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# IS MULTIMODAL ANESTHESIA EFFECTING POSTOPERATIVE NAUSEA AND VOMITING IN LAPAROSCOPIC CHOLECYSTECTOMY?

The comparison between Lidocaine, Ketamine and Magnesium sulfate as an adjuvant analgesics on the intraoperative amount of Fentanyl and postoperative nausea and vomiting (PONV) in patients with laparoscopic cholecystectomy

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## ABSTRACT

**Background**: Multimodal anesthesia represents a technique that can improve analgesia and lower the occurrence of opioid side effects in the postoperative period, such as postoperative nausea and vomiting (PONV). It can be achieved by providing different types of medication during the intraoperative period which can decrease the need for opioids. PONV happens more often in patients who have received large amounts of opioids during laparoscopic cholecystectomy. In this study, our aim was to observe the occurrence of PONV between three different groups of patients who received lidocaine, ketamine and magnesium sulfate in combination with fentanyl in the intraoperative period. We also observed any additional nausea and vomiting in the three groups as well as the amount of fentanyl given to these groups during operation.

**Materials and methods**: 120 patients aged 20-65 years old were included in this randomized and prospective study, ASA classification 1 and 2, scheduled for laparoscopic cholecystectomy. Patients were classified into three groups randomly: Group 1 (lidocaine group-LG), these patients received lidocaine at 1 mg/kg during induction to general anesthesia and 2 mg/kg/h after intubation in continuous intravenous infusion; Group 2 (ketamine group-KG) these patients received ketamine at 0.5 mg/kg during induction to general anesthesia; and Group 3 (magnesium group-MG) these patients received magnesium sulfate at 1.5 gr/hr as a continuous intravenous infusion after intubation. In all three groups, patients additionally received bolus doses of fentanyl. Postoperative nausea and vomiting were monitored in all three groups at 1, 4, 8, 12, and 24 hours after surgery as a primary objective, and if patients had complainant of vomiting, they were treated with 10 mg of metoclopramid. Between the five control time points, additional nausea and vomiting was recorded as well, as a secondary objective. The third objective was to measure of the total amount of fentanyl given in the intraoperative period.

**Results**: Patients from the lidocaine group experienced less PONV and they received less fentanyl compared to patients of ketamine and magnesium groups. Patients from the ketamine group had more nausea than other groups. In the magnesium group, the rate of vomiting was higher, and they received higher amounts of fentanyl during surgery. Additional nausea and vomiting occurred in 3 patients in the LG, 2 in the KG, and 3 in the MG between the five control time points. The patients from the magnesium group received the highest dose of fentanyl during surgery (307.50 ± 130.4), followed by the patients from the ketamine group (292.50 ± 60.5), and then patients from the lidocaine group (258.75 ± 60.9). The doses of fentanyl that patients received during surgery in all three groups were not statistically significant.

**Conclusion**: Multimodal anesthesia has been shown to lower PONV 24 hours after laparoscopic cholecystectomy and can lower need for opioids during laparoscopic cholecystectomy.

**Keywords**: lidocaine, ketamine, magnesium sulfate, postoperative nausea and vomiting

## INTRODUCTION

Laparoscopic cholecystectomy is the gold standard for the treatment of patients with symptomatic cholelithiasis. It is a minimally invasive technique and is associated with reduced surgical trauma, smaller and more cosmetic incisions, reduced blood loss, less postoperative complications, and reduced length of hospital stay. [1] Occurance of postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy is very high compared to other types of surgery and accounts for 46–75 % of patients who did not receive antiemetic therapy after laparoscopic cholecystectomy. [2] The risk of PONV can be reduced by replacing the opioids with nonopioid drugs and by administering opioids less during surgery. Reduced intraoperative opioid administration, in combination with multimodal analgesia, can reduce the incidence of PONV. [3] Lidocaine, ketamine, and magnesium sulfate are nonopioid drugs that are used as a part of a multimodal anesthesia regime and can lower the occurrence of PONV by lowering pain scores in the postoperative period. In our study, we wanted to compare the incidence of postoperative nausea and vomiting in three different groups when lidocaine, ketamine, or magnesium are used individually in combination with fentanyl as a primary objective. This was tested 1, 4, 8, 12 and 24 hours after laparoscopic cholecystectomy. The secondary objective was to see if there is any additional occurrence of PONV in these three groups The third objective was to measure the amount of fentanyl given intraoperatively.

## MATERIALS AND METHODS

120 patients were included in this prospective and randomized study. They were scheduled for elective laparoscopic cholecystectomy under general anesthesia and were between the ages of 20 and 65, having the classifications 1 and 2, according to the American Society of Anesthesiologists (ASA). After approval from the local ethics committee and after obtaining informed consent from each patient, the study was performed at the University Clinic of TOARILUC – KARIL, Clinical Center "Mother Teresa" – Skopje, from December 2018 to March 2020. Exclusion criteria were: ASA classifications 3, 4, and 5, allergy to opioids (fentanyl and tramadol), lidocaine, magnesium, ketamine, paracetamol, ketonal (ketoprofen); patients who chronically use benzodiazepines and opioids, pregnant and breastfeeding women, the presence of chronic pain, patients with heart, renal and hepatic failure; and patients with psychiatric illness. Randomization was done before surgery so that each patient, before signing in the inform consent, had to choose from one of three envelopes. Inside these envelopes was written to which group each patient belongs.

In all patients, induction to general anesthesia was consisted of 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. During surgery, all patients received additionally fractionated bolus doses of fentanyl at 0.5-1 microgram/kg, which was injected to control blood pressure and heart rate within 20% of baseline. In the lidocaine group (LG), 40 patients received lidocaine at 1 mg/kg during induction to general anesthesia after midazolam, and after intubation they received a continuous intravenous infusion with lidocaine at 2 mg/kg/h. They also received bolus doses of fentanyl. In the ketamine group (KG), 40 patients received ketamine at 0.5 mg/kg during induction to general anesthesia after propofol, and bolus doses of fentanyl during surgery. In the magnesium group (MG), 40 patients received a continuous intravenous infusion of magnesium sulfate at 1.5 gr/kg after intubation and bolus doses of fentanyl during surgery.

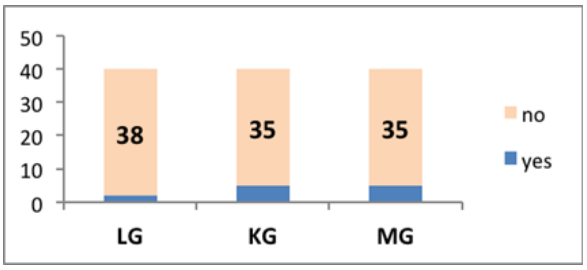
Patients were intubated with an endotracheal tube and mechanically ventilated with a PVC-VG ventilation regimen, with a respiratory volume of 6-8 ml/kg, consisting of a mixture of

gases at a 50:50 (oxygen:air) ratio, I:E = 1:2, with the respiratory rate adjusted according to $EtCO_2$ between 35-45 mmHg, and PEEP at 5 cm $H_2O$. Anesthesia was maintained with sevoflurane 0.7-1 MAC, and all patients received an orogastric tube in situ during surgery. During laparoscopy, the intraabdominal pressure in all patients was adjusted to 12 mmHg via continuous insufflation of carbon dioxide (CO2). After the operation, all patients were transferred to the Post-anesthesia Care Unit (PACU). Postoperative nausea and vomiting were monitored in all patients, and if patients had complaint of vomiting, they were treated with 10 mg of metoclopramid. The first analysis was performed 1 hour after surgery in the PACU. Other analyses as follows: the second analysis - 4 hours after surgery, the third - 8 hours after surgery, the fourth - 12 hours after surgery, and the fifth - 24 hours after surgery. These analyses were performed in the Department of Abdominal Surgery. Between the five control time points, additional nausea and vomiting was recorded as well. We also counted the total consumption of fentanyl in the intraoperative period in all three groups. The intensity of postoperative pain was assessed using a VAS score at rest and when coughing, with evaluations at 1, 4, 8, 12, and 24 hours, postoperatively. In patients with a VAS score above 4, 100 mg of ketonal was administered, while in patients with VAS score above 7, 100 mg of tramadol was administered. The examiner who performed the follow-up with the patients after surgery in the PACU and at the Department was blinded to this study.

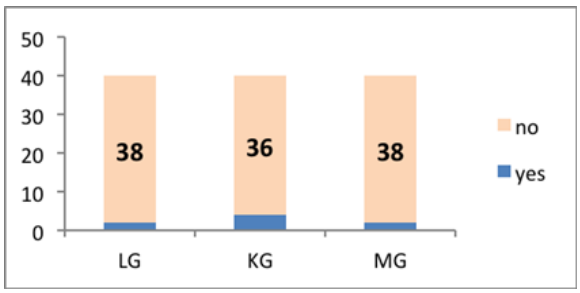
## RESULTS

There was no significant difference with respect to age, weight, sex (with a dominance of female patients - 87 were female and 33 were male), duration of surgery and anesthesia time. For statistics we used Fisher test, Analysis of Variance and Post-hoc (Tukey test).

In the first hour after operation, 2 patients from the lidocaine group (LG), 5 from the ketamine group (KG), and 5 from the magnesium group (MG) had nausea (Graph 1).



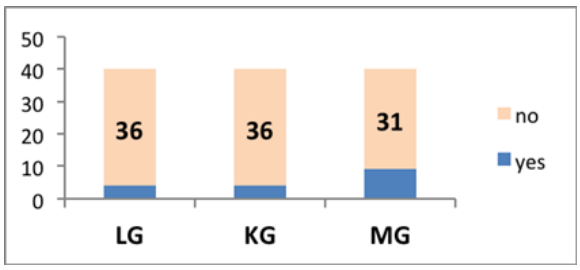

One hour after surgery, 2 patients from the LG, 4 from the KG and 2 patients from the MG had vomiting (Graph 2).




**Graph 2.** *Occurrence of vomiting 1 hour after surgery in the lidocaine, ketamine and magnesium groups*

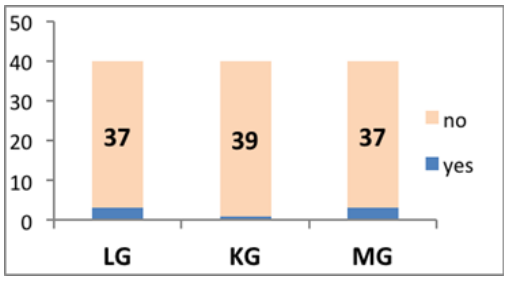
These described differences in the distribution of patients, with and without vomiting, one hour after intervention, were not sufficient to be statistically confirmed as a significant.

4 hours after operation, patients from the LG and KG complained of nausea equally - 4 patients in each of these groups and 9 patients in the MG. This is without statistical significance (Graph 3).




**Graph 3.** *Occurrence of nausea 4 hours after surgery in the lidocaine, ketamine and magnesium groups*

Comparative intergroup differences of vomiting 4 hours after surgery were not statistically significant. A few patients had vomiting in this period, 3 from the LG and MG and 1 patient from the KG (Graph 4).




**Graph 4.** *Occurrence of vomiting 4 hour after surgery in the lidocaine, ketamine and magnesium groups*

Eight hours after surgery, nausea was registered in 2 patients from the LG, 4 from the KG, and 5 from the MG. Nausea was most often experienced by patients who received magnesium after the induction to anesthesia, and rarely by patients who received lidocaine after the induction to anesthesia, without any statistical significance. Eight hours after operation, no significant difference was found between the groups and in the patients registered with vomiting ($p > 0.05$). Two patients from the LG, 2 from the KG, and 2 from the MG had vomiting.

Twelve hours after surgery, 1 patient from the LG, 5 from the KG, and 1 from the MG were reported to have nausea. The patients who received ketamine usually had nausea, but the difference compared to the other groups was not statistically significant ($p > 0.05$). During the same period, 12 hours postoperatively, vomiting was reported in only 1 patient from MG.

At the end of the follow-up, 24 hours after intervention, a total of 2 patients complained of nausea: one patient each from the LG and KG. At the end of the follow-up, no vomiting was reported in any of the three groups.

Between the five control time points, additional nausea and vomiting occurred in 3 patients in the LG, 2 in the KG, and 3 in the MG. Additional nausea and vomiting were reported during different times. In the LG, additional nausea and vomiting occurred in one patient 2 hours after surgery, in the second patient 15 hours after surgery, and in the third patient 21 hours after surgery. In the KG additional nausea and vomiting were observed in one patient 6 hours after surgery and in the second patient 7 hours after surgery. In the MG nausea and vomiting were observed in one patient immediately after surgery, in another patient, 10 hours after surgery, and in the third patient, 16 hours after surgery.

Patients from the magnesium group received the highest dose of fentanyl during surgery (Table 1) ($307.50 \pm 130.4$), followed the patients from the ketamine group ($292.50 \pm 60.5$) and patients from the lidocaine group ($258.75 \pm 60.9$) received the lowest dose of fentanyl. The doses of fentanyl that patients received during surgery in all three groups were not statistically significant.

## DISCUSSION

Nausea and vomiting are most common during the first 2 hours of recovery from anesthesia. [4] The high dose of opioids given during surgery leads to a higher risk of developing PONV. Postoperative use of opioids poses an additional risk for PONV. 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. [5]

Our study shows that in the first 24 hours after surgery, the patients from the ketamine group had the most nausea (almost half - 19 patients), followed by the patients from the mag-

**Table 1.** *Mean amount of fentanyl that was given intravenously to patients in all three groups during surgery*

| Groups | Fentanyl given i.v. during surgery | |
|---|---|---|
| | mean ± SD | range |
| LG | 258.75 ± 60.9 | 150 – 400 |
| KG | 292.50 ± 60.5 | 150 – 400 |
| MG | 307.50 ± 130.4 | 150 – 1000 |

Analysis of Variance F=5.9

nesium group (15 patients with nausea), and patients with the lidocaine group had less nausea: only 10 patients in the LG had nausea measured at five time points in the postoperative period. With regards to the occurrence of vomiting, the patients from the magnesium group vomited the most in all five time intervals in the postoperative period, 8 patients in total. Only 7 patients from the lidocaine and ketamine groups experienced vomiting up to 24 hours after surgery. Patients in the lidocaine group had less nausea and vomiting compared to the other two groups. This is due to the fact that they received less fentanyl in the intraoperative period. The highest dose of fentanyl was given to patients from the magnesium group, and therefore these patients vomited more in the postoperative period. Patients in the ketamine group had more nausea due ketamine's emetic effect.

Lidocaine is a local anesthetic from the amino-amide type. It has several effects: reversible blockade of impulse propagation through nerve fibers (for local or regional anesthesia by binding to sodium channels); antiarrhythmic effect; anti-inflammatory effects (proven to be greater than the same effect of NSAIDs and steroids)6; antibacterial activity [6] and antinociceptive effect. [7] The benefits of intraoperative infusion with lidocaine include pain relief, reduced nausea and vomiting, decreased ileus incidence, reduced opioid needs and reduced hospital stay. [8] A meta-analysis of 45 randomized clinical trials of open and laparoscopic abdominal surgery showed that intraoperative infusion with lidocaine reduces postoperative pain immediately after surgery and up to 24 hours (but not up to 48 hours), accelerates the return of intestinal function, shortens the time of onset of first flatulence and intestinal movement. Patients also had less nausea and their hospital stay was shortened slightly. [9] However, in a recent meta-analysis involving 68 studies of patients undergoing open and laparoscopic abdominal surgery and other surgical procedures, the results showed that it was uncertain whether perioperative infusion with lidocaine had an effect on early postoperative pain, gastrointestinal healing, postoperative nausea, and opioid consumption when compared to the placebo or without treatment. [10] Patients who received a continuous intravenous lidocaine infusion were found to have lower postoperative pain at all times, lower PONV, lower total fentanyl dose, and were more satisfied patients. This is contrast to patients who received ketorolac in bolus doses and as a continuous intravenous infusion. [11]

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, and also binds to both AMPA receptors and sigma opioid receptors. It is a dissociative hypnotic that has several beneficial effects: an analgesic effect,[12] a antihyperalgetic effect, an amnestic effect, [13] a hypnotic effect, [14] an anti-inflammatory effect14, an antidepressive effect, [14] a bronchodilatatory effect, and an emetic effect. Anesthetic doses of ketamine lead to nausea, but given in subanesthetic doses, ketamine leads to a significant reduction in nausea and vomiting, most likely due to its opioid-sparing effect. [12] Side effects from the gastrointestinal tract include nausea, vomiting, loss of appetite, and abdominal pain. [15] Subanesthetic doses of ketamine have been shown to be effective in the treatment of postoperative pain, thereby possibly reducing the morphine requirements during the first 24 hours after surgery and these subanesthetic doses of ketamine can also reduce PONV. [14] A meta-analysis has shown that ketamine added to morphine or hydromorphone for patient-controlled analgesia has little effect on postoperative analgesia, but it reduces PONV and the need for opioids. [16] In another meta-analysis of randomized clinical trials related to the analgesic effect of intravenous ketamine in laparoscopic cholecystectomy, it has been shown that ketamine significantly reduces postoperative pain and the use of opioids.[17]

Magnesium sulfate has several beneficial effects: an analgesic effect (because it is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors and blocks calcium channels), it emphasizes the duration of neuromuscular block, [18,19] it has a neuroprotective effect, [20] it prevents shivering after surgery, [21, 22] it reduces blood hypercoagulability, [23] it and has an anti-inflammatory effect. [24] One study found that the use of magnesium sulfate improved the quality of postoperative recovery, reduced pain, reduced postoperative nausea and vomiting, and reduced the need for opioids in outpatient segmental mastectomy. [25] Magnesium given as a bolus dose [26] or as a continuous intravenous infusion [27] has been shown to potentiate postoperative analgesia, reduce the need for opioids in the postoperative period, and thus nausea and vomiting, and improves pain scores.

## CONCLUSION

Multimodal anesthesia has been shown to be a good alternative and it has an effect on postoperative nausea and vomiting in laparoscopic cholecystectomy. It can reduce opioid administration during surgery, and thus to reduces the side effects associated with fentanyl administration in the postoperative period. Postoperative nausea was lowest in the lidocaine group, and patients in this group received the lowest amount of fentanyl during surgery. The patients from the ketamine group had the most nausea. An equal number of patients in the lidocaine and ketamine groups vomited in the postoperative period. The patients from the magnesium group received the highest amount of fentanyl in the intraoperative period and, therefore, had the most vomiting recorded.

*Limitations to this study*

The methods of medicine administration were also different: one was bolus and infusion, another was only bolus, and the third was infusion alone. We did not use a PONV Intensity Scale in the postoperative period, but only asked the patients with sample questions. We also did not use dexamethasone as an antiemetic drug prior to surgery. We also found it unpleasant to wake up the patients in the middle of the night, just to ask do they have nausea or vomiting.

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**Резиме**

## ДАЛИ МУЛТИМОДАЛНАТА АНЕСТЕЗИЈА ВЛИЈАЕ ВРЗ ПОСТОПЕРАТИВНОТО ГАДЕЊЕ И ПОВРАЌАЊЕ КАЈ ЛАПАРОСКОПСКИ ОПЕРАЦИИ НА ЖОЛЧНОТО ЌЕСЕ?

**Споредба меѓу лидокаинот, кетаминот и магнезиум сулфатот како адјувантни аналгетици врз постоперативната доза на фентанил и постоперативното гадење и повраќање кај пациентите со лапароскопска операција на жолчното ќесе**

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**Вовед**: Мултимодалната анестезија претставува техника што може да ја подобри аналгезијата и да ја намали појавата на несакани ефекти од опиоидите во постоперативниот период, какви што се постоперативното гадење и повраќање (ПОГП). Тоа може да се постигне со давање различни

лекови за време на операцијата, кои можат да ја намалат потребата за опиоиди. ПОГП е почесто кај пациенти што примиле голема количина опиоиди при лапароскопски операции на жолчното ќесе. Целта на оваа студија беше да се проследи појавата на ПОГП меѓу три различни групи пациенти, кои примиле лидокаин, кетамин или магнезиум сулфат во комбинација со фентанил во интраоперативниот период, појавата на гадење и повраќање во овие групи, како и количеството фентанил даден во овие групи за време на операцијата.

**Материјали и методи**: Во оваа рандомизирана и проспективна студија беа опфатени 120 пациенти на возраст од 20 до 65 години, ASA-класификација 1 и 2, закажани за лапароскопска операција на жолчното ќесе. Пациентите беа класифицирани во три групи по случаен избор: Група 1 (лидокаинска група – ЛГ) – пациенти што примаа лидокаин 1 mg/kg при вовед во општа анестезија и 2 mg/kg/h по воведот во анестезија, како континуирана интравенска инфузија. Група 2 (кетаминска група – КГ) – пациенти што примиле кетамин 0,5 mg/kg при индукција во општа анестезија. Група 3 (магнезиумска група – МГ), каде што пациентите примиле магнезиум сулфат 1,5 gr/h, како континуирана интравенска инфузија по воведот во анестезијата. Во сите три групи пациентите дополнително примиле болус-дози фентанил. Постоперативното гадење и повраќање беше следено во сите три групи на 1, 4, 8, 12 и 24 часа по операцијата како примарна цел и, ако кај некој од пациентите се појавеше повраќање, беше третиран со 10 мг метоклопрамид. Меѓу петте контролни временски точки, дополнителното гадење и повраќање беше забележано како секундарна цел. Третата цел беше да се измери вкупната количина фентанил дадена во интраоперативниот период.

**Резултати**: Кај пациентите од лидокаинската група забележана е помала инциденција на ПОГП и помала потреба од фентанил во споредба со пациентите од кетаминската и од магнезиумската група. Кај пациентите од кетаминската група има поголема инциденција на гадење во споредба со другите две групи. Во магнезиумската група инциденцијата на повраќање била поголема и овие пациенти при операцијата имале потреба од поголема количина фентанил. Дополнително гадење и повраќање се јави кај тројца пациенти во ЛГ, двајца во КГ и тројца во МГ, во временските интервали меѓу петте контролни временски точки. Највисока доза фентанил за време на операцијата примиле пациентите од магнезиумската група (307,50 ± 130,4), следуваат пациентите од кетаминската група (292,50 ± 60,5), додека пациентите од лидокаинската група (258,75 ± 60,9) примиле најниска доза фентанил. Разликите во дозите на фентанил што ги примиле пациентите за време на операцијата меѓу групите не беа статистички значајни.

**Заклучок**: Се покажа дека мултимодалната анестезија може да го намали ПОГП 24 часа по лапароскопските операции на жолчното ќесе и може да ја намали потребата за опиоиди за време на операцијата.

**Клучни зборови**: лидокаин, кетамин, магнезиум сулфат, постоперативно гадење и повраќање, лапароскопска операција на жолчното ќесе