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Research Article

Effectiveness of intravenous administration of lidocaine on immediate postoperative evolution in colorectal cancer surgery

[1,4]Tiberiu F. Tat, [2,4]Răzvan Popa, [3,5]Cătalin Constantinescu, [1,5]Alexandru Alexa, [6]Ștefan C. Vesa, [1,5,7]Daniela Ionescu

[1] Department of Anesthesia and Intensive Care I," Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2] Department of Oncological and Gynecology Surgery," Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania [3] Department of Hematology," Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [4] Department of Anesthesia and Intensive Care, The Oncology Institute „Prof Dr. I Chiricuță", Cluj-Napoca, Romania; [5] Department of Anesthesia and Intensive Care, Regional Institute of Gastroenterology and Hepatology „Prof. Dr. Octavian Fodor", Cluj-Napoca, Romania; [6] Department of Pharmacology, Toxicology and Clinical Pharmacology "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [7]Outcome Research Consortium, Cleveland, USA.

Abstract. Aim: to evaluate the clinical effects of lidocaine added to two different anesthetic techniques (inhalation and intravenous anesthesia) on postoperative recovery in patients with colorectal cancer surgery. Material and methods: 200 patients with colorectal cancer were enrolled in this prospective, interventional, single-blind, randomized study and were subdivided into 4 study groups according to the anesthetic technique (inhalation anesthesia or total intravenous anesthesia), respectively with and without administration of iv lidocaine. Lidocaine was administered, for 48 hours, starting with induction (1.5 mg kg-1 bolus), followed by continuous infusion (1 mg kg-1 hour-1) during anesthesia and postoperative period. The following data were evaluated: intra-anesthetic fentanyl dose, postoperative morphine consumption, verbal pain score (0-10), presence of postoperative nausea and vomiting (at 0, 2, 12, 24 hours postoperatively), time interval for bowel resumption, time to postoperative mobilization, incidence of complications and duration of hospitalization and the level of inflammatory markers at 24 hours postoperatively. Results: Comparing the 4 groups, intravenous lidocaine infusion decreased pain scores at recovery ($p=0.019$) and at 8, 12 and 30 hrs. postoperatively ($p<0.01$), determined faster postoperative mobilization ($p<0.01$), decreased the opioid requirement during the first 24 hours postoperatively ($p=0.022$), decreased the duration of hospital stay ($p=0.029$), but did not influence the incidence of nausea and vomiting, and the need for intra-anesthetic opioid dose, or the incidence of postoperative complications or the level of inflammatory markers. Conclusions: In our study, the intravenous lidocaine infusion administered intra and postoperatively reduced postoperative opioid consumption, but not intra-anesthetic opioid use, incidence of postoperative nausea and vomiting, or other complications rate and the level of inflammatory markers.

Key Words: anesthesia, lidocaine, pain, postoperative recovery.

Corresponding Author: C. Constantinescu, email: constantinescu.catalin@ymail.com

Introduction

The anesthetic technique may influence short- and long-term postoperative outcome after oncological surgery. The most common complications that occur early postoperatively are postoperative pain, nausea and vomiting, ileus, hypercoagulability and postoperative cognitive dysfunction (Cassuto et al 2006). Surgery may increase tumor growth and metastasis due to mainly the release of circulating neoplastic cells. Perioperative inflammatory response and immune suppression may also cause tumor growth and recurrence. Lidocaine, as local anesthetic, is a sodium channel blocker, that given as an intravenously (iv.) infusion, diminishes the painful response to mechanical or chemical stimulation in healthy volunteers (Dirks et al 2000). There are numerous recent studies that have shown that iv infusion of lidocaine has beneficial effects on the early resumption of bowel function, pain intensity, postoperative opioid use, duration of intensive care stay or length of hospital stay (Groudine et al 1998; Herroeder et al 2007; Koppert et al 2004; Kaba et al 2007; Lauwick et al 2008).

It has been shown that lidocaine, at these doses, has a relevant intra- and postoperative analgesic effect, attenuates sympathetic response, decreases pain, prevents chronic pain, reduces the use of volatile anesthetics and opioids, accelerates the resumption of intestinal movements and reduces the duration of hospital stay (Groudine et al 1998; Koppert et al 2004; Kaba et al 2007; Grady et al 2012; Rimback et al 1990). In addition, some studies reported a significant reduction in the plasma levels of inflammatory markers, suggesting an anti-inflammatory activity

and a capacity to modulate the stress-induced inflammatory response (Herroeder et al 2007). Lidocaine infusion useful in terms of the cost of pain relief in patients who are not suitable for epidural analgesia (Grady et al 2012).

A literature review showed that in the vast majority of studies, lidocaine was used systemically for analgesic purposes in doses of 1.5-2 mg kg-1 bolus at anesthetic induction, followed by a continuous infusion of 1.5-3 mg kg-1 hour-1 until the end of the surgery, reaching plasma levels below 5 µg ml-1 (1.3-3.7 µg ml-1) (Groudine et al 1998).

The aim of the study was to evaluate the clinical effects of lidocaine added to two different anesthetic techniques (inhalation and intravenous anesthesia) on postoperative recovery in patients with colorectal cancer surgery.

Materials and methods

After obtaining the institutional Ethics Committee consent (no. 58/22 November 2016) and from the University of Medicine and Pharmacy "Iuliu Haţieganu" (no. 53/14 March 2016), a prospective, interventional, placebo-controlled, single-blind, randomized, bicentric, longitudinal study, was performed (March 2016-May 2019), in the Oncological Institute "Ion Chiricuță" and Regional Institute of Gastroenterology and Hepatology in Cluj-Napoca. Two hundred patients ASA 1-3, undergoing elective interventions (resections of tumor) under general anesthesia (either sevoflurane inhalation or TIVA (total intravenous anesthesia) were enrolled in the study. Inclusion criteria were: age of 18 and 80, elective surgery for tumor removal, cancer stage (AJCC) I-II, no metastasis. Exclusion criteria from the study were: patients with pre-existing chronic pain, those with chronic medication that could interfere with pain (antiepileptics, NSAIDs, corticosteroids), contraindications to any of the drugs used in the study, psychiatric disorders (depression, bipolar disorder, schizophrenia), liver disease or renal disease, convulsive disorders under treatment, autoimmune disorders, corticosteroid-dependent asthma, and antiarrhythmic therapy (verapamil, propafenone, amiodarone) that could interfere with the anti-arrhythmic effects of lidocaine. All patients signed an informed consent form before being included in the study.

Patients were randomized into four study groups 50 patients each: the sevoflurane group (patients undergoing sevo anesthesia), TIVA group (patients undergoing total intravenous anesthesia), sevoflurane + lidocaine group (sevo anesthesia + intravenous lidocaine infusion) and TIVA + lidocaine group (TIVA + intravenous lidocaine infusion). The anesthetic protocol included administration of low molecular weight heparin 12 hours prior to surgery and postoperatively as recommended. Patients were premedicated when the case with midazolam 7.5 mg orally approximately one hour prior to intervention. During induction, fentanyl 2-3 µg kg-1, followed by propofol 1.5-2 mg kg-1, and atracurium 0.5-0.6 mg kg-1 were administered. During induction, after inserting the peripheral venous catheter, 1% lidocaine 1.5 mg kg-1 intravenous bolus was given. The patients in the sevoflurane and TIVA groups received equal volumes of saline. During the maintenance of anesthesia, sevoflurane (Et Sevoflurane 1-1.5 MAC (Minimum alveolar concentration)) was administered in inhalation anesthesia group, with increase/decrease in steps of 0.25-0.5 MAC depending on the BIS (Bispectral index) level. In TIVA groups, the Schneider model was used for propofol, with an initial effect concentration = 4 µg ml-1, adjusted according to BIS. BIS was monitored in all patients (Covidien BIS Quatro XP, Medtronic) and kept between 40-55. The patients were mechanically ventilated by volume control ventilation, with a mixture of oxygen and air in a ratio of 50/50, in a semi-closed circuit, with fresh gas flow of 2 l/min, tidal volume=6-7 ml ideal body weight-1 and PEEP of 5 cmH2O).

Intraoperative analgesia was achieved with fentanyl 0.5-1 µg kg-1 as needed (if blood pressure values/heart rate increased by more than 20% of the patient's baseline values, or other signs of inadequate analgesia were present: pupils, tears or sweating). Paracetamol 1 g intravenously was administered 30 minutes before the end of the surgery. Intraoperatively, cristalloids-Ringer-were administered maintenance fluids a mean volume of 1500 ml. At the end of the intervention, the neuromuscular block was antagonized, at TOF>0.9, by the administration of neostigmine 0.04 mg kg-1 and atropine 0.02 mg kg-1. In lidocaine groups following orotracheal intubation until recovery from anesthesia, a continuous infusion of lidocaine 1% 2 mg kg-1 hour-1, up to a maximum of 200 mg hour-1. Intraoperative monitoring included ASA recommended monitoring (blood pressure, heart rate, temperature, peripheral oxygen saturation, EtCO2 (End tidal CO2), BIS monitoring, TOF (train of four) watch and total intraoperative fentanyl consumption.

Postoperative analgesia was provided by morphine 0.1-0.2 mg kg-1 administered 30 minutes before recovery. If necessary, additional morphine boluses of 0.05 mg kg-1 were administered, so that the pain level reached a score≤4 on the verbal pain response scale. Paracetamol 1g at 6 hours interval intravenously was administered postoperatively. Lidocaine infusion 1 mg kg-1 hour-1 (maximum 100 mg hour-1) was maintained for the first 48 hours. Postoperative monitoring included: morphine consumption in the first 24 hours postoperatively, the verbal pain score (VPS) at rest measured at 4 hours in the first 24 hours, then at 6 hours in the next 24 hours, the presence of postoperative nausea and vomiting (evaluated at 2, 12 and 24 hours postoperatively), resumption of intestinal transit bowel movements and time to first flatus, time to postoperative mobilization, length of hospital stay and level of inflammatory markers. Postoperatively patients were monitored high dependency unit (HDU) or on the surgical wards.

Prior to surgery, each patient was trained on the assessment of the verbal pain score (0- no pain, 10- the greatest possible pain) and on recording the time of resumption of bowel movements and first flatus.

Statistical analysis was performed using the MedCalc Statistical Software version 19.0.7 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019). Continuous data was tested for normality of distribution using the Shapiro-Wilk test, and was expressed as median and 25, 75 percentiles. Qualitative variables were expressed as frequency and percent. Comparisons between groups were performed with the Mann-Whitney, Kruskal-Wallis or chi-square test, whenever appropriate. A p value <0.05 was considered statistically significant.

Results

Two-hundred and ten patients were eligible, but 6 patients were excluded from the study due to conversion of resection to rectal

Table 1. Demographic and intra-anesthetic data

Variables	Sevoflurane (N=50)	Sevoflurane+lidocaine (N=50)	TIVA (N=50)	TIVA+lidocaine (N=50)	p
Age (years)	64.5(59-69)	64(54.75-70.5)	63.5(56.75-68.5)	64.5(56.5-70.25)	0.99
BMI (kg/m²)	27.57(24.37-32.03)	24.70(23.21-28.33)	27.22(23.80-31.25)	27.89(23.11-30.01)	0.06
Gender (f/m)(%)	27/23(54/46)	29/21(58/42)	26/24(52/48)	26/24(52/48)	0.92
ASA (I/II/III)(%)	3/37/10(6/74/20)	3/43/4(6/86/8)	2/42/6(4/84/12)	4/35/11(8/70/22)	
Smoking (Y/N)(%)	5/45(10/90)	9/41(18/82)	5/45(10/90)	10/40(20/80)	0.34
Chemotherapy (Y/N)(%)	14/36(28/72)	5/45(10/90)	9/41(18/82)	6/44(12/88)	0.07
Radiotherapy (Y/N)(%)	13/37(26/74)	4/46(8/62)	9/41(18/82)	7/43(14/86)	0.1
Anesthesia duration (min)	157.5(120-193.75)	137.5(110-176.25)	157.5(123.75-181.25)	166(128.75-196.25)	0.08
Duration of surgery (min)	135(103.75-171.25)	107.5(88.75-136.25)	122.5(95-165)	135(105-170)	0.02
Intraanesthetic fentanyl consumption (mg)	0.4(0.3-0.66)	0.52(0.25-0.66)	0.5(0.3-0.62)	0.55(0.3-0.7)	0.82

Table 2. Verbal pain score during the first 48 hours postoperatively and total morphine consumption during first 24 hours postoperatively in study groups

Variables	Sevoflurane (N=50)	Sevoflurane+lidocaine (N=50)	TIVA (N=50)	TIVA+lidocaine (N=50)	p
VPS	5(1-6.25)	2(0-4.25)	3(0-5)	2.5(0-5)	0.019
VPS at 4 hours	4(2.75-6)	4(2-5)	4(2-5)	3(2-5)	0.053
VPS at 8 hours	4(2-6)	3(1-4)	3(1-5)	3(1-4)	0.026
VPS at 12 hours	4(2-5)	3(2-4)	4(2-5.25)	3(1-4)	0.008
VPS at 16 hours	4(2-6)	3.5(2-5)	4(1.75-5)	1(1-4.25)	0.202
VPS at 20 hours	3(2-4)	3.5(1-5)	3(1-4)	2(1-4)	0.081
VPS at 24 hours	2.5(1-4)	2.5(1-5)	3(1-4)	2(1-3)	0.222
VPS at 30 hours	3(2-4)	2(1-4)	3(0-4)	2(1-4)	0.011
VPS at 36 hours	2(1-3)	2(1-3)	2(0-4)	1(0.75-2)	0.487
VPS at 42 hours	2(1-3)	2(1-3)	2(0-3)	1(0-2)	0.112
VPS at 48 hours	2(0.75-3)	1(0-3)	1(0-2)	1(0-2)	0.097
Total morphine consumption/24h (mg)	27(21-35)	21(15.75-31.62)	25.5(18.75-33.5)	20(15.37-28.5)	0.022

Table 3. Results on postoperative nausea and vomiting in study groups

Variables	Sevoflurane (N=50)	Sevoflurane+lidocaine (N=50)	TIVA (N=50)	TIVA+lidocaine (N=50)	p
Recovery (Y/N)(%)	9/46(16.4/83.6)	8/50(13.8/86.2)	3/43(6.5/93.5)	5/40(11.1/88.9)	0.48
2 hours postoperatively(Y/N)(%)	17/38(30.9/69.1)	18/40(31/69)	12/34(26.1/73.9)	8/37(17.8/82.2)	0.41
12 hours postoperatively(Y/N)(%)	19/36(34.5/65.5)	22/36(37.9/62.1)	14/32(30.4/69.6)	15/30(33.3/66.7)	0.88
24 hours postoperatively(Y/N)(%)	13/42(23.6/76.4)	17/41(29.3/70.7)	12/34(26.1/73.9)	11/34(24.4/75.6)	0.9

amputation and another 4 patients did not have complete data. There were 64 hemicolectomies (32%), 9 transverse colon resections (4.5%), 81 rectosigmoid resections (40.5%), 44 rectal resections (22%) and 2 total colectomies (1%). The 4 groups were comparable in terms of age, sex, BMI, nicotine abuse, radiotherapy and neoadjuvant chemotherapy (Table 1). Most of the cases were ASA 2. As can be seen in Table 1, there were no significant differences between the study groups, with one exception related to the duration of the surgery in the sevo group. There were 6 cases that presented bradycardia at induction of anesthesia after administration of the lidocaine bolus.

There were significant differences in VPS between the 4 groups recovery from anesthesia end, at 8, 12 and 30 hours postoperatively, at this time, VPS was lower in lidocaine groups (Table 2). There were also differences related to morphine consumption in the first 24 hours postoperatively between the 4 groups (Table 2). Morphine consumption was significantly reduced in lidocaine groups, in both, inhalation anesthesia and TIVA (p=0.044 for inhalation groups, respectively p=0.023 for TIVA groups). Lidocaine infusion did not influence the incidence of postoperative nausea and vomiting regardless of the anesthetic technique used. There was no significant difference between the 4 study

Table 4. Postoperative mobilization, resumption of intestinal transit, duration of hospitalization

Variables	Sevoflurane (N=50)	Sevoflurane+lidocaine (N=50)	TIVA (N=50)	TIVA+lidocaine (N=50)	p
Postoperative mobilization(h)	22(18-41)	18(14-20)	19.5(18-25.5)	18(13.5-19.5)	<0.01
Resumption of intestinal transit for gas (h)	53(30-72)	49(30.7-68.5)	55(40.5-68.5)	50(33-70)	0.75
Resumption of intestinal transit for feces (h)	65(46-89)	62(47.7-76)	72(54-89.7)	72(48-84)	0.26
Duration of total hospitalization(days)	10(8-13)	9(8-12)	10.5(8.7-13.2)	10(8-11)	0.029

Table 5 Postoperative complications

Variables	Sevoflurane (N=50)	Sevoflurane+lidocaine (N=50)	TIVA (N=50)	TIVA+lidocaine (N=50)	p
Infection Y/N (%)	3/47(6/94)	2/48(4/96)	4/46(8/92)	2/48(4/96)	0.787
Digestive fistula Y/N (%)	2/48(4/96)	1/49(2/98)	4/46(8/92)	3/47(6/94)	0.551
Acute respiratory failure Y/N (%)	1/49(2/98)	0/50 (0/100)	1/49(2/98)	2/48(4/96)	0.564
Acute renal failure Y/N (%)	3/47(6/94)	0/50(0/100)	1/49(2/98)	2/48(4/96)	0.329

Table 6. Serum levels of PCR and leukocytes counts at 24 hours postoperatively

Variables	Sevoflurane (N=50)	Sevoflurane+lidocaine (N=50)	TIVA (N=50)	TIVA+lidocaine (N=50)	p
Leukocytes number	11840(9850-13150)	11965(9865-14615)	11330(8882-13072)	11940(9430-13760)	0.3
PCR serum level	10.25(6.97-14.2)	8.28(6.34-11.33)	8.18(5.58-12.33)	9.85(7.28-11.67)	0.13

groups in the incidence of nausea and vomiting for all time intervals of assessment (Table 3).

Moreover, postoperative lidocaine infusion significantly reduced the time to first postoperative mobilization (p=0.004 in sevo groups and p<0.001 in TIVA groups respectively). However, there were no significant differences regarding time interval to the first flatus. Lidocaine infusion significantly reduced the duration of total hospital stay. The difference was moreover significantly in TIVA groups (p = 0.007) (Table 4).

Lidocaine infusion did not increase the incidence of postoperative complications. There were no statistically significant differences between the study groups regarding the postoperative infection, fistulas, respiratory failure or postoperative renal failure (Table 5). All cases of respiratory failure were due to pneumonia or bronchopneumonia.

Lidocaine infusion did not change significantly serum levels of inflammatory markers. There were no statistically significant differences between the study groups regarding the serum C-reactive protein level and the number of leukocytes (Table 6).

Discussions

In the last years a number quite of studies focused on the potential benefits of lidocaine infusion administered intra and postoperatively for 48 hours.

Studies have shown that intraoperative use of lidocaine decreases postoperative pain in abdominal (Koppert et al 2004; Marret et al 2008), colorectal (Kaba et al 2007; Tikuisis et al 2014; Wongyingsinn et al 2011) and gastric surgery (Yon et al 2014), and respectively in prostate (Groudine et al 1998), kidney (Tauzin-Fin et al 2014), gallbladder (Wu et al 2005) and gynecological surgery (Grady et al 2012). However not all authors reported the same results. Swenson et al (Swenson et al 2010), Kuo et al (Kuo et al 2006) and other studies regarding the effects of lidocaine in colorectal surgery (Herroeder et al 2007), did not find a significant effect on the intensity of postoperative pain. The same lack of effect has been reported in other studies, for example in breast (Soo et al 2012) or stomach (Kang et al 2012) surgery. In our study we found that infusion of lidocaine for 48 hours perioperatively, significantly decreased the pain score in recovery, and respectively at 8, 12 and 30 hours postoperatively. Subsequently the effect diminished, although data from the literature have shown that its effects are enhanced if the intraoperative infusion is followed by a postoperative one for days or even weeks. This may show that lidocaine action is not limited to voltage-dependent sodium channels but extends to other targets and suggests prevention of hypersensitivity in both the peripheral and central nervous system (Wu et al 2005; Tanaka et al 2008).

Most studies in the literature do not refer to intranesthetic fentanyl use but only to postoperative opioid use. In their study, Kuo and colleagues, compared the effect of lidocaine infusion but also of thoracic epidural analgesia with a control group, and found a need for intraoperative fentanyl of less than 50% in patients who received either intravenous or epidural lidocaine, as compared with control group (Kuo et al 2006). Studies on abdominal (Koppert et al 2004), gallbladder (Saadawy et al 2010), stomach (Kang et al 2012), kidney (Tauzin-Fin et al 2014) or in gynecological surgery (Grady et al 2012) have shown that postoperative opioid use is lower in patients receiving intravenous lidocaine. In our study, the combination of intravenous lidocaine with either of the two anesthetic techniques used (inhalation and TIVA) did not statistically significantly decrease intraoperative fentanyl consumption. However, there are some

studies that found the same results like ours in colon and breast surgery (Kuo et al 2006; Soo et al 2012). In our study, morphine use in the first 24 hours postoperatively was significantly reduced by lidocaine.

According to literature, intravenous lidocaine reduced the time to first flatus. The mechanisms by which lidocaine acts on intestinal peristalsis include: the direct excitatory effect on the smooth intestinal musculature, the indirect effect by reducing pain and opioid requirement, blockage of sympathetic reflexes, reducing the release of catecholamines and the anti-inflammatory effect (Rimback et al 1990). This is the reason why intravenous infusion lidocaine was included in ERAS (Enhanced recovery after surgery) protocols. These effects have been demonstrated in abdominal (Marret et al 2008) and colorectal surgery (Herroeder et al 2007; Kaba et al 2007; Tikuisis et al 2014) in particular, but also in surgery of gallbladder (Wu et al 2005; Saadawy et al 2010), prostate (Groudine et al 1998), and kidney (Tauzin-Fin et al 2014) or in the gynecological surgery (Grady et al 2012). In contrast, with these data, Soo et al (Soo et al 2012) found no differences in time to resumption of bowel movements in breast surgery in women receiving lidocaine. The same lack of effect on bowel function was also found by Swenson et al (Swenson et al 2010) in colon surgery or by Kang et al (Kang et al 2012) in gastric surgery. Similar to these results, in our study, lidocaine infusion did not influence the time to the resumption of bowel function.

Postoperative nausea and vomiting (PONV) may increase the length of hospital stay and related costs after surgery. PONV are lower in patients who received intravenous lidocaine, due to lower postoperative opioid use. In a meta-analysis, Marret and co-workers showed that the group receiving lidocaine in major abdominal surgery had less postoperative pain and vomiting (Marret et al 2008). However, in contrast, Koppert and colleagues did not find significant differences in their study between the control group and the group receiving lidocaine (Koppert et al 2004). In our study we did not find significant differences between groups, although we would have expected. This may be due to fact the use of TIVA would decrease the incidence of postoperative nausea and vomiting.

Postoperative mobilization requires effective postoperative analgesia. An adequate analgesia can be ensured by including lidocaine in multimodal analgesia. In their study, Wonguingsinn et al (Wonguingsinn et al 2011) failed to demonstrate that the use of intravenous lidocaine in colorectal surgery provides earlier mobilization. By contrast, Koppert and co-workers demonstrated that patients receiving lidocaine infusion experienced less pain during mobilization and required less morphine within the first 72 hours after abdominal surgery (koppert et al 2004). We found that intravenous lidocaine significantly decreased time to postoperative mobilization.

There are studies that have shown that intravenous lidocaine infusion shortens the length of hospital stay (LOS). LOS after elective surgery is also influenced by the duration of the postoperative ileus, which is longer in patients with colonic resections or with open surgery. Lidocaine may be a solution in these patients because it shortens the ileus duration, LOS, as well as the costs related to hospital admission (Salvador et al 2005). In a recent meta-analysis, Marret and co-workers showed that intravenous lidocaine reduces the length of hospital stay (Marret et al 2008). Herroeder et al also showed that the use of lidocaine decreases LOS by one day without affecting the duration of admission in high dependency unit (Herroeder et al 2007). In our study, we found that intravenous administration of lidocaine shortens the duration of hospital admission.

Herroeder and colleagues found a postoperative morbidity rate of 9.7% in the group receiving lidocaine. In the group with lidocaine, no digestive fistula was registered, and only one patient developed a wound irritation that did not require surgery. One patient in the control group developed subphrenic abscess (Herroeder et al 2007). Tikuisis et all in the study on laparoscopic colon cancers surgery found no significant differences between the control group and the lidocaine group (Tikuisis et al 2014). In our study, postoperative related complications did not differ significantly between study groups.

Lidocaine infusion blocked the activation of polynuclear leukocytes with an anti-inflammatory effect (Hollmann et al 2000; Hollmann et al 2001). In their study, Kaba and collaborators did not find significant differences on the number of leukocytes or in postoperative levels of C-reactive protein between the control group and the group with lidocaine at 2, 6, 24 and 48 hours postoperatively (Kaba et al 2007). In our study there were no significant differences between groups.

The limitations of the study included the small size of study groups and we couldn't measure the plasma concentration of lidocaine.

Conclusions

In our study, continuous postoperative infusion of lidocaine in colorectal surgery decreased the need for opioids within the first 24 hours postoperatively, decreased the postoperative pain score determined faster postoperative mobilization and reduced the length of hospital stay in. Further studies on larger groups of patients are necessary.

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Authors

•Tiberiu Florin Tat, Department of Anesthesia and Intensive Care I, "Iuliu Haţieganu" University of Medicine and Pharmacy, 19-21 Croitorilor Street, Cluj-Napoca, Romania, e-mail: dr_tibi@yahoo.com

•Răzvan Popa, Department of Oncological and Gynecology Surgery, "Iuliu Haţieganu" University of Medicine and Pharmacy, 34-36 Republicii Street, Cluj-Napoca, Romania, e-mail: p.razvan@gmail.com

•Cătălin Constantinescu, Department of Hematology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 73 21 Decembrie 1989 Street, Cluj-Napoca, Romania, e-mail: constantinescu.catalin@ymail.com

•Alexandru Alexa, Department of Anesthesia and Intensive Care, Regional Institute of Gastroenterology and Hepatology„Prof. Dr. Octavian Fodor", 19-21 Croitorilor Street, Cluj-Napoca, Romania, email: alexandrualexa91@gmail.com

•Ştefan Vesa, Department of Pharmacology, Toxicology and Clinical Pharmacology "Iuliu Haţieganu" University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, Cluj-Napoca, Romania, e-mail: stefanvesa@gmail.com

•Daniela Ionescu, Department of Anesthesia and Intensive Care, Regional Institute of Gastroenterology and Hepatology„Prof. Dr. Octavian Fodor", 19-21 Croitorilor Street, Cluj-Napoca, Romania, email: Daniela_Ionescu@umfcluj.ro

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