating in the blood and cerebrospinal fluid due to permeability of the blood-brain barrier. CTZ sends neurons to the NTS, which receives impulses from both, the vagal nerve and vestibular and limbic systems. These impulses are controlled by stimulation of multiple neuroreceptors such as acetylcholine (muscarinic receptor), dopamine (D2 receptor), histamine (H1 receptor), serotonin (5-hydroxytryptamine3 receptor), and neurokinin 1. Blocking these targets is the primary aim of direct antiemetic drugs. CTZ can be triggered by the vestibular nerve during extreme movements or pressure.

Opioids can cause nausea and vomiting by stimulating the area postrema at the basis of fourth ventricle. In order to reduce the intra- and postoperative administration of opioids, Kehlet et al. in the early 1990s introduced the concept of balanced multimodal analgesia [4]. The concept of multimodal analgesia was introduced as a technique to improve analgesia and reduce the occurrence of opioid-related side effects. Multimodal analgesia is achieved by combining different analgesics that act through different mechanisms in different parts of the central nervous system [5]. The aim is to achieve sufficient and appropriate analgesia, through the additive or synergistic effect between different analgesics and at the same time to reduce the dose of each individual drug, and thus the possibility of side effects from the same drugs. Opioid free anesthesia (OFA) is an anesthetic technique in which no systemic, neuroaxial, or intracavitary opioids are used in the intraoperative period [6]. This new technique can provide intraoperative hemodynamic stability, immobility, and postoperative analgesia without administering opioid drugs, and therefore the absence of the numerous side effects caused by opioids. Opioid free anesthesia is a multimodal anesthesia where hypnotics, NMDA antagonists, local anesthetics, anti-inflammatory drugs, and alpha-2 agonists are used. In our study we intend to show the occurrence of PONV in patients who received opioid free anesthesia compared with patients who received opioid based anesthesia.

MATERIALS AND METHODS

The study was a prospective, randomized, controlled clinical trial using parallel groups of randomly selected patients for laparoscopic gallbladder surgery and lasted from January 2018 to December 2019. The study was prepared with the approval of the Ethics Commission for Clinical Research, as well as with the consent of the Department and the Clinic for Anesthesia, Resuscitation and Intensive Care - Skopje.

The study included 80 patients hospitalized for elective laparoscopic cholecystectomy under general anesthesia between the ages of 20 and 65, belonging to classifications 1 and 2 according to the American Society of Anesthesiologists (ASA). Exclusion criteria were: ASA classification 3, 4 and 5; allergy to opioids (fentanyl and tramadol), lidocaine, magnesium, ketamine, paracetamol, ketonal and metamizole; patients which chronically use benzodiazepines and opioids; pregnant and breastfeeding women; patients with the presence of chronic pain; patients with heart, renal and hepatic failure; and patients with psychiatric illness.

Prior to introduction in anesthesia, patients were divided into 2 groups. In patients

from group 1 (fentanyl group – FG), introduction to general anesthesia consisted of giving midazolam 0.04 mg/kg, fentanyl 0.002 mg/kg, 2 mg/kg propofol and 0.6 mg/kg rocuronium bromide. These patients received fractionated bolus doses of fentanyl during surgery. Prior to general anesthesia, these patients did not receive dexamethasone. The patients from group 2 (opioid free anesthesia group - OFAG) received dexamethasone 0.1 mg/kg and 1 g of paracetamol before introduction to anesthesia as pre-emptive analgesia. Introduction to anesthesia consisted of administering midazolam 0.04 mg/kg, lidocaine 1 mg/kg, propofol 2 mg/kg, ketamine 0.5 mg/kg, and 0.6 mg/kg rocuronium bromide. Immediately after intubation, continuous intravenous infusion with lidocaine 2 mg/kg/h and magnesium sulfate 1.5 g/h was given. In this group fentanyl was not given either during the introduction of anesthesia or during the intraoperative period.

Patients were intubated with endotracheal tube and mechanically ventilated with a PVC-VG ventilation regiment, with a respiratory volume of 6-8 ml/kg of a mixture of gases at 50% oxygen and 50% air, ratio I:E = 1:2, with respiratory rate adjusted according to $EtCO_2$ between 35-45 mmHg, and PEEP 5 cm H_2O. Anesthesia was maintained with sevoflurane 0.7-1 MAC. During laparoscopy the intraabdominal pressure in all patients was adjusted to 12 mm Hg by continuous insufflation of carbon dioxide (CO2). Immediately after extraction of the gallblader patients from group 2 (OFAG) received 2.5 g of metamizole intravenously. After the operation, all patients were awakened and transferred to the Post-anesthesia Care Unit (PACU). Postoperative nausea and vomiting were monitored and treated with 10 mg Reglan. The first analysis was performed 1 hour after surgery in the PACU. Other analyses, (the second analysis - 4 hours after surgery, the third - 8 hours after surgery, the fourth - 12 hours after surgery and the fifth analysis - 24 hours after surgery) were performed in the Department of the Abdominal Surgery.

RESULTS

There was no significant difference according to age, weight, sex (with a majority of female patients - 59 were female and 21 were male), duration of surgery and anesthesia time.

In the first hour after the surgery, 5 patients from the fentanyl group (FG) had nausea and none from the opioid free anesthesia group (OFAG) (Fig.1), and this difference reached the limit of statistical significance ($p = 0.055$).

One hour after the operation, 6 patients from the FG and one patient from the OFAG had vomiting (Fig.2). These described differences were not sufficient to confirm they are statistically significant ($p = 0.28$).

In the fourth hour after the operation, 4 patients from the FG and 1 patient from the OFAG complained of nausea. In this period a small number of patients had vomiting, 3 of the FG and none of the OFAG.

Eight hours after surgery, nausea was reported in 6 patients in the FG and 4 in the OFAG (Fig.3), without statistical significance.

Figure 1. *Graph showing the occurrence of nausea 1 hour after operation between patients from fentanyl group (FG) and opioid free anesthesia group (OFAG)*

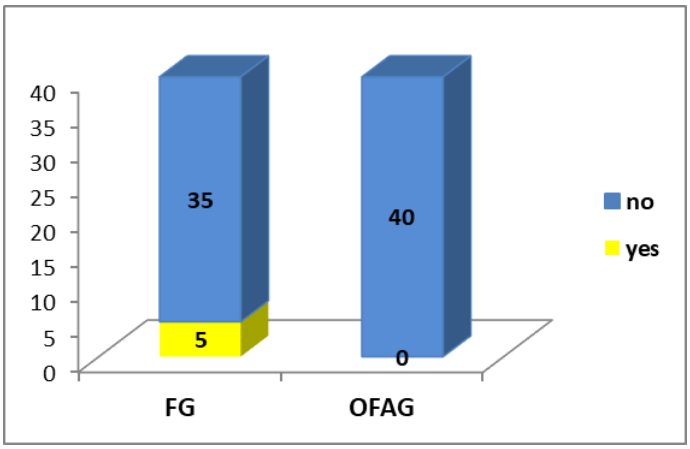


Figure 2. *Graph showing the occurrence of vomiting 1 hour after operation between patients from fentanyl group (FG) and opioid free anesthesia group (OFAG)*

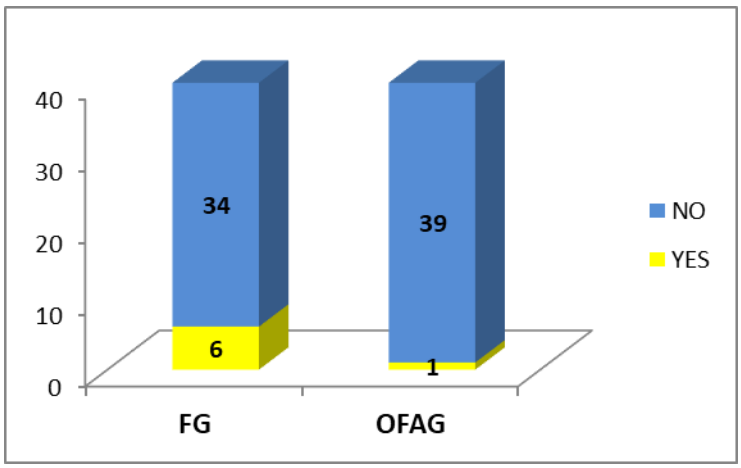


Figure 3. *Graph showing the occurrence of nausea 8 hours after operation between patients from fentanyl group (FG) and opioid free anesthesia group (OFAG)*

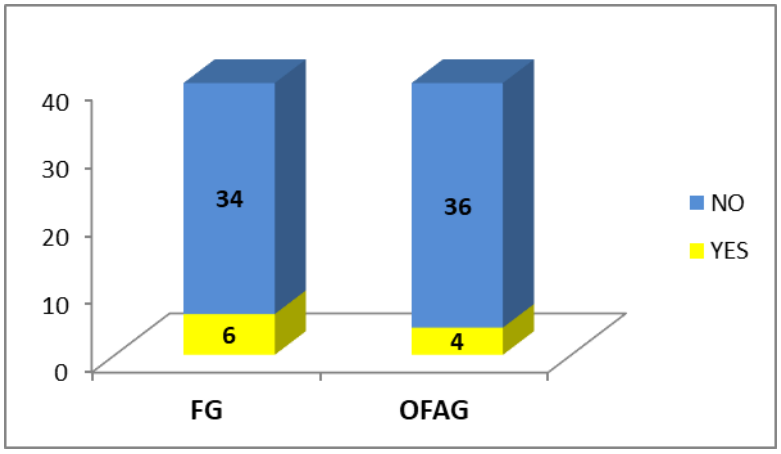
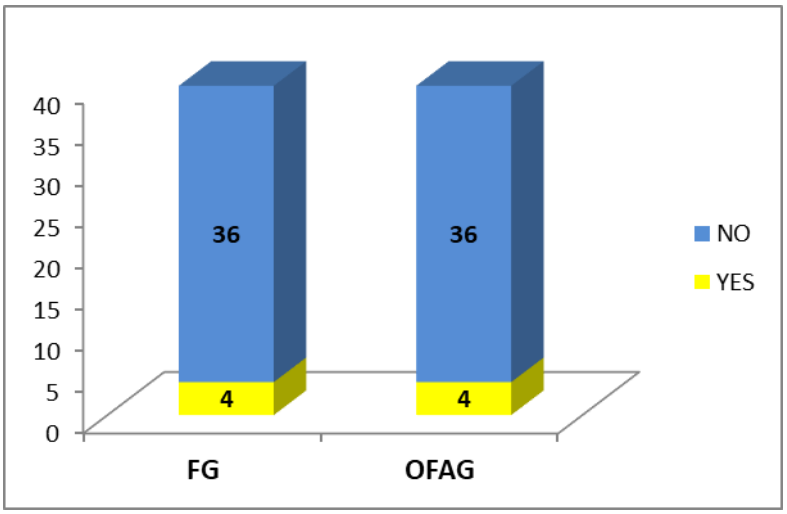


Figure 4. *Graph showing the occurrence of vomiting 8 hours after operation between patients from fentanyl group (FG) and opioid free anesthesia group (OFAG)*



In the eighth hour after operation, no significant difference was found between the groups and in the registered patients with vomiting ($p > 0.05$) (Fig.4). Four patients from FG and 4 patients from OFAG had vomiting.

Twelve hours after surgery, 2 patients from the FG and none of the patients from the OFAG had nausea, and the difference was not statistically significant ($p > 0.05$). During the same time period of 12 hours postoperatively, vomiting was reported in only 2 patients in the FG, and in not one patient of the OFAG.

Twenty-four hours after operation, 2 patients of the FG complained of nausea and vomiting. None of the patients of the OFAG experienced nausea and vomiting during this period.

DISCUSSION

Postoperative nausea and vomiting (PONV) still remains a common complication after anesthesia and surgery and represents a "big, small problem" in the postoperative period. The incidence of PONV after laparoscopic cholecystectomy is very high compared to other types of surgery and presented in 46-75% of the patients who have not received antiemetic therapy [7]. Other factors that may cause PONV in laparoscopic cholecystectomy are: the effect of intraperitoneal carbon dioxide insufflation on residual stretching and irritation of the peritoneum and duration of surgery [8]. The same study showed that subhypnotic bolus doses of propofol 0.5 mg/kg together with 8 mg of dexamethasone at the end of surgery were shown as more effective than giving of the same dose of propofol with 0.2 mg/kg metoclopramide. Opioids are highly emetogenic drugs because they directly activate the chemoreceptor trigger zone, slow down the gastrointestinal motility, and stimulate the vestibular nerve. The risk of PONV can be reduced by replacing opioids with non-opioid drugs and giving them less during surgery. The high incidence of PONV during abdominal open or laparoscopic surgery may be due to intestinal ischemia which release 5-hydroxytryptamine. Another study found that preoperative administration of midazolam at a dose of 0.04 mg/kg significantly reduced PONV for 24 hours after intraabdominal or ambulatory surgery [9]. Midazolam not only reduced PONV, but also significantly reduced administration of antiemetics in the postoperative period in cholecystectomy [10], outpatient breast surgery [11] and middle ear surgery [12].

The appearance of nausea and vomiting are most common during the first 2 hours of recovery from anesthesia [13]. The condition of the pneumoperitoneum also has a direct effect on PONV [13]. In the same study the authors concluded that dexamethasone 8 mg given intravenously was shown to be more effective in the prevention of PONV in laparoscopic cholecystectomy and had fewer side effects compared to 8 mg of ondansetron. Both drugs were given 1 minute before introduction to anesthesia. Each extension of surgery for 30 minutes has been shown to increase the risk of PONV by 60% [1]. Complete non-opioid anesthesia has been shown to reduce PONV. Decreased intraoperative opioid administration in combination with multimodal analgesia reduces the incidence of PONV [14]. Postoperative nausea occurred in 68% of patients receiving anesthesia with sevoflurane and fentanyl, compared with 27% of patients receiving anesthesia with sevoflurane without fentanyl in major breast cancer surgery [14]. In same study, the incidence of vomiting occurred in 32% of patients receiving fentanyl, compared with 8% of patients who did not receive fentanyl during surgery. Also, postoperative opioid use poses an additional risk for PONV [15]. From all volatile anesthetics, sevoflurane and desflurane have less emetogenic effects [15]. Non-opioid total intravenous anesthesia (TIVA) used in bariatric surgery reduces the risk of developing PONV by 17.3% and the severity of PONV, compared with general anesthesia where volatile anesthetics and opioids are used, despite the treatment with triple prophylaxis (transdermal patch with scopolamine, dexamethasone and ondansetron) [15].

The results in our study showed that nausea and vomiting were more common in the fentanyl group (FG) compared to the opioid free anesthesia group (OFAG), but without statistical significance ($p > 0.05$). Patients in the FG had the most nausea at 1, 4 and, especially, at 8 hours after surgery. Most of these patients vomited during the 1st hour after surgery, and less during the 4th and 8th hours after surgery. Patients of the OFAG showed the greatest incidence of nausea and vomiting 8 hours after surgery. None of the patients in this group had nausea or vomiting 12 and 24 hours after surgery.

The occurrence of PONV depends on several risk factors such as: female patients, history of

PONV and/or seasickness disease, smoking, history of nausea and vomiting caused by chemotherapy, general anesthesia (regional anesthesia leads to a lower incidence of PONV), the drugs that are used in the intraoperative period (volatile anesthetics, nitrous oxide, ketamine, opioids, prostigmine over 2.5 mg, sugammadex, parasympathomimetic drugs). Hypovolemia or dehydration associated with preoperative starvation contributes to PONV. As the patient ages, the incidence of PONV decreases. Also, positive pressure ventilation, distension of the stomach (with air during ventilation or with liquid contents), conditions of elevated intracranial pressure, intra-abdominal, gynecological, laparoscopic surgeries, ophthalmic, middle ear and breast surgery lead to PONV [3,16]. In the preoperative period, the state of fear, anxiety, pain, conditionally related nausea with the environment, and stimulation of the vestibular system are central stimuli that may cause nausea and vomiting. Long-term surgery may be more invasive and may require higher doses of opioids in the intra- and postoperative period. These may be maintained with volatile anesthetics and thus lead to increased PONV.

Conditions of hypotension and bradycardia may trigger vomiting and ephedrine has been shown to have a positive effect on reducing PONV and hypotension [17]. Apfel et al. created a risk score for PONV in order to assess the patients in the preoperative period and to implement a preventive strategy that predicts the possible risk of PONV in the postoperative period [2]. This score consists of four highly predictive risk factors: female population, non-smokers, history of previous PONV or seasickness disease, and expected opioid administration in the postoperative period. If there are specific risk factors with points 0, 1, 2, 3, and 4, then it corresponds to the risk of PONV for 10, 20, 40, 60, and 80% respectively. Each risk factor carries 1 point. Patients with a score of 0-1 (10 to 20%) have a low risk factor for PONV, patients with a score of 2 (40%) have a medium risk factor and scores of 3-4 (60 to 80%) have a high risk factor.

The underlying risk of PONV can be reduced by using the following techniques: use of regional anesthesia (if general anesthesia is required, the use of TIVA with propofol is recommended), avoidance of volatile anesthetics (if they must be used, one should use sevoflurane or desflurane), adequate hydration [18], administration of dextrose solutions [19], multimodal postoperative pain control (using regional anesthesia techniques, paracetamol, NSAIDs, and other nonopioid adjuvants), and administration of antiemetics [20]. The most commonly used antiemetics are: serotonin (5-hydroxytryptamine 3) receptor antagonists (ondansetron, granisetron, dolasetron, ramosetron, tropisetron and palonosetron); glucocorticoids (dexamethasone); anticholinergics (scopolamine); butyrophenones (droperidol and haloperidol); neurokinin 1 receptor antagonists (these are a new group of long-acting antiemetics, and examples are aprepitant and rollapitant); antihistamines (dimenhydrinate and diphenhydramine); phenothiazines (promethazine prochlorperazine); propofol; metoclopramide; midazolam; and cannabinoids [21]. Combination therapy using different types of drugs has been shown to be more effective than single-drug therapy in the prevention of PONV [22]. This concept was demonstrated in a study involving 5,199 patients who received different combinations of six prophylactic interventions for PONV: ondansetron, dexamethasone, droperidol, propofol or volatile anesthetic, remifentanil or fentanyl, nitrogen or nitrous oxide. It has been shown that ondansetron, dexamethasone, and droperidol each individually reduce the risk of PONV by 26%; propofol reduces the risk by 19% and nitrogen by 12% [20].

CONCLUSION

Postoperative nausea and vomiting are more common in patients who receive opioids during surgery. Reduced intraoperative opioid administration in combination with multimodal analgesia reduces the incidence of PONV. Opioid free anesthesia has been shown to reduce PONV, leading to faster recovery from surgery, and thus greater patient satisfaction postoperatively. PONV was not registered in the 12th and 24th hours after surgery. Preoperative administration of dexamethasone and the use of nonopioid analgesics have minimized occurrence of nausea and vomiting in patients in the opioid free anesthesia group, but without any statistical significance.

Limitations to this study

We did not use the PONV Intensity Scale in the postoperative period; we only asked the patients sample questions and also did not use dexamethasone as an antiemetic drug prior to surgery.

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Резиме

ПОЈАВА НА ПОСТОПЕРАТИВНО ГАДЕЊЕ И ПОВРАЌАЊЕ КАЈ ПАЦИЕНТИ ШТО ДОБИЛЕ НЕОПИОИДНА АНЕСТЕЗИЈА НАСПРОТИ ОПИОИДНА АНЕСТЕЗИЈА КАЈ ЛАПАРОСКОПСКИ ОПЕРАЦИИ НА ЖОЛЧНОТО ЌЕСЕ

Марија Толеска[1], Александар Димитровски[1], Наташа Толеска Димитровска[2]

[1] Универзитетски клинички центар „Мајка Тереза“, Скопје, Универзитетска клиника за ТОАРИЛУЦ – Оддел за анестезиологија, реанимација и интензивно Лекување (КАРИЛ), Медицински факултет – Скопје, Универзитет „Св. Кирил и Методиј“ во Скопје, РС Македонија

[2] Универзитетски клинички центар „Мајка Тереза“ Скопје, Универзитетска клиника за торакална и васкуларна хирургија, Медицински факултет – Скопје, Универзитет „Св. Кирил и Методиј“ во Скопје, РС Македонија

Вовед: Постоперативното гадење и повраќање (ПОГП) е честа компликација кај пациентите што се подложени на лапароскопски операции на жолчното ќесе. Се покажало дека намалената употреба на опиоиди во текот на операцијата има подобар ефект врз опоравувањето на пациентите. Во оваа студија го оценуваме ефектот на неопиоидната анестезија врз постоперативното гадење и повраќање при лапароскопска операција на жолчното ќесе.

Материјали и методи: Во ова рандомизирана, клиничка и проспективна студија беа опфатени 80 пациенти на возраст од 20 до 65 години, ASA класификација 1 и 2, предвидени за лапароскопска операција на жолчното ќесе. Пациентите беа класифицирани во две групи: група 1 (фентанилска група – ФГ), која вклучуваше 40 пациенти што примаа опиоидна анестезија и група 2 (неопиоидна група – НОГ), која вклучуваше 40 пациенти што примаа анестезија без опиоиди. Кај пациенти од групата 1 (фентанилската група – ФГ) воведувањето во општа анестезија се состоеше од давање мидазолам 0,04 мг/кг, фентанил 0,002 мг/кг, 2 мг/кг пропофол и 0,6 мг/кг рокурониум бромид. Овие пациенти примаа фракционирани болус дози на фентанил за време на операцијата. Пред воведот во општа анестезија, на овие пациенти не им беше дадено дексаметазон. Пациентите од групата 2 (неопиоидна група – НОГ) примија дексаметазон 0,1 мг/кг и 1 гр парацетамол пред воведот во општа анестезија како превентивна аналгезија. Воведот во анестезијата се состоеше од давање мидазолам 0,04 мг/кг, лидокаин 1 мг/кг, пропофол 2 мг/кг, кетамин 0,5 мг/кг и 0,6 мг/кг рокурониум бромид. Веднаш по интубацијата се аплицираше континуирана интравенска инфузија со лидокаин 2 мг/кг/час и магнезиум сулфат 1,5 гр/час. Во оваа група, фентанил не беше даден ниту за време на воведот во анестезија ниту во текот на самата операција. Веднаш по екстракцијата на жолчното ќесе, пациентите од групата 2 (НОГ) примија 2,5 гр метамизол интравенски. Појавата на ПОГП се следеше во постоперативниот период до 24 часа по операцијата.

Резултати: Во однос на возраста, тежината, полот, времетраењето на операцијата и времето на анестезијата, немаше значителна разлика. ПОГП во различни временски интервали статистички не беше значително во сите временски точки по операцијата – 1 час, 4 часа, 8 часа, 12 часа и 24 часа по операцијата во фентанилската групата во споредба со неопиоидната група. ПОГП се јавува почесто кај пациенти што примале опиоидна анестезија, но тоа се покажало дека е статистички незначајно.

Заклучок: Постоперативното гадење и повраќање е почесто кај пациенти што примале опиоиди за време на лапароскопска операција на жолчното ќесе во споредба со пациенти што примале неопиоидна анестезија, но без статистичка значајност.

Клучни зборови: лапароскопска операција на жолчното ќесе, опиоидна анестезија, неопиоидна анестезија, постоперативно гадење и повраќање