ISSN 2466-488X (Online)AbstractIntroduction: Opioid free anesthesia (OFA) is an anesthesiological technique, which uses non-opioid analgesics, such as paracetamol, dexamethasone, lidocaine, ketamine, and magnesium sulfate instead of opioids. In this case, the report about patient who after previous surgeries experienced opioid side effects is followed by a narrative review; we present the OFA method for laparoscopic cholecystectomy. Case report: We present a case of a 55-year-old woman with a history of controlled hypertension and asthma, planned for laparoscopic cholecystectomy. Previously she un-derwent two surgical interventions; bilateral radical mastectomy performed separately with a three year gap. Both an-esthesias were complicated, postoperatively with nausea, vomiting, dizziness, and respiratory depression. Based on the previous postoperative complications, we hypothesized that nausea, vomiting, dizziness, and respiratory depression were caused by opioids, and we decided to perform OFA. Before the induction the patient received dexamethasone 8 mg and paracetamol 1 gr intravenously, followed by induction with midazolam 3 mg, lidocaine hydrochloride 78 mg, propofol 160 mg, ketamine hydrochloride 39 mg and rocuronium bromide 60 mg. After tracheal intubation, con-tinuous intravenous infusion with lidocaine hydrochloride 2 mg/kg/hr and magnesium sulfate 1.5 gr/hr was started. Anesthesia was maintained by using sevoflurane MAC 0.7–1. At the end of the surgery, 2.5 gr of metamizole was giv-en intravenously. Postoperative recovery was uneventful. Conclusion: In our patient, OFA eliminated opioid-related side effects (nausea, vomiting, dizziness, and shortness of breath), and provided satisfying postoperative analgesia.Keywords: opioid free anesthesia; laparoscopic cholecystectomy; pain; nausea vomitingCorresponding author: MarijaToleska Vasil Gjorgov Str, No. 34/11, 1000 Skopje, Telephone: 0038971221228, E-mail: marija\_toleska@yahoo.comCase reportPRACTICING OPIOID-FREE ANESTHESIA FOR LAPAROSCOPIC CHOLECYSTECTOMY OPIOID-FREE ANESTHESIAMarija Toleska¹, Andrijan Kartalov¹, Biljana Kuzmanovska¹, Vladimir Joksimovic2, Aleksandar Dimitrovski¹, Filip Naumovski11University Clinic for TOARILUC, Department of Anesthesia, Reanimation and Intensive care, Faculty of Medicine – Skopje,North Macedonia2University Clinic for Digestive Surgery, Faculty of Medicine – Skopje, North MacedoniaRecevied February 25, 2019, Revision received March 17, 2019, Revision received May 24, 2019, Accepted May 26, 2019IntroductionThe opioid-free anesthesia (OFA) technique is characterized by perioperative opioid omittan-ce1. Although opioids are still the mainstay analge-sics used for the treatment of moderate to severe pain, opioid avoidance leads to less opioid-related side effects in the postoperative period, such as respiratory depression, postoperative nausea, and vomiting (PONV), dizziness, and constipation. We present a case of a patient with previous experien-ce of opioid-mediated side effects, who underwent laparoscopic cholecystectomy with perioperative OFA application.Case reportA 55-year-old woman (height 165 cm, weight 78 kg) was scheduled for laparoscopic cholecys-tectomy under general anesthesia. The patient had a history of hypertension treated with an angio-tensin converting enzyme inhibitor and asthma which was treated with a bronchodilator (amino-phylline). The patient had a bilateral mastectomy, left radical mastectomy was done five years before and right radical mastectomy two years before. Af-ter previous surgeries, postoperative recovery was complicated with nausea, vomiting, dizziness and respiratory depression (SpO2 was 88–90% with an oxygen mask and respiratory rate of 8 breaths per minute), which necessitated the intensive care unit

108SJAIT 2019/5-6admission. The decision was made that for this surgery, an OFA technique is suitable. The day be-fore surgery, the patient was trained to use the Nu-meric Rating Scale (NRS) score (0 means no pain at all, and the number 10 means the worst imagi-nable pain). The patient was premedicated with 5 mg of di-azepam orally two hours before the operation. In the operating room, the patient was placed on con-tinuous hemodynamic monitoring, including elec-trocardiography (ECG), heart rate (HR), non-in-vasive blood pressure measurement (NIBP) every 5 minutes, saturation with oxygen by pulse oxime-try (SpO2%) and capnography. The preinduction vital signs were: NIBP: 157/92 mmHg, HR: 88/min, RR: 16/min, SpO2 = 93%. Before the induc-tion to general anesthesia, dexamethasone 8 mg as an antiemetic agent and paracetamol 1 gr intrave-nously (i.v.), were given. The induction into gener-al anesthesia included midazolam 3 mg, lidocaine hydrochloride 78 mg, propofol 160 mg, ketamine hydrochloride 39 mg, and rocuronium bromide 60 mg. After tracheal intubation continuous intra-venous infusion of lidocaine hydrochloride 2 mg/kg/h was started, and magnesium sulfate (MgSO4) 1.5 gr/h. Anesthesia was maintained by using sevo-flurane MAC 0.7–1 to maintain mean arterial pres-sure with a value of +/- 20% of the baseline val-ue. The patient was mechanically ventilated with PCV-VG ventilation mode, with a breath volume of 6–8 ml/kg from a mixture of gases in propor-tion to 50% oxygen and 50% air, I:E ratio = 1:2, the number of respirations were customized accord-ing to EtCO2 between 35–45 mmHg, PEEP 5 cm H2O. An oral-gastric tube and sequential compres-sion device were placed, and normothermia was maintained with a warming blanket. During the laparoscopy, the intra-abdominal pressure was 12 mmHg with continuous insufflation of CO2. The operation lasted for one hour and was unevent-ful. After the gallbladder removal, the continuous infusion of lidocaine and magnesium sulfate was discontinued, and 2.5 gr of metamizole was given intravenously. At the end of the operation, the gas-tric tube was removed, and the residual neuromus-cular blockade was antagonized with neostigmine 0.05 mg/kg and 0.02 mg/kg of atropine i.v. And the patient was extubated. The patient was pain-free (VAS score 1), no nausea, vomiting, or dizziness complaining. She was transferred to the PACU and stayed there for 60 minutes.Postoperative analgesia plan included 1g of paracetamol for NRS score from 4 to 6, or 100 mg of tramadol for NRS score from 7 to 10, while ketonal 100 mg was used as a rescue analge-sic. The pain at rest and on movement and PONV were recorded at 1, 4, 8, 12, and 24 hours after the surgery. One hour after the surgery, the patient re-ported pain on NRS to score one at rest, and NRS score two on movement, no PONV, no respiratory depression or dizziness. She said that she felt very good like she wasn’t operated and she was trans-ferred to the ward. Postoperative pain was well controlled with NRS score 2 at rest, and NRS score 3 on movement at the fourth hour, and NRS score 3 at rest, and, NRS score 3 on movement on the eighth hour, without PONV. Paracetamol 1 gr was used for the pain management following 12 hours and 24 hours (NRS score 5 at rest, and NRS score 6 on movement and NRS 3 at rest and NRS 4 on movement, respectively), without PONV. Patient felt very comfortable during her stay in the hos-pital; she slept well without nightmare complaints. DiscussionHere we present the case of a patient who was perioperatively managed with OFA as an exam-ple that this method is reasonably used in patients with previously experienced opioid’s side effects. Although opioids are the strongest analgesics and an essential part of most general anesthesias, they have numerous side-effects, short and long term consequences2, including respiratory depression3, nausea4, vomiting5, dizziness6, sedation7, ileus7, delirium8, pruritus4, urinary retention7, hyperal-gesia7,9, opioid tolerance7, opioid-induced immu-nosuppression10, and sleep disorders11.Opioids can be avoided by intraoperative using multi-modal non-opioid analgesics such as par-acetamol, dexamethasone, lidocaine, ketamine and magnesium sulfate, medications acting on receptors centrally and peripherally in the pain pathway12. Paracetamol given before the induction to anes-thesia leads to lower requirements of opioids dur-ing the operation13.Dexamethasone has effective antiemetic effects given in a lower dose. Moreover intermediate doses (0.1–0.2 mg/kg) of dexameth-asone have an opioid-sparing effect and has bene-

109PRACTICING OPIOID-FREE ANESTHESIA FOR LAPAROSCOPIC CHOLECYSTECTOMYficial effects on postoperative pain14.Lidocaine is local anesthetic and has an analgesic, antihyperal-gesic and anti-inflammatory effect, and given in-travenously reduces perioperative opioid consump-tion, provides better pain control and faster return of the bowel function15.Ketamine is a unique in-travenous anesthetic with an analgesic effect, opi-oid-sparing effect, acting on N-methyl D-aspartate (NMDA) receptors through blocking potassium to exit outside of the cell16. Magnesium sulfate acts on NMDA receptors by blocking the entrance of calcium and sodium inside the cell and given as a continuous infusion in the intra-operative pe-riod leads to low pain scores and less nausea and vomiting in the postoperative period17.The occur-rence of PONV after laparoscopic cholecystectomy ranges from 46% to 75%18.Apfel et al. created risk score for PONV with an aim to implement preven-tive strategy for PONV19. This score is consisted of four highly predictive risk factors: female gender, non-smokers, history of previous PONV or motion sickness and expected administration of postopera-tive opioids. Dexamethasone given in intermediate doses (0.1–0.2 mg/kg) has antiemetic effects, and better efficacy if given preventively20. It is also in-dicated in patients with asthma because it improves the efficacy of bronchodilator therapy21. Ketamine also has a bronchodilator effect and is suitable for induction and maintaining of anesthesia in patients with asthma22. Anesthetics dose of ketamine has an emetic effect and leads to nausea, but sub-anesthet-ic dose (< 0.5 mg/kg) reduces nausea and vomiting, probably because of his opioid-sparing effect23.The strategies for PONV reduction are regional anes-thesia and total intravenous anesthesia – TIVA with propofol24, volatile anesthetics avoidance, or use of sevoflurane and desflurane25, adequate hidration26, administration of dextrose27, multimodal post-operative pain control (using regional anesthetic techniques, paracetamol, NSAID, other non-opi-oid adjuvants)28, administration of antiemetics29. Pre-operative administration of midazolam in dose 0.04 mg/kg has shown significantly reduced PONV in the first 24 hours after intra-abdominal or ambu-latory surgery30.In the postoperative period, the patient was treated according to hospital protocol for postop-erative analgesia with the total amount of given an-algesics of 2 gr paracetamol during 24 hours after the surgery. Antiemetics and analgesics (tramadol and ketoprofen as a rescue analgesic) were not giv-en during the post-operative period. No side effects were recorded during the postoperative period. Usually suggested medications for opioid-free an-esthesia like alfa-2 agonists (clonidine and dexme-detomidine) were not registered in our country and therefore not used2,12. This case can serve as an ex-ample of OFA approach. Alfa-2 agonists have many pharmacological characteristics such as sedation, hypnosis, anxiolysis, analgesia, and sympatholysis. OFA is indicated in patients with acute and chronic opioid addiction. It can be used in opi-oid-tolerant patients: patients with persistent non-cancer pain, cancer pain, a substance abuse disorder, and with acute opioid tolerance. Opi-oid-addicted patients planned for surgery have 30–100% increased intra-operative opioid require-ments, compared to opioid-naive patients31.O FA is also indicated to avoid administration of opioids during the perioperative period. Also, OFA can be used in obese patients sched-uled for bariatric surgery, therefore serves for avoiding opioids as this group of patients are particularly in risk to develop respiratory depres-sion32.Majority of obese patients have obstructive sleep apnoea syndrome (OSA) and they are prone to airway obstruction and desaturation in the pe-rioperative period, especially if opioids are given. Mulier et al. evaluated the effect of OFA versus general opioid anesthesia in patients scheduled for elective laparoscopic bariatric surgery2.Patients who received OFA required fewer analgesics in the postoperative period, experienced less postoper-ative PONV and shivering, less postoperative hy-pertension and desaturation, and had an improved quality of recovery after surgery.Samuels et al. compared postoperative opioid consumption in three groups of patients divided into three anesthesia regiments: the first group re-ceived opioid-sparing anesthesia (OSA), the sec-ond group received opioid-free anesthesia (OFA), and the third group received opioid anesthesia (OA)12.These patients were planned for various surgical procedures, including breast reconstruc-tions, cochlear implants, stapedectomies, and mas-toidectomies. In the postoperative period, 73% of the OFA patients didn’t require opioids, compared to 52% of OA patients and 37% of OSA patients. OFA patients also had less nausea and vomiting compared with OSA and OA patients. OFA also

110SJAIT 2019/5-6reduces PONV compared to patients who under-went general anesthesia with volatile anesthetics and opioids33.Additionally, cancer patients can benefit from OFA is also indicated in patients scheduled for cancer surgery opioids have immunosuppressive effects (inhibition of cellular immunity), and po-tentially can stimulate cancer cells growth and an-giogenesis34.Based on the literature data, OFA is suggested for obese patients, patients with OSA, pulmonary disease (asthma, COPD, respiratory insufficiency), history of acute or chronic opioid dependence, hyperalgesia, history of chronic pain, immunode-ficiency, oncologic surgery, and inflammatory dis-eases. Absolute contraindication for OFA is an al-lergy of any non-opioid adjuvant drug, while rela-tive contraindications are cerebrovascular disease, disorders of autonomic failure, acute coronary ischemia, critical coronary stenosis, heart block, extreme bradycardia, non-stabilized hypovolemic shock, polytrauma patient, elderly patients on beta blockers.Opioid-free postoperative analgesia has opi-oid-tolerant more than ten years35, andthe POFA trial is the first prospective, randomized, multicen-tric study evaluating the effects of OFA on severe postoperative opioid-related adverse events36.ConclusionOpioid-free anesthesia technique leads to less opioid-related side effects such as PONV, dizzi-ness, respiratory depression, and more satisfied pa-tient. It’s a safe and effective anesthetic technique, suggested for ambulatory surgery.References 1. Soffin EM, Wetmore DS, Beckman JD, et al. Opioid--free anesthesia within an enhanced recovery after surgery pathway for minimally invasive lumbar spine surgery: a re-trospective matched cohort study. Neurosurg Focus. 2019; 46(4): E8. doi: 10.3171/2019.1.FOCUS18645.2. Mulier JP, Wouters R, Dillemans B, et al. A randomized controlled, double-blind trial evaluating the effect of opioid--free versus opioid general anesthesia on postoperative pain and discomfort measured by the QoR-40. J Clin Anaesth Pain Med 2018; 2(1): 015. https://scientonline.org.3. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression. A closed claims ana-lysis. Anesthesiol 2015; 122(3):659–65. 4. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician. 2006; 74(8):1347–54.5. Apfel CC, Heidrich FM, Jukar-Kao S, et al. Evidence--based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth. 2012; 109(5):742–53. 6. Ng KF, Tsui SL, Yang JC, et al. Increased nausea and dizziness when using tramadol for post-operative patient--controlled analgesia (PCA) compared with morphine after intraoperative loading with morphine. Eur J Anaesthesiol. 1998 Sep; 15(5):565–70.7. Benyamin R, Trescot AM, Datta S, et al. Opioid com-plications and side effects. Pain Physician. 2008; 11(2 Sup-pl):S105–20.8. Ito G, Kanemoto K. A case of topical opioid-induced delirium mistaken as behavioral and psychological symp-toms of dementia in demented state. Psychogeriatrics. 2013; 13(2):118–23. 9. Woodward OB, Naraen S, Naraen A. Opioid-induced myoclonus and hyperalgesia following a short course of low--dose oral morphine. Br J Pain. 2017; 11(1):32–35. 10. Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analge-sic technique during primary cancer surgery affect recurren-ce or metastasis?. Can J Anaesth. 2016; 63(2):184–192.11.Cheatle MD, Webster LR. Opioid therapy and sleep disorders: Risk and mitigation strategies. Pain Med. 2015; 16 Suppl 1:S22–6. 12. Samuels D, Abou-Samra A, Dalvi P, et al. Opioid-free Anesthesia Results in Reduced Post-operative Opioid Con-sumption. J Clin Anesth Pain Med 2017; 1(2):13. 13. Unal SS, Aksoy M, Ahiskalioglu A, et al. The effect of intravenous preemptive paracetamol on postoperative fenta-nyl consumption in patients undergoing open nephrectomy: A prospective randomized study. Niger J Clin Pract. 2015; 18(1):68–74. 14. De Oliveira GS, Almeida MD, Benzon HT, et al. Pe-rioperative single dose systemic dexamethasone for postope-rative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011; 115(3):575–88. 15. Bakan M, Umutoglu T, Topuz U, et al. Opioid-free to-tal intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. Bras J Ane-stesiol. 2015; 65(3):191–9. 16. García-Navia JT, López JT, Egea-Guerrero JJ, et al. Ef-fect of a single dose of lidocaine and ketamine on intraope-rative opioids requirements in patients undergoing elective gynecological laparotomies under general anesthesia. A ran-domized, placebo-controlled pilot study. Farm Hosp. 2016; 40(1):44–51. 17. Ryu JH, Kang MH, Park KS, et al. Effects of mag-nesium sulphate on intraoperative anaesthetic require-ments and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. Br J Anaesth. 2008; 100(3):397–403. 18. Naguib M, el Bakry AK, Khoshim MH, et al. Prop-hylactic antiemetic therapy with ondansetron, tropisetron, ganisetron and metoclopramide in patients undergoing lapa-roscopic cholecystectomy: a randomized, double-blind com-parison with placebo. Can J Anaesth. 1996; 43(3):226–31.

11119. Apfel CC, Laara E, Koivuranta M, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999; 91(3):693–700.20. Wang JJ, Ho ST, Tzeng JI, et al. The effect of timing of dexamethasone administration on its efficacy as a prophylac-tic antiemetic for postoperative nausea and vomiting. Anesth Analg. 2000; 91(1):136–9.21. Shaikh S, Verma H, Yadav N, et al. Applications of steroid in clinical practice: A review. ISRN Anesthesiology. 2012; 2012: 985495. doi:10.5402/2012/985495 22. Goyal S, Agrawal A. Ketamine in status asthmaticus: A review. Indian J Crit Care Med. 2013; 17(3):154–161. 23. Gorlin AW, Rosenfeld DM, Ramakrishna H. Intrave-nous sub-anesthetic ketamine for perioperative analgesia. J Anaesthesiol Clin Pharmacol. 2016; 32(2):160–7. 24. Apfel CC, Kranke P, Katz MH, et al. Volatile anesthe-tics may be the main cause of early but not delayed posto-perative vomiting: a randomized controlled trial of factorial design. Br J Anaesth. 2002; 88(5):659–68.25. Yoon IK, Kang H, Baek CW, et al. Comparison of ef-fects of desflurane and sevoflurane on postoperative nausea, vomiting, and pain in patients receiving opioid-based in-travenous patient-controlled analgesia after thyroidectomy: Propensity score matching analysis. Medicine. 2017; 96(16): e6681. doi: 10.1097/MD.0000000000006681. 26. Apfel CC, Meyer A, Orhan-Sungur M, et al. Supple-mental intravenous crystalloid for the prevention of post-operative nausea and vomiting: quantitative review. Br J Anaesth. 2012; 108(6):893–902. 27. Rao V, Bala I, Jain D, et al. Effect of intravenous dex-trose administration on postoperative nausea and vomit-ing in patients undergoing laparoscopic cholecystectomy: A randomised controlled trial. Eur J Anaesthesiol. 2017; 34(10):705–707. 28. Chandrakantan A, Glass PSA. Multimodal thera-pies for postoperative nausea and vomiting, and pain. Br J Anaesth. 2011; 107 Suppl 1: i27-i40. doi: 10.1093/bja/aer358.29. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nau-sea and vomiting. N Engl J Med. 2004; 350(24):2441–51.30. Bauer KP, Dom PM, Ramirez AM, et al. Preoperative intravenous midazolam: benefits beyond anxiolysis. J Clin Anesth. 2004; 16(3):177–83.31. Goyal R, Khurana G, Jindal P, et al. Anesthesia for opioid addict: Challenges for perioperative physician. J An-aesthesiol Clin Pharmacol. 2013; 29(3):394–6. 32. Lam KKY, Mui WLM. Multimodal analgesia model to achieve low postoperative opioid requirement following bariatric surgery. Hong Kong Med J. 2016; 22(5):428–34.33. Ziemann-Gimmel P, Goldfarb AA, Koppman J, et al. Opioid-free total intravenous anaesthesia reduces postoper-ative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth. 2014; 112(5):906–11. 34. Tripathy S, Rath S, Agrawal S, et al. Opioid-free an-esthesia for breast cancer surgery: An observational study. J Anaesthesiol Clin Pharmacol. 2018; 34(1):35–40.35. Kehlet H, Dahl JB. Anaesthesia, surgery, and challeng-es in postoperative recovery. Lancet. 2003; 362(9399):1921–8.36. Beloeil H, Laviolle B, Menard C, et al. POFA trial study protocol: a multicentre, double-blind, randomized, controlled clinical trial comparing opioid-free versus opioid anaesthesia on postoperative opioid-related adverse events after major or intermediate non-cardiac surgery. BMJ Open. 2018; 8(6): e020873. doi:10.1136/bmjopen-2017-020873