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PAIN AND MULTIMODAL ANALGESIA IN LAPAROSCOPIC CHOLECYSTECTOMY

Marija Toleska[1], Aleksandar Dimitrovski[1], Mirjana Shosholcheva[2], Andrijan Kartalov[1], Biljana Kuzmanovska[1], Natasha Toleska Dimitrovska[3]

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

[2] University Clinic "St. Naum Ohridski" Skopje, Medical Faculty - Skopje, University ″Ss. Cyril and Methodius″ Skopje, RN Macedonia

3 University Clinical Center "Mother Teresa" Skopje, University Clinic for Thoracic and Vascular Surgery, Medical Faculty - Skopje, University ″Ss. Cyril and Methodius″ Skopje, RN Macedonia

Corresponding author: Marija Toleska, MD, MSc, PhD. University Clinical Center "Mother Teresa" Skopje, University Clinic for TOARILUC-Department for Anesthesiology, 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: The administration of high doses of opioids during surgery can lead to higher postoperative pain scores at rest and when coughing. Multimodal analgesia may lower the need for opioids during surgery and the suffering of postoperative pain. Multimodal analgesia can be achieved by providing non-opioid drugs (lidocaine, ketamine, and magnesium sulfate), three different types of drugs. Each of these drugs as different analgesic effects and they belong to three different pharmacological groups. The aim of this study is to develop a better understanding of the effects of each drug (lidocaine, ketamine, and magnesium sulfate) on postoperative analgesia, the needs for rescue analgesics, and analyze the total amount of fentanyl during the intraoperative period in patients undergoing laparoscopic cholecystectomy.

Methods: 120 patients were enrolled in this randomized controlled study. They were classified as ASA 1 and 2 and were scheduled for laparoscopic cholecystectomy. They were further divided into 3 groups. Group 1, or the lidocaine group, had received lidocaine at 1 mg/kg and a continuous intravenous infusion with lidocaine at 2 mg/kg/h. Group 2, or the ketamine group, received ketamine at 0.5 mg/kg. Group 3, or the magnesium sulfate group, received a continuous intravenous infusion of magnesium sulfate at 1.5 gr/kg. The intensity of postoperative pain was assessed using a VAS score at rest and when coughing, with evaluation at 1, 4, 8, 12, and 24 hours, postoperatively. Also, the needs for rescue analgesics and the total amount of fentanyl during the intraoperative period in all groups was also followed.

Results: The patients from the lidocaine group had the highest scores of pain in the postoperative period at rest and when coughing, and the ketamine group had the lowest pain scores. Rescue analgesia was given the most to lidocaine group, and less so in the magnesium group. The magnesium group received the highest dose of fentanyl during surgery and the lowest dose was received by patients from the lidocaine group.

Conclusion: Multimodal analgesia can lower the need for opioids in the intra- and postoperative period after laparoscopic cholecystectomy.

Keywords: laparoscopic cholecystectomy, lidocaine, ketamine, magnesium sulfate, postoperative pain

INTRODUCTION

Intraoperative use of high bolus doses of opioids may increase postoperative pain as a result of their rapid elimination and the development of acute tolerance. [1] Various drugs and techniques have been recently used as part of multimodal analgesia in order to improve the treatment of postoperative pain, to reduce opioid use, and to reduce the side effects associated with opioid administration. [2] Multimodal analgesia is based on the administration of small doses of opioids in combination with regional anesthesia (epidural analgesia and peripheral nerve blocks) and non-opioid drugs: alpha-2 agonists, beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), lidocaine, dexamethasone, magnesium sulfate, ketamine, paracetamol, gabapentanoids, and metamizole. In 2002, White described the role of non-opioid analgesics and analgesic techniques in the treatment of pain after one day (or outpatient surgery.1 Mulier) explained in his study that being painless is only important in the postoperative period, when patients are awake, and that the postoperative needs for analgesics are different from intraoperative needs. [3] Opioids can be avoided during anesthesia without hemodynamic instability. Suppression of circulatory changes caused by surgical stimulation can be provided by the administration of ketamine, alpha-2 agonists, beta-blockers, systemically administered lidocaine, magnesium, and NSAIDs. Non-opioid analgesics can be used as first-line drugs, with opioids as "rescue" drugs. Lidocaine, ketamine, and magnesium belong to the group of non-opioid analgesics that bind to certain receptors and block the transmission of painful stimuli.

The aim of this study is to develop an understanding of the effects of each drug (lidocaine, ketamine, and magnesium sulfate) on postoperative analgesia (primary outcome), the needs for rescue analgesics (secondary outcome), and the total amount of fentanyl in the intraoperative period (tertiary outcome) in patients undergoing laparoscopic cholecystectomy. This study shows the effects of each drug, individually.

MATERIALS AND METHODS

120 patients were enrolled in this randomized controlled study. They were classified as ASA 1 and 2, and they were scheduled for laparoscopic cholecystectomy. The study was performed at the University Clinic of TOARILUC – KARIL, Clinical Center "Mother Teresa" – Skopje, after approval from the local ethics committee and after obtaining informed consent from each patient, during the period from January 2017 to March 2019. Excluded patients from this study were patients with an ASA classification of 3-5, a history of allergy to ketonal (ketoprofen) and tramadol, patients with a chronical use of benzodiazepines and opioids, pregnant and breastfeeding women, those who had the presence of chronic pain, and patients with psychiatric illness. During the preoperative visit, the Visual Analogue Scale (VAS) score ranging from 0 (no pain) to 10 (the worst imagined pain) was explained to every patient.

Prior to the introduction of anesthesia, patients were randomly divided into three groups. In all patients, the induction to general anesthesia was 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. In Group 1, or 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. In Group 2, or the ketamine group (KG), 40 patients received ketamine at 0.5 mg/kg during induction to general anesthesia after propofol. In Group 3, or the magnesium sulfate group (MG), 40 patients received a continuous intravenous infusion of magnesium sulfate at 1.5 gr/kg after intubation. 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 of a mixture of gases at 50% oxygen and 50% air, ratio I:E = 1:2, with the 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 and an orogastric tube was inserted. During laparoscopy, the intraabdominal pressure in all patients was adjusted to 12 mm/Hg by continuous insufflation of carbon dioxide (CO2). During surgery, all patients received an

additionally fractionated bolus dose of fentanyl 0.5-1 microgr/kg, which was injected to control blood pressure and heart rate within 20% of the baseline.

After operation, all patients were transferred to the Post-anesthesia Care Unit (PACU). The anesthesiologist following up with the patient was blinded to the groups. The time of arrival at the PACU was defined as zero (0) hour, postoperatively. The intensity of postoperative pain was assessed using a VAS score at rest and when coughing, with evaluation 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. We followed the patients who still had pain after receiving analgesic, and, as a rescue analgesic treatment, we used paracetamol at 1 gr. We also measured the total amount of fentanyl that was provided to all groups.

RESULTS

In the first 24 hours after surgery, the subjects were examined for the intensity of pain they felt, using the VAS scale, at rest and when coughing. The intensity of pain at rest and when coughing was our primary outcome. Statistics were computed by the using Kruskal-Wallis test, Mann-Whitney test, Friedman ANOVA Chi Sqr, and Wilcoxon Matched Pairs Test.

In the 1st hour, postoperatively at rest, the subjects in the lidocaine group had the highest average score on the VAS scale (5.70 ± 1.7) (fig.1), followed by the magnesium group (5.27 ± 1.8) (fig.3), and then ketamine group (4.95 ± 2.5) (fig.2). A statistically significant difference in the VAS pain score was not confirmed between patients from the three groups, one hour after surgery, and when coughing ($p > 0.05$). Patients in the lidocaine, ketamine, and magnesium groups had similar scores in VAS scale (6.72 ± 1.6, 6.15. 2.2, 6.4 ± 1.9, respectively).

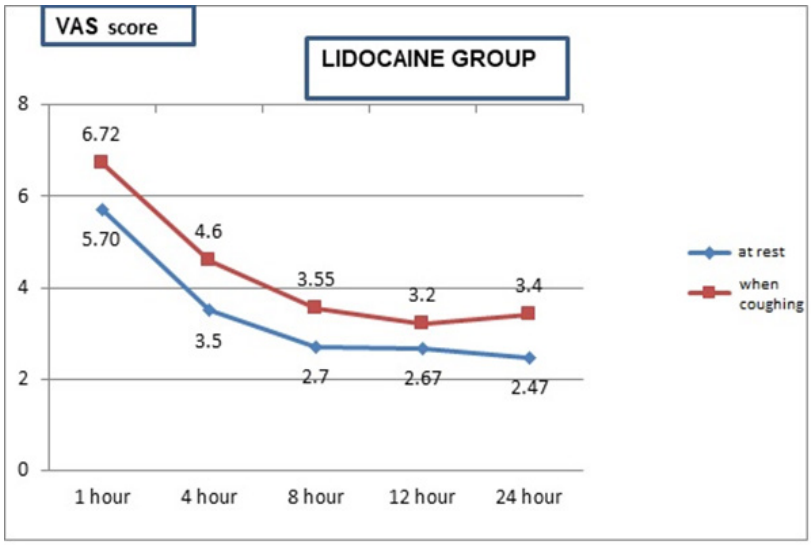

Figure 1. *Graph showing the mean VAS scores at rest and when coughing, 24 hours after surgery in the lidocaine group*

At rest: Friedman ANOVA Chi Sqr. = 63.8$p<0.0001$ 1h / 4 hrs. / 8 hrs. / 12 hrs. / 24 hrs.; Wilcoxon Matched Pairs Test $Z=5.3$ $p<0.0001$ 24 hrs. / 1 h
When coughing: Friedman ANOVA Chi Sqr. = 58.3$p<0.0001$ 1h / 4 hrs. / 8 hrs. / 12 hrs. / 24 hrs.; Wilcoxon Matched Pairs Test $Z=4.9$ $p=0.000001$ 24 hrs. / 1 h

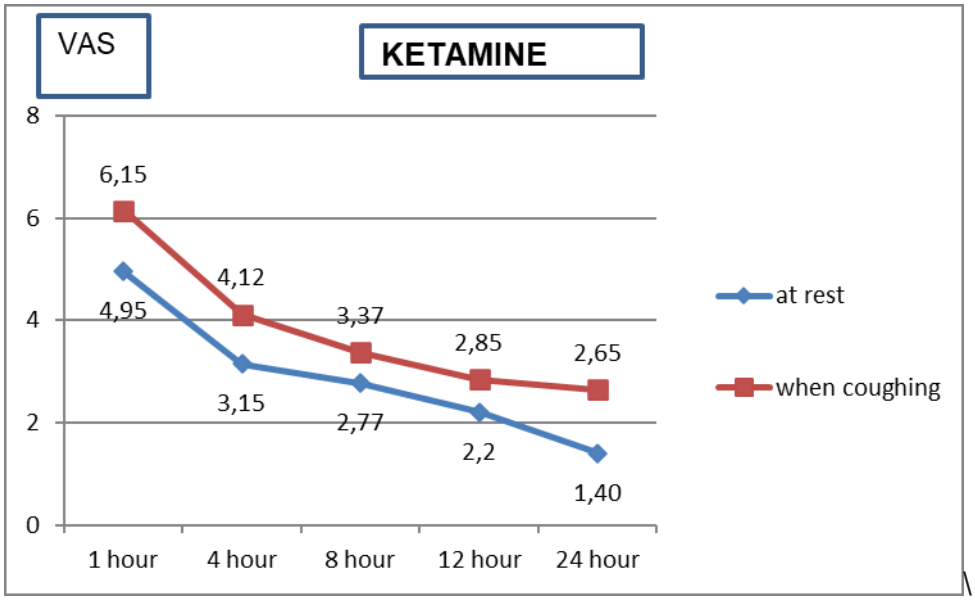

Figure 2. *Graph showing the mean VAS scores at rest and when coughing, 24 hours after surgery in the ketamine group*

At rest: Friedman ANOVA Chi Sqr. = 50.1p<0.0001 1h / 4 hrs. / 8 hrs. / 12 hrs. / 24 hrs. Wilcoxon Matched Pairs Test Z=4.9 p=0.000001 24 hrs. / 1 h
When coughing: Friedman ANOVA Chi Sqr. = 51.2p<0.0001 1h / 4 hrs. / 8 hrs. / 12 hrs. / 24 hrs. Wilcoxon Matched Pairs Test Z=4.9 p=0.000001 24 hrs. / 1 h

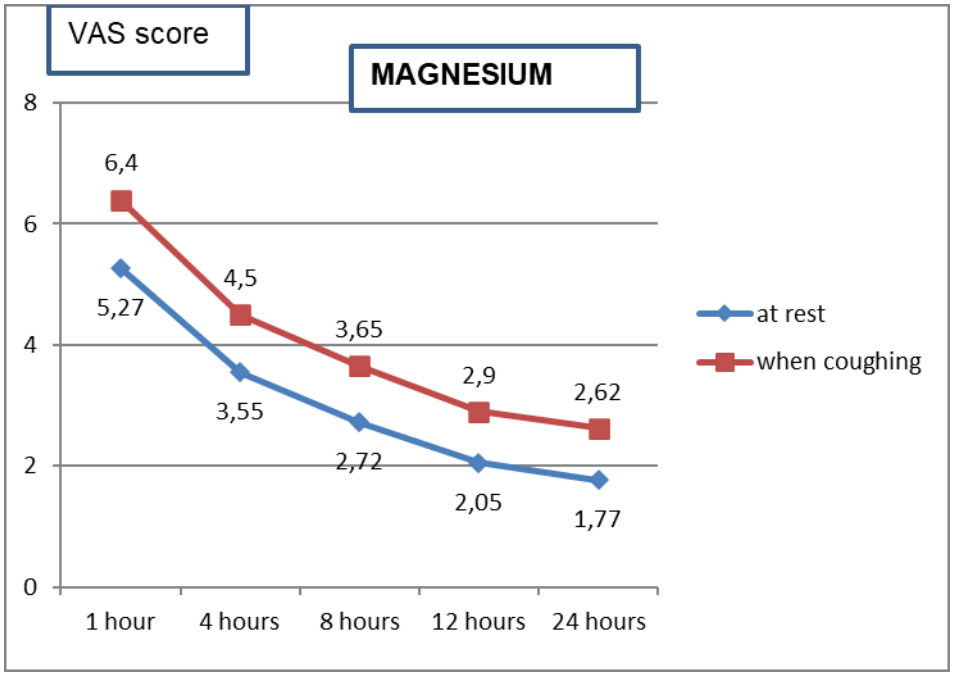

Figure 3. *Graph showing the mean VAS scores at rest and when coughing, 24 hours after surgery in the magnesium group*

At rest: Friedman ANOVA Chi Sqr. = 78.5 p<0.0001 1h / 4 hrs. / 8 hrs. / 12 hrs. / 24 hrs. Wilcoxon Matched Pairs Test Z=5.3 p<0.0001 24 hrs. / 1 h
When coughing: Friedman ANOVA Chi Sqr. = 74.6 p<0.0001 1h / 4 hrs. / 8 hrs. / 12 hrs. / 24 hrs. Wilcoxon Matched Pairs Test Z=5.3 p<0.0001 24 hrs. / 1 h

For a period of 4 hours after surgery, the VAS scale showed higher scores in patients receiving magnesium (3.55 ± 2.1) (fig.3), then lidocaine (3.5 ± 1.8) (fig.1), and then ketamine (3.15 ± 2.9) (fig.2), but without confirmed statistical significance (p = 0.22). The graphs indicate the following VAS scores in the 4th hour postoperatively, when coughing: lidocaine (4.60 ± 2.1), magnesium (4.5 ± 2.2), and ketamine groups (4.12 ± 3.2).

Eight hours after surgery, at rest and coughing, no significant difference in pain intensity was registered between the patients in all three analyzed groups. At rest, the VAS score for the lidocaine group was 2.70 ± 2.04 (fig.1), for the ketamine group, 2.78 ± 1.8 (fig.2), and for the magnesium group, 2.73 ± 1.8 (fig.3). When coughing, the VAS score was slightly higher at 3.55 ± 2.2 for the lidocaine group (fig.1), 3.37 ± 2.2 for the ketamine group (fig.2), and 3.65 ± 1.9 for the magnesium group (fig.3).

At 12 hours after surgery at rest, patients from the lidocaine group had the highest mean VAS score (2.67 ± 2.2) (fig.1), followed by patients from ketamine group (2.20 ± 2.4) (fig.2), and then patients in the magnesium group (2.05 ± 1.5) (fig.3). When coughing, the VAS scale had the highest mean value in the lidocaine group (3.20 ± 2.6) (fig.1), followed by the magnesium group (2.90 ± 1.9) (fig.3), and the lowest values were in the ketamine group (2.85 ± 2.4) (fig.2).

At the end of the follow-up, 24 hours after surgery, the VAS pain score at rest had a mean value of 2.47 ± 1.5 in the lidocaine group (fig.1), 1.40 ± 1.8 in the ketamine group (fig.2), and 1.77 ± 1.7 in the magnesium group (fig.3). At this time point when coughing the VAS pain scores have an average value of 3.40 ± 2.1 in the lidocaine group (fig.1), 2.65 ± 2.3 in the ketamine group (fig.2), and 2.62 ± 2.2 in the magnesium group (fig.3).

In our study we followed the additional administration of analgesic (rescue analgesia), which was our secondary outcome. Additional analgesic was given to 32.5% (13 patients) of the lidocaine group, 17.5% (7 patients) of the ketamine group and 10% (4 patients) of the magnesium group. The more frequent administration of analgesic to the patients from the lidocaine group compared to the patients from the magnesium group was confirmed as statistically significant (p = 0.014). After administering an analgesic, patients were re-evaluated at rest and when coughing for pain intensity on the VAS score. After giving the analgesic, no statistically significant difference was confirmed in terms of pain intensity between the three analyzed groups, at rest (p = 0.46) and when coughing (p = 0.29). At rest, the VAS score had an average score of 4.54 ± 1.1 in the lidocaine group, 5.0 ± 1.0 in the ketamine group, and 5.0 ± 1.4 in the magnesium group. When coughing, the VAS score had an average score of 5.46 ± 1.3 in the lidocaine group, 5.71 ± 2.4 in the ketamine group, and 6.0 ± 1.4 in the magnesium group.

Our third research outcome was to measure of the total amount of fentanyl that was given in the intraoperative period to all three groups. Patients from the magnesium group the highest dose of fentanyl during surgery received (307.50 ± 130.4), followed by the patients from the ketamine group (292.50 ± 60.5), and patients from the lidocaine group (258.75 ± 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

Defining pain as the "fifth vital sign" [4] and liberalizing opioid use for the treatment of acute and chronic pain [5] has led to more aggressive use of opioid analgesics by physicians. Pain during laparoscopic cholecystectomy consists of two clinically distinct components: somatic and visceral pain.

The pain on the day of surgery is typically diffuse abdominal pain, more pronounced in the right upper quadrant and right shoulder. [6] The pain is most intense on the day of surgery and the next day, and the pain subsequently decreases in the next 3 to 4 days. [7] But it may remain very intense in 13% of patients during the first week after laparoscopic cholecystectomy. [8] In the first 24 hours, the areas where the strongest pain was felt, were in the upper abdominal quadrant and port wounds. [9] In 30-40% of the patients, the second peak of pain occurs after 24 hours, and it is usually shoulder pain. [10] In 17–41 % of patients, the pain was the main reason for staying in the hospital overnight after surgery. This was also a dominant complaint and the primary cause for prolonged recovery after laparoscopic cholecystectomy. [7] Intensive acute pain

after laparoscopic cholecystectomy may also occur due to the clinical entity called "cholecystectomy syndrome". [11] This syndrome is characterized by the appearance of symptoms such as nausea, vomiting, jaundice, bloating, diarrhea, or abdominal pain, which occur at any time after cholecystectomy. There is no exact definition for this syndrome and it occurs in 5–63 % of patients. Factors associated with the development of this syndrome are: previous attacks of acute cholecystitis, the presence of other comorbidities (especially diabetes), elevated preoperative alkaline phosphatase and previous abdominal surgery.

In our study we wanted to compare the analgesic effect of three different types of drugs that have different analgesic effects and belong to three different pharmacological groups (lidocaine, ketamine, and magnesium sulfate) and also to compare the pain in the postoperative period in all three groups. Results have shown that patients in the lidocaine group (fig. 1) have the highest scores of pain in the postoperative period, at rest and when coughing, and patients from ketamine group have the lowest pain scores (fig. 2) in all examined periods. Among patients from magnesium group (fig. 3) the highest pain scores were recorded 4 h after surgery, at rest, and 8 h after surgery when coughing. Patients in the ketamine group have the highest pain scores only 8 h after surgery and at rest (fig.2). Additionally, an analgesic was given to 32.5 % (13 patients) of the lidocaine group, 17.5 % (7 patients) of the ketamine group and 10 % (4 patients) of the magnesium group. This means that rescue analgesia was given the most to lidocaine group, and less in the magnesium group. VAS scores after the patients received rescue analgesia were the highest in the magnesium group and lowest in lidocaine group. 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). Patients from the lidocaine group (258.75 ± 60.9) received the lowest dose of fentanyl during surgery. Whereas the patients from lidocaine group received the lowest doses of fentanyl during surgery, they had the highest pain scores at rest and when coughing and the highest needs for rescue analgesia in the postoperative period, when compared with the other two groups.

This type of analgesia can also be part of the so-called preventive analgesia. Preventive analgesia includes multimodal pre-, intra- and postoperative analgesic treatments. It is more effective in terms of reducing postoperative pain, reducing the need for analgesics in the postoperative period, enables faster recovery, reduces side effects from opioids, and enables to patients to have an early discharge from the hospital. [12]

The antinociceptive effect of lidocaine is most commonly due to the blockade of sodium channels, and to a lesser extent, due to blockage of potassium and calcium channels, and the blockade of presynaptic muscarinic and dopamine receptors. Because it is a local anesthetic, it has been shown to block sodium and potassium channels centrally – at the level of the spinal cord, specifically affecting the posterior horns of the spinal cord (this is the purpose of central neuroaxial anesthesia). Lidocaine also acts on protein G receptors, N-methyl D-aspartate (NMDA) receptors, and A-delta and C nerve fibers. It indirectly blocks NMDA receptors by inhibiting protein kinase C, receptors which affect postoperative hyperalgesia and opioid tolerance. [13] The dose of lidocaine which is needed for analgesia in the intraoperative period is 1-2 mg/kg as a bolus dose and further with a continuous i.v. infusion of 0.5-3 mg/kg/h. In most clinical trials the effective dose that was given was 1-2 mg/kg/h. [14] In terms of the analgesic effect, lidocaine given intravenously causes three different levels of pain relief. The first level is during continuous infusion and 30 to 60 minutes after its completion. The second level is about 6 hours after infusion, and the third level occurs 24 to 48 hours after the infusion and lasts from 21 to 47 days. [15]

The analgesic effect of ketamine is due to NMDA receptor antagonism in the posterior horns of the spinal cord, playing a role in central sensitization. NMDA receptors are present throughout the CNS (except acting on the spinal cord), indicating that they have multiple effects on pain processing. [16] The analgesic effect is due to the binding of ketamine to sigma and delta opioid receptors. [17] Ketamine blocks the release of potassium out of the cell and thus prevents the transmission of painful impulses. Ketamine given as a preemptive bolus dose (0.1 mg/kg) has an opioid-sparing effect and can be used as a sedative in illicit drug users. In subanesthetic and repeated doses, it prevents the development of pain sensitivity and opioid tolerance. Subanesthetic doses of ketamine have

been shown to be effective in the treatment of postoperative pain, reducing morphine requirements in the first 24 hours after surgery and reducing PONV. [18] Ketamine has been shown to be effective in treating cancer pain as monotherapy or as an opioid adjuvant even in opioid-resistant cancer pain. [19]

Magnesium alone is not primarily an analgesic. It has this effect because it is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors and blocks calcium channels. By giving magnesium we can stop the conduction of the painful impulse. It blocks the uptake of sodium and calcium into the cell and thus prevents the transmission of pain. Magnesium sulfate is given as an initial dose of 30 to 50 mg/kg and is followed by a maintenance dose of 6-12 mg/kg/h as a continuous infusion until the end of surgery. [20] Given either as a bolus dose [21] or perioperatively as a continuous intravenous infusion, [22] has been shown that magnesium sulfate can potentiate postoperative analgesia, reduce the need for opioids in the postoperative period, and thus improve pain scores.

CONCLUSION

Administration of high doses of opioids during surgery can lead to higher postoperative pain scores at rest and when coughing. Multimodal analgesia may lower the need for opioids during surgery and the lower the pain scores in the postoperative period. Non-opioid analgesics such as lidocaine, ketamine, and magnesium sulfate have different analgesic effects and belong to three different pharmacological groups. It has been shown that they can be safely used in the intraoperative period as a part of a multimodal analgesia. They can also lower the pain scores and need for opioids in the postoperative period and can lower the need to use opioids in the postoperative period. Pain that patients have from all three groups after surgery was moderate.

Limitations to this study

This study had some limitations. Patients from all groups received various dosages of fentanyl in the intraoperative period but that depended on the value of blood pressure and heart rate. We did find it not too pleasant to wake up the patients and ask about pain during the night while they sleep, but nevertheless it was very important for us to get obtain results, even if we explained to them during enrollment into this study that this would happen, and they accepted that they'd be woken up.

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Резиме

БОЛКА И МУЛТИМОДАЛНА АНАЛГЕЗИЈА КАЈ ЛАПАРОСКОПСКИ ОПЕРАЦИИ НА ЖОЛЧНОТО ЌЕСЕ

Марија Толеска[1], Александар Димитровски[1], Мирјана Шошолчева[2], Андријан Карталов[1], Билјана Кузмановска[1], Наташа Толеска Димитровска[3]

[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] Универзитетска клиника „Св. Наум Охридски“ Скопје, Медицински Факултет – Скопје, Универзитет „Св. Кирил и Методиј“ во Скопје, РС Македонија

[3] 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: Употребата на високи дози опиоиди за време на операцијата може да доведе до повисоки скорови на болка по операција при мирување и при кашлање. Мултимодалната аналгезија може да ја намали потребата за опиоиди за време на операцијата, како и постоперативната болка. Тоа може да се постигне со давање неопиоидни лекови (лидокаин, кетамин и магнезиум сулфат), кои се три различни видови лекови, имаат различно аналгетско дејство и им припаѓаат на три различни фармаколошки групи.

Оваа студија е направена со цел да се одреди ефектот на секој лек посебно (лидокаин, кетамин и магнезиум сулфат) врз постоперативната болка, потребата за дополнително давање аналгетик и тоталната потреба за фентанил во текот на операцијата кај пациентите на кои е направена лапароскопска операција на жолчното ќесе.

Материјал и методи: Во оваа рандомизирана контролирана студија беа вклучени 120 пациенти ASA 1 и 2 класификација, планирани за лапароскопска операција на жолчното ќесе, поделени во 3 групи. Пациентите во групата 1, или лидокаинска група, примиле лидокаин 1 mg/kg и континуирана интравенска инфузија со лидокаин 2 mg/kg/h. Пациентите во групата 2, или кетаминска група, примиле кетамин 0,5 mg/kg. Пациентите во групата 3, или магнезиумска група, добија континуирана интравенска инфузија на магнезиум сулфат 1,5 gr/kg. Интензитетот на постоперативната болка беше проценет со помош на визуелната аналогна скала (ВАС) за болка при мирување и при кашлање 1, 4, 8, 12 и 24 часа по операцијата. Исто така, се следеше потребата за дополнително давање аналгетик и вкупната количина фентанил дадена во текот на операцијата кај сите групи.

Резултати: Највисоки скорови на болка во постоперативниот период при мирување и при кашлање имале пациентите од лидокаинската група, а најниски скорови на болка имале пациентите од кетаминската група. Дополнителна аналгезија беше дадена најмногу во лидокаинската, а најмалку во магнезиумската група. Највисока доза фентанил за време на операцијата добија пациентите од магнезиумската група, а најниска доза добија пациентите од лидокаинската група.

Заклучок: Мултимодалната аналгезија може да ја намали потребата за опиоиди во интра- и постоперативниот период по лапароскопски операции на жолчното ќесе

Клучни зборови: лапароскопска операција на жолчното ќесе, лидокаин, кетамин, магнезиум сулфат, постоперативна болка