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COMPARATION AMONG OPIOID-BASED, LOW OPIOID AND OPIOID FREE ANESTHESIA IN COLORECTAL ONCOLOGIC SURGERY

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" in Skopje, RN Macedonia

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

Corresponding author: Marija Toleska, MD, MSc, PhD. 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

Introduction: Opioids are the "gold standard" for pain treatment during and after colorectal surgery. They can inhibit cellular and humoral immunity and it is assumed that can promote cancer cell proliferation and metastatic spread. Adequate pain management can be achieved not only with opioids, but also with non-opioid drugs, which can be used together in small doses, i.e., multimodal analgesia, and can lower the need for opioids during and after surgery. Opioid free anesthesia (OFA) is part of multimodal analgesia, where opioids are not used in the intraoperative period.

Materials and methods: In this prospective and randomized clinical study 60 patients scheduled for open colorectal surgery were enrolled. They were between the ages of 45 and 70 with the American Association of Anesthesiologists (ASA) classifications 1, 2 and 3, divided in three groups. The first group of patients, or Opioid-based anesthesia group (OBAG), received the following for induction to anesthesia: lidocaine at 1 mg/kg, fentanyl 100 at μgr, propofol at 2mg/kg and rocuronium bromide at 0.6 mg/kg. They intermittently received 50-100 μgr fentanyl intravenously and 0.25 % bupivacaine 2-3 ml every 30-45 minutes, given in the epidural catheter during surgery. The second group of patients, or Low opioid anesthesia group (LOAG), received the following for induction to anesthesia: lidocaine at 1 mg/kg, fentanyl at 100 μgr, propofol at 2mg/kg and rocuronium bromide at 0.6 mg/kg. Prior to surgery, 50 μgr of fentanyl with 5 ml 0.25% bupivacaine was given into the epidural catheter, and the same dose was received at the end of surgery. The third group, or Opioid free anesthesia group (OFAG), received the following before the induction to general anesthesia: dexamethasone at 0.1 mg/kg and 1 gr of paracetamol. Induction to general anesthesia was with lidocaine at 1 mg/kg, propofol at 2mg/kg, ketamine at 0.5 mg/kg and rocuronium bromide at 0.6 mg/kg. After intubation, intravenous continuous infusion with lidocaine was at 2 mg/kg/h, ketamine 0.2 mg/kg/h and magnesium 15 mg/kg/h loaded on and intermittently 0.25 % bupivacaine 2-3 ml every 30-45 minutes given in the epidural catheter during surgery. The primary goal was to measure the patients' pain after the first 72 postoperative hours in all three groups (2, 6, 12, 24, 36, 48 and 72 hours after surgery). The secondary goal was to measure the total amount of morphine given in the epidural catheter in the postoperative period in all three groups. Other secondary goals were: to compare the total amount of fentanyl given intravenously during surgery in the first and second groups, determine if there was a need to use rescue analgesia in the postoperative period, measure the occurrence of PONV, and to measure the total amount of bupivacaine given in the epidural catheter during operation in all three groups.

Results: Visual Analogue Scale (VAS) score comparisons between groups showed patients from the OBA and LOA groups had significantly higher VAS scores, compared to the patients from the OFA group 2, 12, 24 and 48 hours after operation. After 6 hours postoperatively, patients from the LOA group had significantly higher VAS scores, compared to patients from the OBA and OFA groups. After 36 hours postoperatively, patients from the OBA group had significantly higher VAS scores compared to patients from the LOA and OFA groups. At the last follow-up point, 72 hours after the intervention, the patients from the OBA and

LOA groups had significantly higher VAS scores compared to the patients from the OFA group. All patients from the OBA and LOA groups, and only 9 from the OFA group received morphine in the postoperative period via epidural catheter. Patients from the Opioid group received significantly higher amounts of fentanyl during surgery. Additional administration of another analgesic drug in the postoperative period was prescribed in 55% of patients in the OBAG, in 50% in the LOAG and in 35% of the OFA group. PONV was registered in 60% of patients from the OBAG and in 40% of patients from the LOAG. In the OFA group did not register PONV in any of the patients. The biggest amount of bupivacaine given during surgery was in the OBAG (26.37 ± 2.6 mg), in LOAG was 25.0 ± 0 and the less in OFAG group (24.50 ± 4.3).

Conclusion: Patients from OFA group, compared with patients from OBAG and LOAG, have the lowest pain score in first 72 hours after open colorectal surgery, received fewer opioids via an epidural catheter in the postoperative period, had less need for rescue analgesia, no occurrence of PONV, and less need for bupivacaine via an epidural catheter in the intraoperative period.

Keywords: opioid-based anesthesia, low-opioid anesthesia, opioid free anesthesia, colorectal surgery, postoperative pain

INTRODUCTION

Colorectal cancer is one of the most frequent types of cancer worldwide and surgery is the first choice of treatment in most cases. Choice of anesthesia and use of opioids can modulate the neuroendocrine stress response [1]. It has been shown that opioids can inhibit cellular and humoral immunity, can facilitate cancer cell proliferation and increase angiogenesis and migration [2, 3], but some studies have shown the opposite effect of opioids, that they have an inhibitory effect on cancer cells. Opioids still remain the main analgesic drugs for the treatment of pain during and after general anesthesia. Pain is declared as the fifth vital sign [4], and is defined as a conscious unpleasant perception of a noxious stimulus. Thus, effective pain management is very important in the perioperative period. Pain can be described and evaluated in patients who are both awake and conscious. Unfortunately, patients under general anesthesia cannot express the level of pain and thus instead of using the term "intraoperative analgesia", we should use term nociception, which is defined as a stimulation of noxious receptors [5]. Only under general anesthesia is possible to have nociception without pain. To have adequate pain management during surgery and to avoid or minimize the concurrent usage of opioids is only possible with the use of multimodal anesthesia. The concept of multimodal anesthesia is to achieve optimal analgesia with the combination of many non-opioid drugs, together with regional anesthesia. The goal is to lower opioid usage and opioid-related adverse side effects (ORADEs). Opioid free anesthesia is a new method of multimodal analgesia, whereby a combination of many non-opioid drugs, given together in a small dose as a "cocktail", act synergistically and additively, through different mechanisms in different parts of the central nervous system. This can provide adequate analgesia and hemodynamic stabile anesthesia without opioid use [6]. Opioid free anesthesia (OFA) is an anesthetic technique in which no systemic, neuroaxial, or intracavitary opioids are used in the intraoperative period. Hypnotics, NMDA antagonists, local anesthetics, anti-inflammatory drugs and alpha-2 agonists are used in OFA. The goals are to have sufficient analgesia during and after surgery without the administration of opioids, to provide intraoperative hemodynamic stability, and to avoid the numerous side effects caused by opioids in intra- and postoperative period.

In our study, we wanted to compare the pain during the first 72 postoperative hours in all three groups (2, 6, 12, 24, 36, 48 and 72 hours after surgery). The secondary goal was to measure the total amount of morphine given in the postoperative period in all three groups. Other secondary goals were: measure the total amount of fentanyl given intravenously during surgery in first and second group, the need for rescue analgesia in the postoperative period, measure the occurrence of postoperative nausea and vomiting (PONV), and the total amount of bupivacaine given during operation in all three groups.

MATERIALS AND METHODS

Sixty (60) patients scheduled for open surgery of colorectal carcinoma were enrolled in this prospective and randomized clinical study. The study was prepared with the approval of the Ethical Committee for Clinical Research and randomization was done by selecting one envelope from three that were offered and inside was group to which the patient belongs. First group was Opioid-based anesthesia group (OBAG), second group was Low-opioid anesthesia group (LOAG) and the third group was Opioid free anesthesia group (OFAG). Inclusion criteria for participating to this study were as follows: patients scheduled for open colorectal surgery between the ages of 45 and 70 with American Association of Anesthesiologists (ASA) classification 1, 2 and 3, and patients who will accept to receive thoracic epidural analgesia. Exclusion criteria for this study were patients with ASA classification 4 and 5, patients who chronically use benzodiazepines and opioids, patients with history of chronic pain and psychiatric illness. In the preoperative visit the Visual Analogue Scale (VAS) score for pain was explained to the patients, where the number 0 means absence of pain, and number 10 indicates the greatest imaginable pain.

At the day of surgery every patient received continuous hemodynamic monitoring: electrocardiographic record (ECG), heart rate, non-invasive blood pressure measured every 5 minutes, oxygen saturation from pulse oximetry and capnography. Prior to the surgery, all patients received a thoracic epidural catheter, done under aseptic conditions in Th9-Th10 level, and the patients received 2 ml 0.5 % bupivacaine (10 mg) as a test dose. The induction to general endotracheal anesthesia was the same in first and second group of patients and was followed by the administration of lidocaine at 1 mg/kg, fentanyl at 100 μgr, propofol at 2mg/kg and rocuronium bromide at 0.6 mg/kg.

First group of patients, or OBAG, received lidocaine at 1 mg/kg, fentanyl at 100 μgr, propofol at 2mg/kg and rocuronium bromide at 0.6 mg/kg for induction to anesthesia. These patients intermittently received 50-100 μgr of fentanyl intravenously and 0.25% of bupivacaine at 2-3 ml every 30-45 minutes, given in the epidural catheter during surgery.

The second group of patients, or LOAG, received lidocaine at 1 mg/kg, fentanyl at 100 μgr, propofol at 2 mg/kg and rocuronium bromide at 0.6 mg/kg for induction to anesthesia. Prior to surgery, 50 μgr of fentanyl with 5 ml 0.25% bupivacaine was given into epidural catheter and the same dose was received at the end of surgery.

The third group, or OFAG, received dexamethasone at 0.1 mg/kg and 1 gr of paracetamol before the induction to general anesthesia. Induction to general anesthesia was done with lidocaine at 1 mg/kg, propofol at 2mg/kg, ketamine at 0.5 mg/kg and rocuronium bromide at 0.6 mg/kg. After intubation, they received an intravenous continuous infusion with lidocaine at 2 mg/kg/h, ketamine at 0.2 mg/kg/h and magnesium 15 at mg/kg/h, loaded on and intermittently of 0.25 % bupivacaine 2-3 ml every 30-45 minutes. This was given in the epidural catheter during surgery.

All patients were mechanically ventilated with PVC-VG, with a volume of 6-8 ml/kg and a mixture of gases in proportion oxygen:air = 50%:50%, PEEP 5 cm H2O and anesthesia were maintained with sevoflurane 0.7-1 MAC, in order to maintain mean arterial pressure (MAP) +/- 20% of the baseline value. In all patients, a nasogastric tube and urinary catheter were inserted as well. All patients had two intravenous canula and the anesthesia depth was followed by using entropy with value between 40-60. The surgery lasted approximately 150±30 minutes.

At the end of surgery, all patients received 2 gr of metamizole intravenously. The neuromuscular blockade was antagonized with prostigmin at 0.05 mg/kg and atropine at 0.02 mg/kg, the nasogastric tube was removed and patients were extubated in operating room and transferred to the Post-Anesthesia Care Unit (PACU). In the PACU the patients measured their VAS score of pain at rest, occurrence of nausea and vomiting (PONV), and administration of any rescue analgesic drug. If the VAS score was 4-6/10, 1 gr of metamizole was given and when VAS score was 7-10/10, 2 mg of morphine were given into epidural catheter together with 7 ml saline. As a rescue analgesia, 1 gr of paracetamol was used. All patients stayed for 2 hours and afterwards were transported to the Department of Digestive Surgery, where further analysis was performed. Also, 24 hours after surgery all patients received 1 gr of metamizole three times daily.

The primary goal was to measure patient pain during the first 72 postoperative hours in all three groups (2, 6, 12, 24, 36, 48 and 72 hours after surgery).

The secondary goal was to measure the total amount of morphine given in the postoperative period in all three groups. Other secondary goals were: to measure total amount of fentanyl given intravenously during surgery in first and second group, the need for rescue analgesia in the postoperative period, the occurrence of PONV, and the total amount of bupivacaine given during operation in all three groups.

STATISTICAL ANALYSIS

Statistical analysis of the data was done with the statistical package SPSS for Windows 26.0. The Kolmogor-Smirnov test for normality and the Shapiro-Wilk's W test were used to test the normality of the data. Continuous variables are shown with descriptive parameters (mean±SD, min-max or with median (IQR), categorical variables with absolute numbers and percentages, that is, with frequency distributions. Bivariate analysis was done to compare the analyzed groups, using Student t-test for independent samples, Analysis of Variance or Kruskal-Wallis test, to compare continuous parameters, while Chi-square was used to compare groups in terms of the categorical variables. Values of $p<0.05$ were considered statistically significant.

RESULTS

Sixty (60) patients participated in this research, of which 31 (51.7%) were female and 29 (48.3%) were male. The patients ranged in age from 38 to 70 years, with a mean age of 57.8±8.9 years. Patients from the three groups were homogeneous in terms of gender and age ($p>0.05$). In the Opioid and Low-opioid groups, patients of both sexes were equally represented; in the OFA group, 11 (55%) were female patients, 9 (45%) were male. The mean age of the patients was 58.2 ± 7.4 years, 56.6 ± 9.7 years, and 58.6 ± 9.8 years, respectively, in the opioid, low-opioid, and OFA groups.

In all 6 analyzed time points, 2 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours and 72 hours postoperatively, the VAS scale had significantly different scores depending on the type of anesthesia (Analysis of Variance, $p<0.001$).

Comparisons between groups showed that 2 hours after operation the patients from the Opioid and Low-opioid groups had significantly higher VAS scores, that is, stronger pain compared to the patients from the OFA group (8.30 ± 1.03 and 8.10 ± 1.1 vs 4.90 ± 2.6, $p<0.001$).

Six hours postoperatively, patients from the Low-opioid group had significantly higher VAS scores, that is, stronger pain compared to patients from the Opioid and OFA groups (6.90 ± 1.4vs 5.60 ± 0.9vs 5.40 ± 1.1, $p<0.001$).

After 12 hours the patients from the Opioid and Low-opioid groups had significantly higher VAS scores, that is, stronger pain compared to the patients from the OFA group (7.40 ± 0.9 and 6.35 ± 1.4 vs 3.10 ± 2.4, $p<0.001$).

After 24 hours patients from the Opioid and Low-opioid groups had significantly higher VAS scores (bigger pain) compared to patients from the OFA group (8.10 ± 0.9 and 5.90 ± 1.99 vs 3.60 ± 2.1, $p<0.001$). At this time, patients from

Table 1. *Descriptive characteristics in all three analyzed groups: Opioid-based, Low-opioid and Opioid free anesthesia groups*

variables		n	GROUPS			p-level
			Opioid n=20	**LOA** n=20	**OFA** n=20	
GENDER n(%)	female	31	10 (50)	10 (50)	11 (55)	X^2=0.1 p=0.93
	male	29	10 (50)	10 (50)	9 (45)	
AGE	mean ± SD	58.2 ± 7.4		56.6 ± 9.7	58.6 ± 9.8	F=0.3 p=0.8
	min - max	46 – 70		38 – 69	38 – 70	
BMI	mean ± SD	25.26 ± 2.03		27.35 ± 1.8	24.83 ± 1.6	F=11.1 p=0.000086 1vs2 p=0.0017 2 vs 3 p=0.00025
	min - max	22.35 – 29.75		23.87 – 32.27	22.04 – 17.06	

X^2 (Pearson Chi-square) , F(Analysis of Variance)

the Opioid group had significantly higher scores compared to the Low-opioid group (8.10 ± 0.9vs 5.90 ± 1.9, p<0.001).

After 36 hours of operation, patients from the Opioid group had significantly higher VAS scores compared to patients from the Low-opioid and OFA groups (6.35 ± 1.2 vs. 5.25 ± 1.2 vs. 4.30 ± 1.7, p<0.05 and p<0.001).

After 48 hours of operation, the patients from the Opioid and Low-opioid groups had significantly higher VAS scores, that is, stronger pain compared to the patients from the OFA group (4.70 ± 0.8 and 4.85 ± 1.1 vs 3.45 ± 1.6, p<0.001).

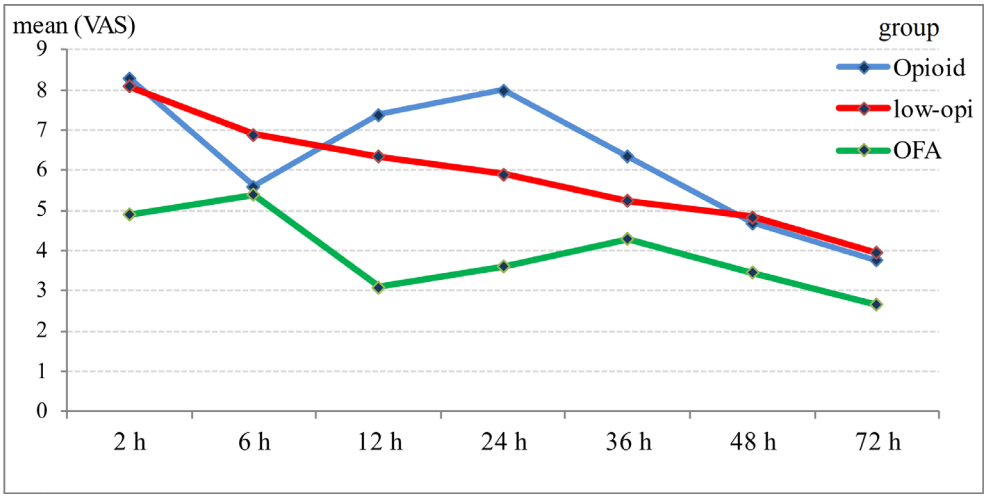
At the last follow-up point, 72 hours after the intervention, the patients from the Opioid and Low-opioid groups had significantly higher VAS scores compared to the patients from the OFA group (3.75 ± 0.8 and 3.95 ± 1.1 vs 2.65 ± 1.9, p<0.05 and p<0.001).

Table 2. *Visual Analogue Scale (VAS) scores in all three analyzed groups: Opioid, Low-opioid and Opioid-free anesthesia groups*

VAS	GROUPS	Descriptive statistics		p-value
		mean ± SD	min - max	
VAS – 2 h	Opioid	8.30 ± 1.03	7 – 10	F=23.6 ***p=0.00000 1vs3 ***p=0.0001 2vs3 ***p=0.0001
	LOA	8.10 ± 1.1	6 – 10	
	OFA	4.90 ± 2.6	0 – 8	
VAS – 6 h	Opioid	5.60 ± 0.9	4 – 8	F=10.0 ***p=0.000185 1vs2 **p=0.0022 2vs3 ***p=0.0005
	LOA	6.90 ± 1.4	5 – 9	
	OFA	5.40 ± 1.1	3 – 8	
VAS – 12 h	Opioid	7.40 ± 0.9	6 – 9	F=33.5 ***p=0.00000 1vs3 ***p=0.0001 2vs3 ***p=0.0001
	LOA	6.35 ± 1.4	3 – 8	
	OFA	3.10 ± 2.4	0 – 7	
VAS – 24 h	Opioid	8.10 ± 0.9	7 – 10	F=32.7 ***p=0.00000 1vs2 ***p=0.00073 1vs3 ***p=0.00012 2vs3 ***p=0.00045
	LOA	5.90 ± 1.9	0 – 9	
	OFA	3.60 ± 2.1	0 – 8	
VAS – 36 h	Opioid	6.35 ± 1.2	5 – 9	F=10.9 ***p=0.000 1vs2 *p=0.04 2vs3 ***p=0.00017
	LOA	5.25 ± 1.2	3 – 8	
	OFA	4.30 ± 1.7	0 – 7	
VAS – 48 h	Opioid	4.70 ±0.8	3 – 6	F=8.05 ***p=0.00083 1vs3 **p=0.005 2vs3 ***p=0.0004
	LOA	4.85 ± 1.1	3 – 8	
	OFA	3.45 ± 1.6	1 – 7	
VAS – 72 h	Opioid	3.75 ± 0.8	3 – 5	F=5.4 ***p=0.0071 1vs3 *p=0.03 2vs3 **p=0.009
	LOA	3.95 ± 1.1	2 – 6	
	OFA	2.65 ± 1.9	0 – 6	

F (Analysis of Variance), post hoc (Tukey honest test); *p<0.05, **p<0.01, ***p<0.0001

Graph 1: *VAS scores in all three groups – Opioid, Low-opioid and Opioid free anesthesia groups in all time points*



All patients from the Opioid and Low-opioid groups, and 9 (45%) from the OFA group received morphine in the postoperative period via an epidural catheter. Mean values of morphine that was given to all three groups in the postoperative period were in OBAG 6.60 ± 1.3 mg morphine, LOAG 4.50 ± 2.0 mg and the OFA group received 1.30 ± 1.6 mg morphine. The total amount of morphine that was given was significantly different among the three groups ($p<0.0001$); a significantly higher amount was given to patients in the Opioid and Low-opioid groups compared to patients in the OFA group ($p<0.0001$ and $p=0.0015$, respectively), and to patients from the Opioid group in comparison with the Low-opioid group ($p=0.04$).

Intraoperatively, all patients from the Opioid and Low-opioid received fentanyl, but patients from the Opioid group received a significantly higher amount ($p<0.0001$). Patients from the Opioid group received an average of 382.25 ± 106.3 micrograms, while all patients from the Low-opioid group received 200 micrograms fentanyl.

Additional administration of another analgesic in the postoperative period to patients who had pain was prescribed to 11 (55%) of the patients in the Opioid group, 10 (50%) patients in the Low-opioid group, 7 (35%) patients in the OFA group. The difference in distribution of patients with and without additional administration of another analgesic among the three groups was statistically insignificant ($p=0.4$).

Postoperative nausea and vomiting was registered in 12 (60%) patients from the Opioid group and 8 (40%) patients from the Low-opioid group. The OFA group did not register nausea and vomiting in any of the patients.

During the intervention, all patients received bupivacaine through an epidural catheter. The mean total amount of bupivacaine given during surgery was in Opioid group was 26.37 ± 2.6 mg, in LOA group 25.0 ± 0 and in OFA group 24.50 ± 4.3.

DISCUSSION

Opioid free anesthesia is a new concept of anesthesia where opioids are not used during surgery and in the postoperative period. With the combination of various non-opioid anesthetic drugs with different mechanism, such as lidocaine, ketamine, magnesium, non-steroidal anti-inflammatory drugs (NSAIDs), dexamethasone, gabapentin, paracetamol and alpha-2 agonists with or without regional anesthesia techniques [7, 8]

OFA has been shown how one can rationalize the usage of opioids in the perioperative period by avoiding opioids during surgery, reducing opioid use in postoperative period, lowering the unwanted adverse effects from opioids, thus leading to faster recovery and discharge from hospital, and preventing persistent postsurgical pain and thus chronic pain [8, 9]. By avoiding opioids, we avoid the known "opioid paradox": the more opioids are used in the intraoperative period, much more

Table 3. *Morphine needs in the postoperative period, fentanyl given in the intraoperative period, rescue analgesia, PONV and total amount of bupivacaine given in all three analyzed groups*

Variable		n	groups			p-level
			OBA n (%)	**LOA n (%)**	**OFA n (%)**	
Morphine	mean ± SD	6.60 ± 1.3		4.50 ± 2.0	1.30 ± 1.6	H=37.4 ***p=0.0000 1vs 2 *p=0.04 1 vs 3 ***p=0.0000 2 vs 3 **p=0.0015
	min - max	4 – 8		2 – 8	0 – 4	
	median (IQR)	6 (6 – 8)		4 (2 – 6)	0 (0 – 2)	
Fentanyl	mean ± SD	382.25 ± 106.3		200.0 ± 0		t=7.7 ***p=0.0000
	min - max	45 – 500		200		
Rescue Analgesia	yes	28	11 (55)	10 (50)	7 (35)	X^2=1.7 p=0.4
	no	32	9 (45)	10 (50)	13 (65)	
PONV	yes	20	12 (60)	8 (40)	0	X^2=16.8 ***p=0.000225
	no	40	8 (40)	12 (60)	20 (100)	
Total amount of Bupiv. 0.25% op. (mg)	mean ± SD	26.37 ± 2.6		25.0 ± 0	24.50 ± 4.3	F=2.3 p=0.11
	min - max	20 – 30		25 – 25	15 – 30	

X^2 (Pearson Chi-square), F (Analysis of Variance); *p<0.05, **p<0.01, ***p<0.0001

will be required in the postoperative period for treatment of pain, because of increased perception of pain [10]. Also, the risk of opioid abuse and opioid-induced hyperalgesia in the postoperative period will be less too.

Our study results support the usage of Low-opioid anesthesia, especially OFA, compared with Opioid-based anesthesia in colorectal cancer surgery. VAS scores comparisons between groups showed patients from the Opioid-based (OBA) and Low-opioid (LOA) groups had significantly higher VAS scores (stronger pain) compared to the patients from the OFA group 2, 12, 24 and 48 hours after operation. At 24 hours after surgery patients from the Opioid group had significantly higher scores compared to the Low-opioid group. After 6 hours postoperatively, patients from the Low-opioid group had significantly higher VAS scores compared to patients from the Opioid and OFA groups. After 36 hours postoperatively, patients from the Opioid group had significantly higher VAS scores compared to patients from the LOA and OFA groups. At the last follow-up point, 72 hours after the intervention, the patients from the Opioid and LOA groups had significantly higher VAS scores, compared to the patients from the OFA group. All patients from the Opioid and Low-opioid groups, and only 9 (45%) from the OFA group received morphine in the postoperative period via epidural catheter. A significantly higher amount of morphine was given to patients in the Opioid (6.60 ± 1.3 mg) and Low-opioid (4.50 ± 2.0) groups, compared to patients in the OFA group (1.30 ± 1.6). Total amount of fentanyl during surgery in the intraoperative period was recorded only in Opioid and LOA groups. All patients from the Opioid and Low-opioid received fentanyl, but patients from the Opioid group received significantly higher amount ($p<0.0001$). Patients from the Opioid group received an average of 382.25 ± 106.3 micrograms, while all patients from the Low-opioid group received 200 micrograms of fentanyl. Additional administration of another analgesic drug in the postoperative period to patients who had pain was prescribed to 11 (55%) patients in the Opioid group, 10 (50%) patients in the Low-opioid group, and in 7 (35%) patients in the OFA group. Postoperative nausea and vomiting was registered in 12 (60%) patients from the Opioid group and 8 (40%) patients from the Low-opioid group. In the OFA group none of the patients registered nausea and vomiting. During the intervention, all patients received bupivacaine through an epidural catheter. The mean total amount of bupivacaine given during surgery was in Opioid group was 26.37 ± 2.6 mg, in LOA group 25.0 ± 0 and in OFA group 24.50 ± 4.3.

In our study we used 1 gr of paracetamol as a preemptive analgesic drug. Dexamethasone has an antiemetic effect and an anti-inflammatory effect on the wound. Lidocaine given prior to surgery at 1 mg/kg and during surgery at 2 mg/kg/h intravenously leads to the reduced need for opioids during and after surgery, less PONV and faster return of bowel movement [11]. Ketamine, given at 0.5 mg/kg during induction to general anesthesia, has preemptive analgesic effect and continuous intravenous infusion at 0.2 mg/kg/h during surgery has an opioid sparing effect during surgery and decreases the need for opioids in the postoperative period, thanks to its NMDA antagonistic effect [12]. Magnesium given as a continuous intravenous infusion of 15 mg/kg/h has analgesic effect (due to NMDA-receptors antagonism), reducing PONV in the postoperative period and the need for opioids [13]. All these non-opioid drugs, given together in a non-toxic dose during surgery, can improve the intraoperative analgesia (nociception), can reduce the need of opioids in the intra- and postoperative period and thus can reduce opioid related adverse drug events (ORADEs).

Some authors think that use of propofol as a hypnotic, together with neuroaxial or locoregional analgesia techniques with reduced/avoided opioids and postoperative use of NSAIDs and local anesthetics, might be a promising anesthesia strategy for surgical cancer patients [14]. In other review article, it is suggested to use opioids as a primary rescue analgesia for acute postoperative and for chronic cancer pain management, but to consider using multimodal opioid sparing strategies [9]. One meta-analysis included 1934 patients from 26 RCTs scheduled for laparoscopic gynecological surgery, upper gastrointestinal and breast surgery. The results showed that postoperative opioid consumption was significantly lower in the opioid-free group comparing with opioid group, and nausea and vomiting were also decreased in opioid-free groups [15]. Basto and Machado, in their meta-analysis, find the same results: pain scores at rest are lower in the OFA group, there is a decrease in PONV and a reduced use of postoperative rescue analgesia and intravenous morphine consumption, compared to patients from the opioid based anesthesia group [16].

Other studies compare the effect of anesthesia (inhalational versus total intravenous) on cancer recurrence in 534 patients scheduled for colorectal surgery, and no statistically significant differences were found [1]. Multimodal opioid-sparing analgesia and use of thoracic epidural anesthesia are the cornerstone of modern control of intra- and postoperative pain in patients undergoing colorectal surgery [17].

We still need more RCTs and meta-analysis to declare which type of anesthesia and analgesia is the best option for the patients scheduled for colorectal cancer surgery. It is also important to know when the ideal time is to use opioids, if it is necessary to use opioids during surgery or we should keep them for treatment of acute postoperative and chronic pain? Can we involve OFA in all Enhanced Recovery After Surgery (ERAS) protocols or should we decide which patient is ideal for OFA? Connection between opioid exposure, immune function, cancer surgery and cancer recurrence must be evaluated and declared.

CONCLUSION

Patients from the Opioid free anesthesia (OFA) group, compared with patients from the Opioid-based anesthesia (OBA) and the Low-opioid anesthesia (LOA) groups have the lowest pain score in first 72 hours and in all time intervals after open colorectal surgery. Also, these patients received fewer opioids (morphine) via epidural catheter in the postoperative period and have less need for additional analgesics (rescue analgesia) postoperatively. None of these patients had the occurrence of PONV and the needs of bupivacaine via epidural catheter in the intraoperative period was low too.

Limitations to this study:

There were some limitations to this study. Epidural administration of 0.25 % bupivacaine (mg) during surgery was not equal in all groups. Because of the deficiency of equipment and special solutions for continuous epidural analgesia, we still use morphine for the postoperative treatment of high scoring pain. No complications, as in respiratory depression, were recorded. In the OFA group, 9 patients received morphine in the postoperative period, but none of all the 20 patients received opioids during intraoperative period.

REFERENCES

1. Crone V, Hasselager RP, Fransgaard T, Gögenur I. Anaesthetic technique and outcomes after colorectal cancer surgery. Dan Med J 2020; 67(4): A04190255. PMID:32285797.
2. Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis? Can J. Anesth. 2016; 63: 184–192.
3. Connolly C, Buggy DJ. Opioids and tumour metastasis: Does the choice of the anesthetic-analgesic technique influence outcome after cancer surgery? Curr. Opin. Anaesthesiol. 2016; 29: 468–474.
4. Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DG, Manning MW. The rising tide of opioid use and abuse: The role of the anesthesiologist. Perioper Med 2018; 7:16.
5. Egan TD. Are opioids indispensable for general anesthesia? Br J Anesth 2019; 122: e127-e135.
6. Brown EN, Pavone KJ, Naranjo M. Multimodal general anesthesia: theory and practice. Anesth Analg. 2018; 127: 1246-1258.
7. Beloeil H, Laviolle B, Menard C, Paugam-Burtz C, Garot M, Asehnoune K, et al. POFA trial study protocol: A multicentre, double-blind, randomised, 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: e020873.
8. Forget P. Opioid-free anaesthesia. Why and how? A contextual analysis. Anaesth Crit Care Pain Med 2019; 38: 169-172.
9. Thota RS, Ramkiran S, Garg R, Goswami J, Baxi V, Thomas M. Opioid free onco-anesthesia: Is it time to convict opioids? A systematic review of literature. J Anaesthesiol Clin Pharmacol 2019; 35: 441-52.
10. Mulier J, Dekock M. Opioid free general anesthesia, a new paradigm? Best Pract Res Clin Anaesthesiol 2017; 31: 441-3.
11. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018; 6: CD009642.
12. Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous sub-anesthetic ketamine for perioperative analgesia. J Anaesthesiol Clin Pharmacol 2016; 32: 160-7.
13. Hyun Jung Shin, Sang Hwan Do. Magnesium Sulfate: A Versatile Anesthetic Adjuvant. J Anest & Inten Care Med. 2017; 4(5): 555646.

14. Forget P, Aguirre JA, Bencic I, Borgeat A, Cama A, Condron C, Eintrei C, Eroles P, Gupta A, Hales TG, Ionescu D, Johnson M, Kabata P, Kirac I, Ma D, Mokini Z, Guerrero Orriach JL, Retsky M, Sandrucci S, Siekmann W, Štefančić L, Votta-Vellis G, Connolly C, Buggy D. How Anesthetic, Analgesic and Other Non-Surgical Techniques During Cancer Surgery Might Affect Postoperative Oncologic Outcomes: A Summary of Current State of Evidence. Cancers (Basel). 2019 Apr 28; 11(5): 592. doi:10.3390/cancers11050592
15. Olausson A, Svensson CJ, Andréll P, Jildenstål P, Thörn S-E, Wolf A. Total opioid-free general anaesthesia can improve postoperative outcomes after surgery, without evidence of adverse effects on patient safety and pain management: A systematic review and meta-analysis. Acta Anaesthesiol Scand. 2022; 66: 170–185. doi:10.1111/aas.13994
16. Basto T, Machado HS. Effect of Opioid-Free Anaesthesia on Perioperative Period: A Review. Int J Anesthetic Anesthesiol 2020; 7: 104. doi.org/10.23937/2377-4630/1410104
17. Kelliher LJS, Jones CN, Fawcett WJ. Enhanced recovery for gastrointestinal surgery. BJA Education 2015 Dec; 15(6): 305-310..

Резиме

СПОРЕДБА МЕЃУ ОПИОИДНАТА АНЕСТЕЗИЈА, АНЕСТЕЗИЈАТА СО НИСКА ДОЗА НА ОПИОИДИ И НЕОПИОИДНАТА АНЕСТЕЗИЈА КАЈ ОПЕРАЦИИ НА КОЛОРЕКТАЛЕН КАРЦИНОМ

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: Опиоидите се „златен стандард“ за третман на болка во текот и по операција на карциномот на дебелото црево. Тие можат да го инхибираат клеточниот и хуморалниот имунитет и на тој начин да промовираат пролиферација на карциномските клетки и метастатско ширење. Адекватниот третман на болката може да се постигне не само со користење опиоиди туку и со давање неопиоидни лекови, кои можат да се користат заедно во мали дози и можат да ги намалат потребите за опиоидни лекови за време и по операција, што се нарекува мултимодална аналгезија. Неопиоидната анестезија (НОА) е дел од мултимодалната аналгезија, при која нема употреба на опиоиди во интраоперативниот период, а понекогаш и во постоперативниот период.

Материјали и методи: Во оваа проспективна и рандомизирана клиничка студија беа вклучени 60 пациенти предвидени за отворена операција на колоректален карцином на возраст меѓу 45 и 70 години, кои им припаѓаат на класификациските групи 1, 2 и 3 според Американската асоцијација на анестезиолозите (ASA). Пациентите беа поделени во три групи. Првата група, или групата со анестезија базирана на опиоиди (АБОГ), прими лидокаин 1 мг/кг, фентанил 100 микрогр, пропофол 2 мг/кг и рокурониум бромид 0,6 мг/кг за вовед во општата анестезија. Потоа за време на операцијата пациентите од оваа група примаа интермитентно по 50–100 микрогр фентанил интравенски и наизменично 0,25 % бупивакаин 2–3 мл на секои 30–45 минути дадени преку епидурален катетер. Втората група пациенти, или пациенти со анестезија со ниска доза на опиоиди (ЛОАГ), доби лидокаин 1 мг/кг, фентанил 100 микрогр, пропофол 2 мг/кг и рокурониум бромид 0,6 мг/кг за вовед во анестезија. Пред операцијата, 50 микрогр фентанил со 5 мл 0,25 % бупивакаин беа дадени преку епидурален катетер и истата доза беше дадена уште еднаш при крајот од операцијата. Третата група, или пациенти со анестезија без опиоиди (НОАГ), пред воведот во општата анестезија прими дексаметазон 0,1 мг/кг и 1 гр парацетамол. Воведот во општата анестезија беше со лидокаин 1 мг/кг, пропофол 2 мг/кг, кетамин 0,5 мг/кг и рокурониум бромид 0,6 мг/кг. По ендотрахеална интубација беше дадена

интравенска континуирана инфузија со лидокаин 2 мг/кг/час, кетамин 0,2 мг/кг/час и магнезиум 15 мг/кг/час и интермитентно 0,25 % бупивакаин 2–3 мл на секои 30–45 минути преку епидуралниот катетер за време на операцијата. Во ова испитување примарна цел беше мерењето на болката во првите 72 постоперативни часа во сите три групи (2, 6, 12, 24, 36, 48 и 72 часа по операцијата). Секундарна цел беше мерењето на вкупната количина морфин дадена во постоперативниот период кај сите три групи. Други секундарни цели беа: мерења на вкупната количина на фентанил дадена интравенски за време на операцијата во првата и во втората група, потребата од дополнителна аналгезија во постоперативниот период, појава на постоперативно гадење и повраќање и вкупна количина бупивакаин дадена за време на операцијата во сите три групи.

Резултати: Споредбите на вредностите добиени според Визуелната аналогна скала (ВАС) за болка меѓу трите групите покажаа дека пациентите од групите АБОГ и ЛОАГ имале значително повисоки вредности на скалата ВАС во споредба со пациентите од групата НОАГ 2, 12, 24 и 48 часа по операцијата. По 6 часа постоперативно, пациентите од групата ЛОАГ имале значително повисоки ВАС-вредности во споредба со пациентите од групите АБОГ и НОАГ. По 36 часа постоперативно, пациентите од групата АБОГ имале значително повисоки вредности на ВАС во споредба со пациентите од групите ЛАОГ и НОАГ. На последната точка на следење, 72 часа по интервенцијата, пациентите од групите АБОГ и ЛОАГ имале значително повисоки вредности на ВАС во споредба со пациентите од групата НОАГ. Сите пациенти од групите АБОГ и ЛОАГ и само 9 од групата НОАГ примиле морфин во постоперативниот период преку епидурален катетер. Значително поголема количина фентанил за време на операцијата примиле пациенти од групата АБОГ. Дополнително давање друг аналгетик во постоперативниот период имало кај 55 % од пациентите во АБОГ, кај 50 % во ЛОАГ и само кај 35 % во групата НОАГ. Постоперативно гадење и повраќање (ПОГП) е регистрирано кај 60 % од пациентите од АБОГ и кај 40 % од пациентите од ЛОАГ. Во групата НОАГ не беше регистриран ПОГП кај ниту еден од пациентите. Најголемото количество на бупивакаин дадено за време на операцијата беше кај АБОГ (26,37 ± 2,6 мг), кај ЛОАГ беше 25,0 ± 0 и помалку во НОАГ групата (24,50 ± 4,3).

Заклучок: Пациентите од групата НОАГ во споредба со пациентите од АБОГ и од ЛОАГ имаа најнизок скор на болка во првите 72 часа по отворена колоректална операција, примале помалку опиоиди преку епидурален катетер во постоперативниот период, имале помали потреби за дополнително давање аналгетици, немало појава на ПОГП и помали биле потребите за давање бупивакаин преку епидурален катетер во интраоперативниот период.

Клучни зборови: анестезија базирана на опиоиди, анестезија со ниска доза опиоиди, неопиоидна анестезија, колоректална хирургија, постоперативна болка