Original Article

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# Pain perception after colorectal surgery: A propensity score matched prospective cohort study

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**Summary** **The purpose of this prospective cohort study was to compare multimodal pain management and pain perception after open *vs.* laparoscopic colorectal surgery within enhanced recovery care. Pain scores at rest and at mobilization were prospectively assessed in consecutive patients using Visual Analog Scales (VAS 0-10) and consumption of different analgesics was recorded daily until 96 hours postoperatively. Uni- and multivariate risk factors for pain peaks (≥ 4/10) were identified by logistic regression and compared between two propensity score matched groups (open *vs.* laparoscopic). 156 open and 176 laparoscopic procedures were included. Mean VAS scores were consistently < 3 until 96 hours at rest and at mobilization. Patients operated by laparoscopy experienced more pain peaks (≥ 4) within 24 hours ($p < 0.05$), while patients operated by open approach experienced more pain peaks (≥ 4) during mobilization at 72 hours ($p < 0.05$). Independent risk factors for insufficient pain control (≥ 4) within 24 hours from surgery were duration of the procedure (OR 3.37, 95%CI 2.03-5.59), emergency surgery (OR 3.01, 95%CI 1.72-5.31), wound infiltration (OR 3.23, 95%CI 0.97-10.70), age < 70 years (OR 2.03, 95% CI 1.18-3.48) and ASA I-II score (OR 2.06, 95% CI 1.19-3.56). The perioperative adding of lidocaine ± ketamine to opioids did not improve postoperative pain perception nor decrease morphine equivalents. In conclusion, overall pain scores were low after colorectal surgery. However, pain peaks remained a concern early after minimally invasive surgery and after epidural removal for open surgery. Multimodal strategies were not superior to opioids alone.**

***Keywords:*** Enhanced recovery, pain management, laparoscopy

## 1. Introduction

Minimally invasive approach for colorectal surgery promotes functional recovery and reduces length of stay without compromising oncological outcome (*1-3*). Enhanced recovery after surgery (ERAS) pathways advocate minimally invasive surgery to decrease surgical stress, morbidity, length of stay and costs (*4*). ERAS care protocols including multimodal pain management strategies aim to facilitate recovery by an opioid-sparing attitude to avoid opioid-related side effects (*5*). Epidurals have been shown to be efficient after open surgery (*6*), and modern pain management strategies including intravenous lidocaine, wound infiltration or transverse abdominis plane (TAP) block emerge as alternatives for minimally invasive surgery (*7*). Most studies comparing open and laparoscopic surgery stated less pain after minimally invasive surgery (*8,9*), but only scarce data reporting on pain scores and actual analgesics consumption is available.

The aims of the present study were to compare pain management strategies in patients undergoing open and minimally invasive colorectal surgical procedures, to analyse pain perception in both settings and to

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identify risk factors for insufficient pain control in the postoperative period.

## 2. Materials and Methods

### 2.1. *Study design*

This is a prospective cohort study including all consecutive adult patients (≥ 18 years) who underwent elective or emergent colorectal surgery in the Department of Visceral Surgery at Lausanne University Hospital (CHUV), Switzerland, between January 2014 and April 2015. Perioperative confusion or language disorders represented exclusion criteria. For patients operated several times, only the first procedure was retained for the present analysis.

The prospective pain database was part of a quality improvement project and informed consent was waived by the Institutional Review Board. The study was carried out in line with the STROBE statement (*10*) and registered under *www.researchregistry.com* (UIN researchregistry 2292).

### 2.2. *Surgical details*

Colorectal surgical procedures included open and minimally invasive surgeries. Converted procedures were accounted for in the minimally invasive group in an *intention-to-treat* analysis. Rectum resection, proctocolectomy and total colectomy were regrouped as extended surgery, in contrast to segmental colectomy, stoma procedures (*i.e*. ileostomy closure and Hartmann reversal) and small bowel surgery. Small bowel surgery regrouped segmental resections of the terminal ileum and different procedures related to Crohn's disease. Further were recorded the setting (elective *vs*. emergency) and the duration of the procedure. All patients were treated within a comprehensive Institutional enhanced recovery (ERAS) protocol (*11*) with standardized care maps.

### 2.3. *Pain management*

Type and amount of administered analgesics was recorded in a prospectively maintained database. Intraoperatively, fentanyl or sufentanyl were administered in most patients followed by paracetamol, metamizole and ibuprofen (according to ERAS caremap) at the end of the procedure unless contraindicated. Perioperative pain was managed as follows: Epidural analgesia (EDA) was applied for open procedures unless contraindicated (anticoagulant therapy, sepsis or patient refusal) and maintained for 48 or 72 hours according to ERAS protocol and type of surgery with a relay medication comprising oxycodone (oxycontin® and oxynorm®). EDA was inserted at thoracic level (Th 8-10) before induction, and iterative boluses of bupivacaïne 0.25% or 0.5% were administered during the intervention, followed by a solution containing bupivacaine 0.0625%, fentanyl 2 ug/mL and adrenaline 2 ug/mL for the postoperative period. For minimally invasive procedures and open procedures with EDA contraindication, iv lidocaine (1.5 mg/kg for induction, then 2 mg/kg/h until recovery room) (*12*) and iv ketamine (0.25 mg/kg bolus followed by 0.25 mg/kg/h, maximum 1mg/kg) (*13*) were applied unless contraindicated (lidocaine: hepatic failure or lidocaine intolerance, ketamine: age > 70 years, ischemic heart disease or psychotic pathology). As an alternative, ultrasound-guided transversus abdominis plane (TAP) blocks and surgical wound infiltration using bupivacaine 0.25% or naropin 0.25% were applied upon anaesthesiologists' discretion.

Postoperative use of opioids (morphine, oxycodone, buprenorphine, tramadol) were recorded from recovery room (RR) until 96 hours postoperatively.

Standardized conversion factors were used to calculate morphine equivalents (*14*): *iv* or *sc* morphine (3×), oral oxycodone (2×), oral buprenorphine (75×), oral tramadol (0.1×). Total morphine equivalents were recorded for the following time periods: 24 h (including RR until the end of the first postoperative day), 48 h, 72 h and 96 h.

### 2.4. *Data collection*

Data regarding different demographic (age, gender, body mass index (BMI) and American Society of Anaesthesiologists (ASA) score), surgery- and pain management-related items as specified above was entered in a computerized database, which was prospectively maintained by the anaesthesiology care team (MC and CB) and a dedicated study nurse. Visual analogue scales (VAS) were used by two clinical nurses to assess pain at rest and at mobilization (0: no pain-10: maximal pain) at the following time points: RR, arrival patient's room, 2 h, 6 h, 12 h, 24 h, 36 h, 48 h, 72 h and 96 h. Clinical nurses were blinded to pain management protocols and/or actual pain medication consumption of the patient. Insufficient pain control was defined as VAS score of ≥ 4 (*15*).

### 2.5. *Outcomes/study endpoints*

The primary endpoint was postoperative pain perception as measured by VAS. After propensity score matching, patients experiencing insufficient pain control (VAS ≥ 4) were compared with patients with sufficient pain control (VAS < 4), and independent risk factors for insufficient pain control within 24 hours from surgery were identified by multivariate logistic regression.

### 2.6. *Statistical analysis*

Anonymized data analysis was performed using the Stata Software v. 14.2 (StataCorp, College Station, TX, USA). Categorical data was summarized as raw

**Table 1. Demographic, surgical and anaesthesia-related items**

| Items | All patients ($n$ = 332) | Open ($n$ = 156) | Minimal invasive ($n$ = 176) | $P$ |
|---|---|---|---|---|
| Age (years) (median, IQR) | 64, 53-75 | 68, 56-78 | 62, 51-72 | 0.004 |
| Gender | | | | 0.3 |
| Female (%) | 159 (48) | 70 (45) | 89 (51) | |
| Male (%) | 173 (52) | 86 (55) | 87 (49) | |
| BMI (kg/m$^2$) (median, IQR) | 25, 21-28 | 24, 21-29 | 25, 21-28 | 0.581 |
| ASA group | | | | < 0.001 |
| I-II (%) | 214 (65) | 86 (55) | 128 (73) | |
| III-IV (%) | 118 (36) | 70 (45) | 48 (27) | |
| Type of surgery (%) | | | | < 0.001 |
| Left colectomy | 73 (22) | 14 (9) | 59 (34) | |
| Right colectomy | 60 (18) | 22 (14) | 38 (22) | |
| Rectum resection | 44 (13) | 14 (9) | 30 (17) | |
| Stoma procedure | 74 (22) | 69 (44) | 5 (3) | |
| Small bowel | 81 (25) | 37 (24) | 44 (25) | |
| Extended (%) | 51 (15) | 15 (10) | 36 (21) | 0.006 |
| Emergency (%) | 100 (30) | 48 (31) | 52 (30) | 0.808 |
| Duration of surgery (min) (median, IQR) | 175, 113-243 | 163, 98-224 | 181, 124-261 | 0.016 |
| Duration of procedure (min) (median, IQR) | 220, 152-298 | 205, 140-276 | 235, 163-306 | 0.014 |
| Epidural (%) | 72 (22) | 57 (37) | 15 (9) | < 0.001 |
| Lidocaine (%) | 114 (34) | 17 (11) | 97 (55) | < 0.001 |
| TAP Block (%) | 27 (8) | 20 (13) | 7 (4) | 0.003 |
| Infiltration (%) | 38 (11) | 25 (16) | 13 (7) | 0.014 |

MI – Body Mass Index, ASA – American Society of Anesthesiologists, TAP – Transversus Abdominis Plane. Bold characters indicate significant values ($p < 0.05$).

frequencies and group percentages. Differences in categorical data distributions between groups were assessed using the chi-squared test, or the Fisher's exact test in case of insufficient sample size. Continuous data distribution was analyzed using Normal QQ-Plots. Gaussian data were summarized as mean and standard deviation (SD), while non-Gaussian data were summarized as median, interquartile range (IQR) and range. Differences in means between two groups for Gaussian data were assessed using the Student's *t*-test. Differences in distribution between two groups for non-Gaussian data were assessed using the Wilcoxon-Mann-Whitney ranksum test.

As the two study groups (open *vs*. laparoscopic) differed on several major characteristics, propensity score matching was performed. The propensity score was derived using a probit regression model with the following cofactors: age, gender, ASA score, surgery type (right colectomy, left colectomy, stoma procedure, rectum resection, small bowel) and setting (elective *vs*. emergency). Matching of the laparoscopic group to the open group was performed to the nearest neighbour with replacement. Figure 1 shows the Kernel plot of the propensity score. Univariate and multivariate logistic regression was used to assess the association between several factors and binary outcomes. A $p$-value < 0.05 was considered statistically significant.

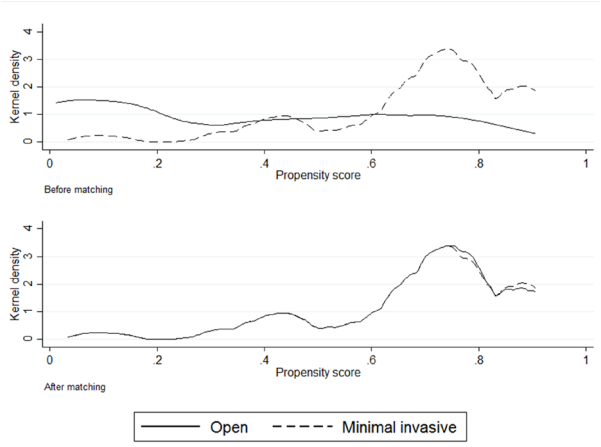


**Figure 1. Propensity score matching.** Kernel density plot with comparison of the two groups (open *vs*. minimally invasive) before (above) and after (below) propensity score matching.

## 3. Results

### 3.1. *Patients*

Three hundred and thirty-two consecutive patients underwent colorectal procedures during the study period. One hundred and fifty-six (47%) were performed by an open approach, while 176 (53%) were performed by laparoscopy. Nineteen (6%) laparoscopic procedures were converted to open approach and remained assigned to minimal invasive procedures according to the *intention-to-treat* principle. Demographic, surgery-related and pain management-related items before propensity score matching are displayed in Table 1.

### 3.2. *Pain scores*

Propensity score matching of the two groups (open *vs*. laparoscopic) led to a dropout of 125 patients

(38%) (Figure 1). Mean VAS scores for pain were < 3 for both comparative groups throughout the entire postoperative observation period, at rest and at mobilization. Mean VAS scores for minimal-invasively operated patients were significantly higher than for open procedures until 48 hours, at rest and mobilization ($p < 0.05$), while patients undergoing open procedures had significantly higher mean VAS scores at 72 and 96 hours at mobilization ($p < 0.05$) (Figure 2). More patients operated by minimally invasive surgery had insufficient pain control (VAS≥4) at 24 hours (19% *vs*. 5%, $p < 0.05$), while more patients in the open group experienced pain peaks (≥ 4) during mobilization at 72-96 hours (45% *vs*. 22%, $p < 0.05$) (Figure 3). Among the minimally invasive procedures, mean scores were similar throughout the observed time span when comparing patients receiving opioids only, patients receiving opioids and lidocaine and patients receiving opioids, lidocaine and ketamine, at rest and at mobilization (Figure 4). Morphine equivalent consumption was similar when comparing these 3 groups (Figure 4c).

3.3. *Risk factors for insufficient pain control (VAS ≥ 4) within 24 hours*

Independent risk factors for insufficient pain control (≥ 4) were duration of procedure (Odds Ratio (OR) 3.37, 95% Confidence Interval (CI) 2.03-5.59), emergency surgery (OR 3.01, 95%CI 1.72-5.31), wound infiltration (OR 3.23, 95%CI 0.97-10.70), age < 70 years (OR 2.03, 95% CI 1.18-3.48) and ASA I-II score (OR 2.06, 95% CI 1.19-3.56) (Figure 5).

## 4. Discussion

Despite overall low pain scores throughout the observed time span, insufficient pain control (VAS ≥ 4) represented a problem in the early postoperative phase in patients operated by minimal invasive approach, while open procedures were associated with pain peaks (≥ 4) at 72-96 hours. This coincides with retrieval of epidurals within ERAS care and hence insufficient management of pain relay. Further, multimodal pain management concepts did not appear to be beneficial in

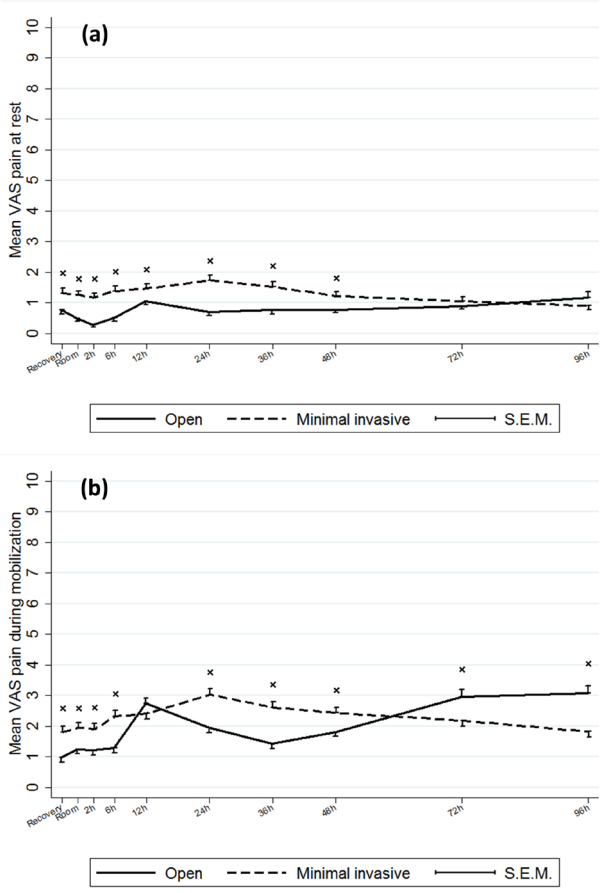


**Figure 2. Evolution of pain scores over time (a) at rest, (b) at mobilization.** Evolution of mean pain scores over time by comparing open and minimally invasive procedures at rest and at mobilization. × indicates statistical significance ($p < 0.05$). VAS – Visual Analog Scale, S.E.M. – Standard Error of the Mean, Recovery – Recovery room, Room – Arrival patient's room, h – hours.

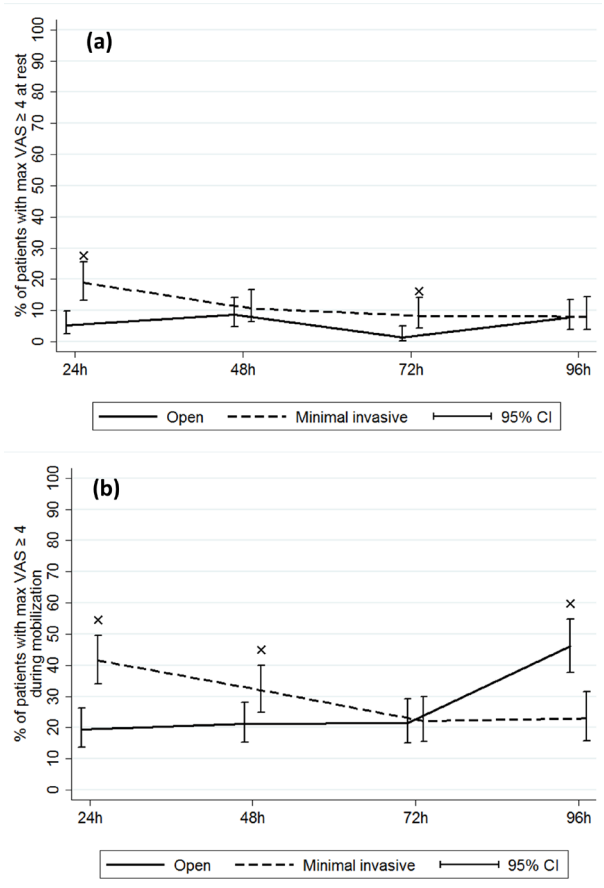


**Figure 3. Patients with insufficient pain control (VAS ≥ 4) (a) at rest, (b) at mobilization.** Percentage of patients experiencing pain peaks (VAS ≥ 4) over time by comparing open and minimal invasive procedures at rest and at mobilization. × indicates statistical significance ($p < 0.05$). VAS – Visual Analog Scale, 95% CI – 95% Confidence Interval

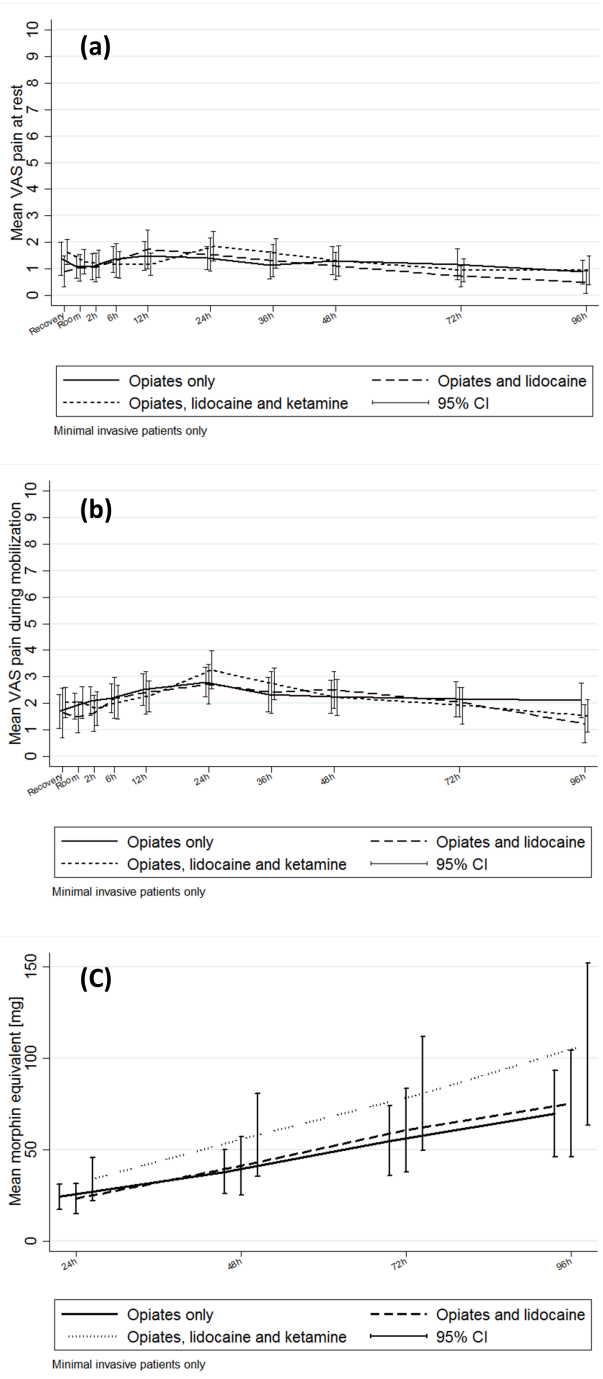


**Figure 4. Pain scores and morphine requirements after laparoscopy (a) at rest, (b) at mobilization.** Evolution of mean pain scores over time by comparing minimally invasively operated patients receiving perioperative opiates, opiates and lidocaine or opiates, lidocaine and ketamine. **(c) Morphine requirements.** Mean morphine equivalent consumption over time by comparing minimally invasively operated patients receiving perioperative opiates, opiates and lidocaine or opiates, lidocaine and ketamine. VAS – Visual Analog Scale, 95% CI – 95% Confidence Interval, Recovery – Recovery room, Room – Arrival patient's room, h - hours

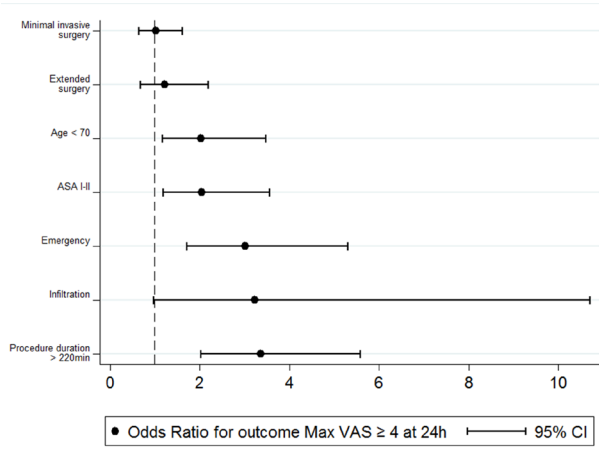


**Figure 5. Independent risk factors for pain peaks (VAS ≥ 4) at 24 hours.** Multivariable analysis of univariate risk factors for pain peaks (VAS ≥ 4) at 24 hours postoperatively. ASA – American Society of Anaesthesiologists, min – minutes, VAS – Visual Analog Scale, 95% CI – 95% Confidence Interval, Infiltration – perioperative wound infiltration

the present cohort.

Adequate pain control after major abdominal surgery is the major concern of patients before surgery and directly related to their opinion on caregivers (*16,17*). Pain management is one important item of ERAS in colorectal surgery (*18*). Mid-thoracic epidural anaesthesia (EDA) is advocated for open procedures (*6*), while the evidence is less clear for minimal invasive surgery. EDA was associated with controversial results regarding postoperative morbidity (*19,20*) and slowed down recovery after laparoscopic surgery without evident benefits in recent randomized trials (*21,22*). Instead, numerous alternatives for peri- and postoperative pain management have been suggested for minimal invasive surgery, and the combination of different strategies in a multimodal concept has been advocated (*7,23*). However, despite this diversity, pain remains undermanaged even within enhanced recovery protocols (*24*), and a recent meta-analysis did not show any superiority of pain management within ERAS care regarding pain scores, length of stay and functional recovery (*25*).

Multimodal pain management strategies including non-opioid analgesia (*i.e.* acetaminophen and non-steroidal anti-inflammatory drugs), local infiltration or TAP blocks and intravenous lidocaine aim to decrease opioid consumption. This is important within enhanced recovery protocols, since opioids have been shown to impede prompt functional recovery by favoring postoperative nausea and vomiting, ileus and respiratory depression (*24*). However, despite a consensus for opioid-sparing management, multimodal treatment is not standardized, as shown by a recent large quality improvement survey (*26*), and opioids in different forms and combinations including patient controlled analgesia remain a mainstay of postoperative pain management (*27*).

In the present analysis, all patients were treated within an enhanced recovery protocol, and thus opioid-sparing therapy was part of perioperative care. EDA, intravenous lidocaine, TAP block and wound infiltration were used in different combinations according to

anaesthesiologist's discretion. Overall pain scores were low in the present cohort and compare well to previous reports on pain perception (*26,27*). However, pain scores were higher after minimally invasive surgery compared to open surgery, with up to 45% of patients experiencing pain peaks at mobilization during the first postoperative day. This contrasts with the repeatedly proven efficiency of minimal invasive surgery in decreasing postoperative pain (*8,28,29*). Two explanations might account for this discrepancy. First, EDA was efficient after open surgery in the present cohort, as pictured by a low number of patients with significant pain during the first 2, respectively 3 postoperative days with EDA in place. However, a significant increase of insufficient pain control (VAS ≥ 4) at 72 hours indicates suboptimal management of pain relay. Since pain relay medication was standardized according to guidelines within ERAS care maps, reasons for this insufficient backup strategy might be the lack of proper surveillance of pain at EDA retrieval (*30*). Second, pain management after minimally invasive surgery was suboptimal and wound infiltration was even retained as independent risk factor for insufficient pain control within 24 hours in the present analysis (Figure 5). Park found in a recent randomized controlled trial that wound infiltration was less effective than TAP block in decreasing postoperative opioid consumption (*31*). A recent meta-analysis showed that novel infiltration techniques such as wound catheter, TAP block, and intraperitoneal instillation led to a decrease in pain scores (*32*). TAP block was rarely applied in the present cohort, but might represent an alternative to conventional wound infiltration (*5,33*). Another reason for insufficient pain relief by wound infiltration might be a lack of proper follow-up with consequent insufficient administration of backup pain medication. Taken together, the main reasons for higher pain levels in laparoscopic patients in the first 24 hours are an underestimation of actual pain after minimally invasive surgery and an overrating of multimodal pain strategies. The latter aspect was clarified by a subgroup analysis of 3 different pain strategies in laparoscopic patients as shown in the following paragraph.

In the present study, patients consumed the same amount of morphine equivalents postoperatively, regardless of adding on lidocaine and ketamine (Figure 4c). Intravenous lidocaine has been shown to reduce pain scores, intra- and postoperative analgesic requirements and to promote functional recovery (*34*). However, a recent Cochrane review questioned the efficiency of intravenous lidocaine and particularly its impact on pain scores, especially in the early postoperative phase, similar to the findings of the present cohort (*12*). Ketamine as a powerful blocker of nociceptive and inflammatory pain transmission proved efficiency in decreasing postoperative pain in recent trials (*35,36*). However, the optimal dose needs to be determined by further clinical trials (*37*).

The present study showed thus inconclusive results using the applied multimodal pathway, and opioids remained a mainstay treatment even within an enhanced recovery pathway.

Several limitations need to be addressed. The study cohort was heterogeneous and modest in size, and no data on chronic pain issues was available for this analysis. Further, intraoperative pain management strategies were not standardized. However, perioperative care pathway was standardized (ERAS care) and applied with high compliance and in line with current recommendations. Furthermore, consecutive non-selected patients ("all-comers") were reported limiting selection bias and reflecting a "real-world" situation.

In conclusion, overall, pain was well controlled in a non-selected cohort of colorectal surgical patients, but pain peaks remained a major concern despite close adherence to ERAS guidelines including modern pain strategies. Multimodal pain concepts could not decrease morphine consumption in the present cohort. Efforts should focus on providing evidence-based standardized care protocols regarding pain management in minimally invasive surgery and for patients after open surgeries without or after removal of epidural catheter.

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