ORIGINAL ARTICLE

Improvement of recovery parameters using patient-controlled epidural analgesia after oncological surgery. A prospective, randomized single center study*

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Abstract

Purpose: The aim of this study was to compare patient-controlled epidural analgesia (PCEA) versus conventional opioid intravenous (IV) infusion after gastrointestinal cancer surgery regarding several post-surgery parameters of recovery.

Methods: One hundred and one patients were prospectively randomized to receive either thoracic/lumbar PCEA (PCEA group) or the standard analgesia technique used in our hospital, conventional IV infusion of morphine (IVMO group) after gastrointestinal cancer surgery. Pain intensity, time of mobilization and bowel function recovery were analyzed post-surgery. We also evaluated postoperative complications and length of Postoperative-Intermediate Intensive Care Unit (PI-ICU) stay and hospital stay.

Results: Pain intensity was significantly less in the PCEA group in comparison with the IVMO Group at awakening 2, 8, 24, 30 and 48 hours after surgery ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.043$, $p = 0.036$, and $p = 0.029$, respectively). The latency to bedside mobilization, walking, first postoperative flatus and apparition of first stool were significantly faster (1.74 versus 2.26 days, 3.06 versus 3.78 days, 2.1 versus 3.14 days and 3.73 versus 5.28 days, respectively) in the PCEA group than in the IVMO group ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The incidence of nausea/vomiting was significantly lower in the PCEA group in comparison with the IVMO group ($p = 0.001$). Surgical-associated complications were significantly lower in the IVMO Group than in the PCEA group ($p = 0.023$). Length of PI-ICU stay was similar in the two groups but length of hospital stay was significantly shorter in PCEA group (4 versus 5 days $p = 0.2849$, 9 versus 12 days; $p < 0.001$).

Conclusions: PCEA provides better postoperative pain control, improves postoperative recovery after gastrointestinal cancer surgery compared with conventional intravenous morphine infusion. Therefore, it is more acceptable than conventional pain management.

Keywords: gastrointestinal cancer surgery, patient-controlled epidural analgesia, postoperative analgesia

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Introduction

Colorectal cancer is the third most common cancer in men (10%) and the second (9.2%) in women [1]. Also, gastric cancer is the fifth most common malignancy in both sexes worldwide [1]. Surgery represents the cornerstone in the management of solid malignant tumors but it is associated with high incidence of postoperative complaints and complications [2-4]. Acute postoperative pain, nausea and vomiting, delay in gastrointestinal motility and mobilization have all been associated with reduced early postoperative well-being and prolonged hospitalization [5-7]. The provision of good symptom relief following gastrointestinal cancer surgery is important for limiting morbidity and mortality [8, 9]. Intravenous patient-controlled analgesia (IV

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PCA) has been considered the optimal methods for pain treatment after major laparotomy, but intravenous continuous morphine analgesia (IVMO) is still the most commonly used technique in our department [10, 11]. Patient-controlled epidural analgesia (PCEA) decreases the stress response after surgery, provides a good postoperative pain control but controversies still exist about its effects on the patient's outcome after abdominal surgery [3, 7, 12 -15]. The principal aim of this study was to compare the effects of PCEA and IVCA on postoperative morbidity, especially on pain, gastro-intestinal function recovery and capacity of self-mobilization for patients undergoing digestive cancer surgery. Another aim of our study was to evaluate the influence of the analgesia type on postoperative complications, length of postoperative intermediate intensive care unit (PI-ICU) stay and length of hospital stay.

Methods

The study was performed in the Department of Surgery of the Ion Chiricuta Oncology Institute Cluj-Napoca (IOCN), Romania, between February 2015 and November 2016. The ethical approval for this study was provided by the Ethical Committee of the IOCN (n 3327/22.04.2013). Written informed consent was obtained from all patients before the inclusion in the study.

Participants

A prospective study of patients undergoing gastro-intestinal surgery for cancer under general anaesthesia was designed with a random allocation of postoperative analgesia to either PCEA or IVMO for a period of 48 hours after surgery. Inclusion criteria were: all patients undergoing elective surgery for gastro-intestinal cancer, with physical status I, II or III accordingly with American Society of Anesthesiologists Physical Status Classification System (ASA) and age greater than 18 years. Exclusion criteria were: emergency surgical interventions, contraindication to the epidural catheter placement, such as local skin infection, genetic or acquired coagulopathy, permanent neurologic sequels of the legs, prior lumbar spine surgery, patients who were not able to use the PCEA technique, patient's refusal and drugs allergies (opioids, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and local anaesthetics).

Outcomes

The main outcome of this study was postoperative pain intensity. The secondary outcomes were the time of bedside mobilization and walking, first postoperative flatus, first postoperative stool postoperative complications (respiratory, cardiovascular, digestive and surgical associated complications), length of ICU and hospital stay.

Clinical Scores

Numerical Rating Scale (NRS) is a good, quick and easy tool for the evaluation of pain intensity in post-surgery settings [16, 17]. This is a 11-point numeric scale ranging from '0' representing "no pain" to '10' representing 'unbearable pain" and the patients have to choose a whole number (0-10 integers) that best reflects the severity of pain [16-18].

Clinical and demographical measurements

The preoperative demographic and clinical data were collected from the medical charts: sex, age, body mass index (BMI), demographic area, pathology, chronic treatment, anaesthesiological risk. The intra-operative variables were recorded from the anaesthesia charts: total intraoperative opioid consumption and the surgery time defined as the time from the skin incision until anaesthesia was discontinued. Postoperative pain intensity was assessed immediately after arrival in the ICU, at 2, 8, 12 and 24 hours in the day of surgery and every 6 hours in the first day after surgery, for a period of 48 hours post-surgery. Pain severity was assessed using NRS by the anaesthesiologists and by the nurses from PI-ICU. The post-surgery variables were obtained from the medical charts. We evaluated the time of bedside mobilization defined as the number of days elapsed after surgery until the patients were able to mobilize bedside and walk in the ward, respectively; the time of the first postoperative flatus and of the first defecation. Also, we assessed postoperative complications such as respiratory, cardiovascular, digestive and surgical complications. The length of PI- ICU stay and respectively, the length of hospital stay, defined as days of PI-ICU admission and respectively, days of hospital admission, were also evaluated.

Study procedure

The patients were randomly assigned to either Patient Controlled-Epidural Analgesia Group (PCEA group) or to Intravenous Morphine Analgesia Group (IVMO group). An external clinical researcher was designed for the patient's allocation, using online software for randomization [19]. Before surgery, the researcher and the anaesthesiologists had explained and instructed the patients regarding the use of NRS for assessing the postoperative acute pain. Also, the patients included in the PCEA group were instructed about the patient-controlled analgesia technique. All the operations were performed by experienced surgeons following the local surgery protocol, under the same protocol of general inhalational anaesthesia, with neuromuscular block as standard. In the PCEA group, an epidural catheter was placed under standard monitoring, before induction of general anaesthesia. The epidural catheter was inserted at a level ranging from T8 to L2, depending on the surgery type and level of surgical incision. Intravascular and subarachnoid

placement of the catheter was ruled out with a test-dose of 3 ml of 1% lidocaine with adrenaline. Thirty minutes before the end of surgery the patients from the PCEA group received 5-7 mL of mixture of 0.3 % ropivacaine through the epidural catheter and patients from IVMO Group received 100 mg ketoprofen intravenously and 5 mg of morphine (IV). After surgery, all the patients were transferred to the PI-ICU. Postoperative analgesia consisted of ketoprofen 100 mg, IV every 8 hours and paracetamol 1 g IV every 6 hours for all the patients in both groups. In the PCEA group an epidural mixture of ropivacaine and fentanyl was administered as follows: during the first 24 hours after surgery, 0.3% ropivacaine and 2 µg/mL fentanyl which was lowered during the second day to 0.2% ropivacaine and 2 µg/mL fentanyl. The PCEA regimen was 5-7 ml/h basal rate and 5-7 mL bolus as request with a lock-out period of 20 min. The patients from IVMO group received IV continuous infusion of morphine: 2 mg/h as basal infusion and 3-5 mg IV bolus administration every time when required in order to obtain NRS below 3/10. Vital signs and NRS for pain assessment were registered accordingly to local protocol for all the patients. In the patients with epidural catheter the motor block was evaluated using the Modified Bromage Score until the catheter was removed (after 48 hours for colon and rectum surgery postoperatively and 72 hours for gastric surgery postoperatively). Sedation and respiratory depression were recorded for the patients who received intravenous morphine. Postoperative variables were assessed by nurses and anaesthesiologists involved in the study. Postoperative management of the patients and the treatment of post-surgery complications were performed by the anaesthesiologist and surgeon team, coordinated by the study researcher.

Statistical analyses

The sample size was calculated for a primary out-come of NRS after surgery, considering a difference of 1 between groups as being clinically meaningful. We estimated this for a comparison made with a t-test for independent samples, with 95% power, a level of significance of 0.05, a bidirectional p value, and equal sample sizes in the compared groups. We identified a standard deviation of 1.36 in a previous study as a base of variability in our calculations [20]. A sample size of 45 subjects per group was found, and we increased it to 50 to allow for loss to follow up. Categorical data were presented as counts and percentages. Continuous data were presented as mean and standard deviation for normally distributed data, or by median and quartiles for data not following the normal distribution, and graphically as box plots. The relation between two categorical variables was assessed with the chi-square test or the Fisher exact test. Comparison

between the two treatments groups were performed with the independent t-test, for normally distributed data and the Wilcoxon rank sum test for data not following the normal distribution. For all statistical tests we used a 0.05 level of significance and the two tailed p value. We used the R environment for statistical computing and graphics version 3.2.3 [21].

Results

Patient characteristics

A total of 127 consecutive patients were screened and 26 patients were excluded due to refusal of study enrolment (19 patients) and because they did not meet inclusion criteria (7 patients: 5 – NSAIDs allergies, 2 – previous spine surgery). Also, one patient from PCEA was excluded during the study because he died 24 hours after surgery secondary to hemorrhagic shock (Figure 1). One hundred and one patients fulfilled the inclusion criteria and consented to the study. Fifty-one patients were assigned to the PCEA group and 50 patients were enrolled to the IVMO group. One patient from PCEA group died because of postoperative complications before the end of study evaluation and was excluded from the analyses.

Fifty patients from each group completed the study (Figure 1). We did not identify significant statistically differences between the two groups regarding the age, gender, body mass index (BMI), associated pathology, chronic treatment and anaesthetic risk score ASA. The surgery time was significantly longer and intra-operative opioid consumption was significantly higher in the PCEA group as compared to the IVMO group (Table 1).

Postoperative pain scores

Patients receiving PCEA experienced less pain after surgery than IVMO group patients, especially during the first 8 hours after surgery. More specifically, post-operative NRS pain scores were lower in the PCEA group compared to IVMO group, as follows: immediately after awakening median (IQR) NRS 0 (0-3.75) versus 7 (5-8); $p < 0.001$, at 2 hours median (IQR) 0 (0-4) versus 6 (4-6.75); $p < 0.001$, at 8 hours median (IQR) 0 (0-1.75) versus 3 (1-4.75); $p < 0.001$, at 24 hours median (IQR) 0 (0-1.75) versus 1 (0-3); $p < 0.045$, at 30 hours median (IQR) 0 (0-1) versus 1 (0-2.75); $p = 0.017$ and at 48 hours the median (IQR) 0 (0-0) versus 0 (0-0); $p = 0.034$. Pain intensity was similar in the two groups at 12 ($p = 0.067$) and 36 ($p = 0.514$) hours after surgery (Figure 2, Table 2).

Indices of clinical postoperative outcome

The first postoperative flatus and first stool were noticed significantly earlier in the PCEA Group compared with IVMO Group ($p < 0.001$). The PCEA group also showed a significantly shorter time to
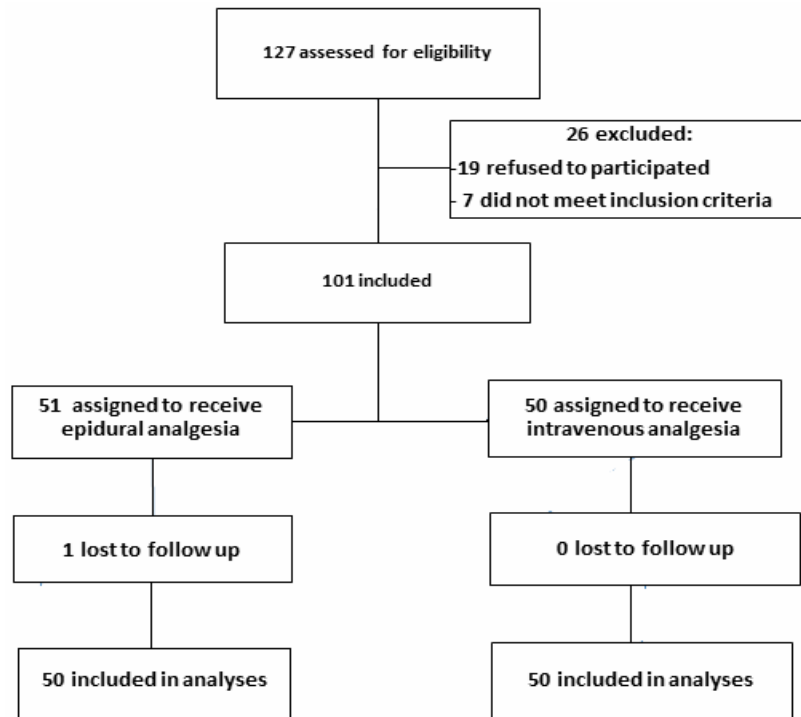
Fig. 1. Study flow diagram

Table 1. Clinical and demographic data

	IVMO group (n = 50)	PCEA group (n = 50)	p-value
Sex (M), n (%)	32 (64)	33 (66)	0.834
Age (years), mean (SD)	64.8 (9.3)	60.76 (11.13)	0.052
BMI (kg/m^2), mean (SD)	28.73 (4.75)	28.53 (5.13)	0.836
Associated pathology n (%)	37 (74)	39 (78)	0.64
Chronic treatment n (%)	34 (68)	26 (52)	0.102
Anaesthesiological risk (ASA) n (%)	19: 9 (18) 29: 37 (74) 39: 4 (8)	19: 5 (10) 29: 45 (90) 39: 0 (0)	0.053
Surgery time (min) median (IQR)	122.5 (110-143.75)	143.5 (130-180)	<0.001
Intraoperative opioid consumption (mg) median (IQR)	0.3 (0.2-0.3)	0.3 (0.26-0.35)	0.012

SD = standard deviation, IQR = quartiles, statistical significance if p-value <0.05

Table 2. Mean acute postoperative pain scores (NRS) at different times

After surgery time (hours)	IVMO group (n = 50) median (IQR)	PCEA group (n = 50) median (IQR)	p-value
0	7 (5-8)	0 (0-3.75)	<0.001
2	6 (4-6.75)	0 (0-4)	<0.001
8	3 (1-4.75)	0 (0-1.75)	<0.001
12	1 (0-3)	0 (0-2)	0.067
24	1 (0-3)	0 (0-1.75)	0.045
30	1 (0-2.75)	0 (0-1)	0.017
36	0 (0-2)	0 (0-1)	0.514
48	0 (0-0)	0 (0-0)	0.034

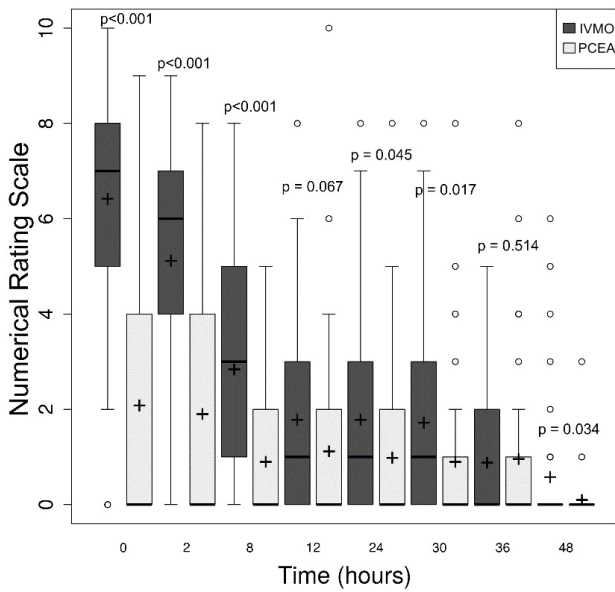IQR = quartiles; statistical significance if p-value <0.05

Fig. 2. Pain evolution in time. The + sign represents the mean, the circles the outliers, while the boxes the median and the interquartile range

bedside mobilization and walking as compared to the IVMO group (p <0.001) (Table 3).

Nausea and vomiting were significantly less frequent in the PCEA group (16.33%) IVMO Group (66%) in comparison with the IVMO group (66%) (p <0.001) (Table 3).

Surgery-related complications, such as enteral fistula and wound infections, were more frequent in the PCEA group than in the IVMO group but the difference was not statistically significant (p = 0.023) (Table 3 and 4). One patient from each group died from intra-abdominal infectious complications, after more than 48 hours post-surgery.

There were no significant differences regarding respiratory and cardiovascular complications between the groups. We did not identify serious adverse events related to the analgesia technique. The ICU length of stay was similar in the two groups of patients (p = 0.284). However, the length of hospital stay was signifi-cantly shorter in the PCEA group (9 ± 2 days) than in the IVMO group (12 ± 3 days) (p <0.001) (Table 3).

Discussion

Despite progress in understanding pain physio-pathology and improved analgesia techniques, pain remains the most common and frightening problem after surgery. Good pain relief after surgery is achieved in only 25% of the patients [9]. Moreover, it was de-monstrated that insufficient pain control is associated with negative postoperative outcomes such us delay in mobilization and bowel function recovery, cardio-vascular and respiratory complications and prolonged hospital stay [7, 8, 22, 23]. Consequently, an optimal pain control is mandatory after surgery. The studies

Table 3. Indices of clinical postoperative outcome

	IVMO group (n = 50)	PCEA group (n = 50)	p-value
Bedside mobilization (day after surgery), mean (SD)	2.26 (0.56)	1.74 (0.49)	<0.001
Walking (days after surgery), mean (SD)	3.78 (0.76)	3.06 (0.62)	<0.001
Time to first postoperative flatus (day), mean (SD)	3.14 (0.64)	2.1 (0.81)	<0.001
Time to defecation (day), mean (SD)	5.28 (0.67)	3.73 (0.88)	<0.001
Respiratory complications (bronchopneumonia) n (%)	1 (2)	3 (6.12)	0.362
Cardiovascular complications (bradycardia) n (%)	2 (4)	0 (0)	0.495
Nausea, vomiting n (%)	33 (66)	8 (16.33)	<0.001
Surgery-associated complications n (%)	2 (4)	9 (18.37)	0.023
PI-ICU length of stay, median (IQR)	4 (3-5)	5 (4-5)	0.284
Hospital length of stay, median (IQR)	12 (10-13.75)	9 (8-11)	<0.001

SD = standard deviation, IQR = quartiles, statistical significance if p-value <0.05

Table 4. Surgery-associated complications

Category	IVMO Group n = 2	PCEA Group n = 9	Total n = 11
Enteral fistula, n (%)	1 (2)	4 (8)	5 (5)
Incisional hernia, n (%)	1 (2)	1 (2)	2 (2)
Wound infections, n (%)	0	4 (8)	4 (4)

reported that epidural analgesia is superior to intravenous opioid analgesia in patients undergoing major thoracic, abdominal and pelvic surgery, including colorectal and gastric cancer surgery [3, 6, 7, 10, 11, 13, 15, 24]. PCA is an effective and safe method for pain relief after major, open, abdominal surgery [10-15, 24, 25]. PCEA analgesia is an important tool of anaesthetists assuring a good pain control, a decrease of several postoperative complications and thus improving safety and early well-being of the patients after surgery [25, 26]. Our finding of improved postoperative pain scores by PCEA is in concordance with previous reports in pelvis and abdominal surgery [3, 6, 7, 10, 11, 15, 24, 26, 27]. We noticed a significantly prolonged surgery time in the PCEA group. This may imply that the postoperative pain and analgesic needs in patients from the PCEA Group might have been expected to be higher, which was not the case in our study. On the contrary, we obtained better pain scores in the PCEA Group, further sustaining the superiority of epidural analgesia after major abdominal surgery. Inadequate pain relief may negatively affect postoperative mobilization. Our results showed that the PCEA is associated with early postoperative mobilization. Gastrointestinal paralysis is common after abdominal surgery and is caused by the inflammatory cascade secondary to the stress response to surgery [28]. Prolonged postoperative ileus is associated with prolonged hospitalization and increased costs [7, 23, 24, 29]. The time to first postoperative flatus and stool commonly defines the gastrointestinal function recovery post-surgery and is generally chosen as an outcome measure in clinical studies assessing rehabilitation after surgery [6, 29]. We demonstrated the effectiveness of epidural analgesia on the early returning of gastrointestinal transit after major open laparotomy. The majority of studies founded similar results. Guay et al. concluded that epidural analgesia accelerates the recovery of gastrointestinal transit after open abdominal surgery [6]. Also, Carli et al. founded that thoracic epidural analgesia shortens the duration of postoperative ileus after colorectal surgery as compared with PCA with IV morphine [30]. Moreover, Liu et al. founded that PCEA is associated with a quicker return of bowel activity as compared with PC with IV morphine [31]. As opposed to this, Rimaitis et al. could not find an improvement in bowel function after colorectal cancer when epidural analgesia was compared with intravenous opioid administration [32]. The incidence of postoperative nausea and vomiting varies between 20-30% and up to 80% in high-risk patients, following surgery under general inhalational anaesthesia [32, 34]. We demonstrated a notably increased incidence of nausea and vomiting associated with IVMO. However, Rimaitis et al. did not find any difference regarding nausea and vomiting after colorectal cancer surgery when comparing epidural analgesia with systemic opioid analgesia [3].

Patients undergoing major abdominal and thoracic surgery are at an increased risk of various types of complications but studies suggest that epidural analgesia can decrease the incidence of respiratory, cardiovascular, infectious and thromboembolic complications [35-37]. Epidural analgesia may ameliorate tissue oxygenation and pulmonary function by decreasing pain, sedation scores and improved diaphragmatic function [38, 39]. Interestingly, in our study, we noticed an increased incidence of respiratory complications (bronchopneumonia) in patients who received epidural analgesia, although not statistically significant. This may be secondary to the low incidence of respiratory complications in our study.

Epidural analgesia is usually associated with cardiovascular complications such as hypotension but we did not identify this complication in the PCEA group [20, 35]. We found a greater incidence of fistula in patients who received epidural analgesia but the difference was not statistically significant due to the very low incidence. Controversies still exist about this topic. Some studies have found an increased incidence of anastomotic leakage in patients receiving epidural analgesia after abdominal surgery; it was suggested that fluid administration for the treatment of hypotension secondary to epidural analgesia may be responsible for sutures edema and secondary dehiscence [3, 6]. In our study the administration of extra fluid was not necessary because hypotension was not present in our patients. However, other studies reported that there is no difference in the incidence of this complication after abdominal surgery regardless of the analgesia type [40].

The length of PI-ICU and hospital stay may reflect the quality of postoperative recovery. Discharge from PI-ICU and from hospital may be influenced by many factors including medical decisions, expectance of patients, and socio-economic factors [41]. In our study, the analgesic modality did not influence the length of stay in the PI-ICU but we found a significant decrease of the length of the hospital stay for the patients receiving PCEA. The return of gastrointestinal function represents an important objective after abdominal surgery and a prerequisite with respect to hospital discharge [7]. The shorter length of hospital stay in the PCEA group can be explained by the faster returning of the intestinal transit and possibly with faster mobilization. In a study of 100 patients with colorectal surgery, Rimaitis et al. could not find any influence of epidural analgesia on the length of the hospital stay [3].

Some tendency of increased surgical complications and especially enteral fistulas with enteral fluid leakage may raise some questions about the safety of the epi-

dural technique but other factors may be responsible for this, such as the longer surgery time in this group. The results of our study reveal some advantages but also risks associated with PCEA. Consequently, PCEA has to be used balancing benefits and potential side-effects and complications on a case by case basis. One limitation of our study is that we compared two different and unblended analgesia techniques which may have caused some bias in data collection. The patient-controlled epidural technique was compared with a continuous morphine infusion analgesia; morphine given also as PCA would have been a more fair comparison, but we compared PCEA with the standard analgesia technique used in our hospital.

In *conclusion*, we report our results of two series of patients whose postoperative pain was treated by either PCEA or IVMO after digestive tract cancer surgery. The severity of acute pain was significantly reduced for the first 48 hours after surgery in patients who benefited from PCEA. Also, PCEA was associated with fewer nausea and vomiting episodes, earlier gastrointestinal function recovery, postoperative mobilization and reduced length of hospital stay. Surgery-associated complications were more frequent after PCEA.

Conflict of interest

Nothing to declare

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