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Journal: Annals of surgery

Year: 2015 Apr

Issue: 261

Volume: 4

Pages: 648-53

DOI: 10.1097/SLA.0000000000000838

Ann Surg. 2015 Apr;261(4):648-53. doi: 10.1097/SLA.0000000000000838

Randomized clinical trial on Epidural *versus* Patient-controlled Analgesia for laparoscopic colorectal surgery within an enhanced recovery pathway

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Disclosures: No funding or conflict of interest

Key words: Epidural, colorectal surgery, laparoscopy, enhanced recovery.

Abbreviations: EDA – epidural analgesia, PCA – patient-controlled analgesia, ERAS® - enhanced recovery after surgery.

Statistics Abstract 250 words, Manuscript 2876 words, 5 inserts (1 Table, 4 Figures), references 33, Online material.

Running title: Epidurals for laparoscopic colorectal surgery

Miniabstract

128 patients undergoing elective laparoscopic colorectal resections were randomized to epidural (EDA) *versus* patient-controlled opioid-based analgesia (PCA). Medical recovery and high dependency stay were longer in EDA patients but hospital stay was similar. 30% of EDA patients needed transitory vasopressor treatment. There was no difference in postoperative pain scores.

Abstract

Objective: To compare epidural analgesia (EDA) to patient-controlled opioid-based analgesia (PCA) in patients undergoing laparoscopic colorectal surgery.

Summary background data: EDA is mainstay of multimodal pain management within enhanced recovery pathways (ERAS®). For laparoscopic colorectal resections, the benefit of epidurals remains debated. Some consider EDA as useful, while others perceive epidurals as unnecessary or even deleterious.

Methods: A total of 128 patients undergoing elective laparoscopic colorectal resections were enrolled in a randomized clinical trial comparing EDA *versus* PCA. Primary endpoint was medical recovery. Overall complications, hospital stay, perioperative vasopressor requirements, and postoperative pain scores were secondary outcome measures. Analysis was performed according to the intention-to-treat principle.

Results: Final analysis included 65 EDA patients and 57 PCA patients. Both groups were similar regarding baseline characteristics. Medical recovery required a median of 5 days (IQR 3;7.5) in patients with EDA and 4 days (IQR 3;6) in the PCA group (P= 0.082). PCA patients had significantly less overall complications (19 (33%) *vs.* 35 (54%); P= 0.029) but a similar hospital stay (5 days (IQR 4;8) *vs.* 7 days (IQR 4.5;12); P= 0.434). Significantly more EDA patients needed vasopressor treatment perioperatively (90 *vs.* 74%, P= 0.018), the day of surgery (27 *vs.* 4%, P< 0.001), and on postoperative day 1 (29 *vs.* 4%, P< 0.001), while no difference in postoperative pain scores was noted.

Conclusions: Epidurals appear to slow down recovery after laparoscopic colorectal resections without adding obvious benefits. EDA can therefore not be recommended as part of ERAS® pathways in laparoscopic colorectal surgery.

Registration number: NCT00508300 (http://www.clinicaltrials.gov).

Introduction

Enhanced recovery (ERAS®) pathways have proven to reduce significantly complications, postoperative length of stay and costs after colorectal surgery[1-3]. The multimodal treatment bundle contains about 20 individual items to attenuate surgical stress response and thus to improve recovery[4, 5]. High compliance with the recommended pathway was strongly correlated with favorable clinical outcomes[6]. Previous randomized trials identified optimized fluid management, minimal invasive surgery, and epidural analgesia (EDA) as key items of ERAS® concepts[2, 7].

The benefit of EDA however remains controversial especially when combined with minimal invasive surgery[8-12]. Expert laparoscopic centers have reported excellent outcomes without use of EDA[13-16]. Moreover, a recent prospective study suggested even slower recovery if EDA was employed after laparoscopic colectomy[16]. Furthermore, novel strategies for pain management rendered promising results[17, 18]. This obvious mismatch of recommendations, available evidence and current practice can only be reconciled with more prospective data.

The aim of this prospective randomized trial was therefore to test the hypothesis that EDA improves recovery after laparoscopic colorectal resections when compared with patient-controlled opioid-based analgesia (PCA).

Methods

Study design

A single center, prospective parallel-group superiority study with balanced randomization (1:1) was performed to compare the clinical effects of EDA vs. morphine-based PCA (EvA trial) in patients undergoing laparoscopic colorectal resections.

The institutional ethics committee approved the study (# 166/07), and all patients provided written informed consent before enrollment. The trial was registered under clinicaltrial.gov (trial # NCT00508300) before patient recruitment was started.

Patients and setting

All patients undergoing elective laparoscopic colorectal surgery at the University Hospital of Lausanne (CHUV), a tertiary referral center in Switzerland, were assessed for eligibility. Exclusion criteria included age below 18 years, inability to provide informed consent, and medical contraindication for EDA according to institutional guidelines[19, 20].

Enrolment and randomization

Patients were assessed for eligibility at outpatient consultation by the operating surgeon once the indication for surgery was established. Patients received oral and written information on the study before written consent was obtained.

Patients were randomly assigned by a dedicated study nurse using an online randomization program (Randomizer, Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria; URL: http://www.randomizer.at).

For medical and logistic reasons, blinding was not performed, as it appeared neither feasible nor realistic for this present study.

Interventions, anesthesia and pain strategy

Patients were randomized the day prior to surgery to allow for appropriate information on the anesthesia technique.

In the EDA group, epidural catheter was inserted at thoracic level (Th 8-10) before induction of anesthesia. A bolus of 5ml of bupivacaine 0.5% was started as soon as the epidural catheter was in place, and a continuous perfusion of bupivacaine 0.5% at 5 ml/h was initiated until the end of surgical procedure.

In both groups, induction of anesthesia was performed with propofol 1-2 mg/kg, fentanyl 2-3 µg/kg and cisatracurium (0.15-0.2 mg/kg) for muscle paralysis. After tracheal intubation, maintenance of anesthesia was performed with sevoflurane in a mixed oxygen/air fresh gaz, and cisatracurium as needed. Analgesia was assured by the bupivacaine solution in the epidural group and by fentanyl as needed in the PCA group.

At the end of surgery, a solution of bupivacaine 0.1%, fentanyl 2 µg/ml and adrenaline 2 µg/ml was initiated in the epidural group at a rate of 6-10 ml/h (target: VAS<4) with bolus of 3 ml of the solution allowed every 40 minutes (Patient Controlled Epidural Analgesia)[20]. In the PCA group, iv PCA with morphine 1 mg/ml, with bolus of 1 ml at every 5 minutes and a locked of 40 mg/4 hours was inserted. All patients received paracetamol 4x1g/day and metamizole 4x500mg/day as baseline analgesic treatment unless contraindicated. Pain assessment was done twice daily at rest and on mobilization or coughing by a dedicated institutional analgesia team. Failure of either technique (VAS persistently >3) was recorded by the analgesia team and rescue pain relief was administered if necessary (morphine

subcutaneously 0.1 mg/kg maximum 6x/d or buprenorphine sublingual 0.2-0.4 mg maximum 3x/d). Both interventions were planned to be discontinued on postoperative day (POD) 2 following international recommendations[21, 22]. EDA and PCA could be continued if the analgesia team judged that a prolonged application was beneficial for the patient. The day of discontinuation was documented.

During anesthesia and for the following postoperative days, maintenance of blood pressure >60mmHg or diuresis > 0.5 ml/kg/h was aimed for, first by administration of volume, Ringer-lactate 500 ml or 500 ml colloids (Voluven®). Noradrenaline at a dose of 0-10µg/h was used as vasopressor if blood pressure was not corrected by volume administration. Substitution of blood products was done if hematocrit < 25%, or at the discretion of the anesthetist in charge of the procedure.

Perioperative care pathway

Enhanced recovery was introduced in our institution in 2006 using a protocol which was adapted after a first randomized trial from our group[2]. After the recruitment for the present EvA trial had started, it was decided in June 2011 to adapt the pathway according to the in meantime published ERAS® recommendations[21] and to reinforce application of the pathway by a structured implementation program. Our ERAS® pathway complies with the most recent ERAS® guidelines[4, 5] and was reported along with clinical and economic outcomes in 2013[3].

Outcomes/study endpoints

Outcomes were analyzed according to the intention-to-treat principle. Medical recovery was chosen as primary endpoint and was defined as meeting *all* of the three following criteria: (I) sufficient *pain control* by oral analgesics, (II) *fully mobilized* or at least comparable with preoperative status, and (III) tolerance of oral food which

was defined as ≥2/3 of normal meal (hospital portion)[23]. Medical recovery was considered as more specific outcome parameter than hospital stay, as social and logistic factors are not interfering[24, 25]. Secondary endpoints were postoperative hospital stay and length of stay in the high dependency unit. Postoperative 30-day morbidity was graded by use of the Dindo-Clavien classification[26]; major complications were defined as complication grade 3-5. Use of perioperative vasopressor treatment was documented for every patient until 4 days after surgery. Pain relief was assessed by use of a visual analogue scale (VAS: 0-10) with a baseline value the day before surgery; routine evaluation twice daily started the evening of the surgery day and was continued until POD 4.

Demographic information (age, gender, body mass index, Charlson co-morbidity index [27], and the American Society of Anesthesiologists (ASA) grade) as well as pertinent surgical information (indication, type of surgery, conversion rate, operation time, estimated blood loss) were all predefined. Outcomes were assessed by dedicated study nurses who entered data in a specifically designed computerized database.

Subgroup analyses

EDA group happened to have more overall and major complications that could not be attributed to the allocated analgesic interventions as suggested by previous studies[1, 8]. Major complications prolong medical recovery and hospital stay and entail thus an obvious bias in favor of the PCA group[28]. For this reason, a *post hoc* subgroup analysis excluding patients with major complications was additionally performed.

Primary and secondary endpoints depend not only on the allocated analgesic intervention but also heavily on the global perioperative care strategy[3, 6, 15, 25]. With

the adaptation of the institutional enhanced recovery pathway to ERAS® guidelines during the study period, it was decided to analyze patients within the full ERAS® pathway separately as a subgroup.

The main purpose of these two additional analyses was to assess for potential bias of those influencing factors in order to filter the intrinsic effect of EDA *vs.* PCA on medical recovery and length of stay.

Statistics

Sample size computation based on a mean reduction of medical recovery time of 1.5±2.25 days by use of EDA[2, 8, 29]. Adopting a power of 90%, a two-sided type I error (α) of 0.05 and an anticipated drop-out rate of 10%, the calculated sample size was 64 patients per group.

Descriptive statistics were reported as absolute or relative frequencies for categorical variables and as median (range or interquartile range - IQR) or mean (± SD) for continuous variables as appropriate. Fisher's exact test was employed to analyze categorical variables. Student's *t* test and Mann-Whitney U test were used to compare normal and non-normal continuous variables, respectively.

Data was analyzed by use of the Statistical Package for the Social Sciences (SPSS 21.0, Inc., Chicago, IL USA) and Prism 6.03 (GraphPad® Software**,** Inc**.** 2236 Avenida de la Playa La Jolla, CA 92037 USA).

The trial was conducted and the results are presented according to the CONSORT guidelines [30].

Results

Between February 10th 2010 and October 15th 2013, 266 consecutive patients were assessed for eligibility. 138 patients did not meet the inclusion criteria or refused to participate. The remaining 128 patients were randomized to receive either EDA (n=67) or PCA (n=61) as allocated treatment. Two EDA patients and four PCA patients dropped out after randomization and no patient was lost to follow-up. Final analysis compared therefore 65 EDA patients with 57 patients with PCA (**Figure 1**).

Both comparative groups were similar in terms of pertinent demographic parameters and surgical aspects as displayed in **Table 1**.

Technical success rates and duration of EDA and PCA treatment

Eight EDA were judged non-functioning and removed consistently on POD 0 (n=2) and POD 1 (n=6). Overall failure rate was thus 12%. EDA and PCA were discontinued according to the study protocol on POD 2 in 47 (72%) and 55 (96%) of patients, respectively (P=0.005). EDA was left in place in twelve of the remaining 18 patients until POD 3 and in 3 patients until POD 4. EDA was removed on POD 5, 6, and 7 in one patient each. Treatment time was therefore significant longer in the EDA group (2.33±1.17 days vs. 1.65±0.66 days, P<0.001). The urinary catheter was removed on POD1 according to the protocol in 44 EDA patients (68%) and 28 patients (49%) of the PCA group (P=0.044). Urinary retention requiring reinsertion of the Foley catheter occurred in 11 (17%) EDA and 7 (12%) PCA patients, respectively (P=0.611).

Medical recovery, complications and length of stay

Medical recovery required a median of 5 (IQR 3;7.5) days in the EDA group and 4 (IQR 3;6) days in patients with PCA (P=0.082). The 3 mandatory preconditions

for medical recovery were analyzed separately as well. *Full mobilization* and *oral pain control* were achieved in both groups after a median of one and two days, respectively. The last requirement met was *sufficient oral intake* after a median of 4 (IQR 2;6) days in EDA patients vs. 3 (IQR 2;4) days in the PCA group (*P*=0.114). Median stay at the high dependency unit was 1 (IQR 1;2.5) day *vs.* 1 (IQR 0;1) day for EDA and PCA group, respectively (*P*=0.213).

Thirty-five out of 65 EDA patients and 19 of 57 PCA patients developed postoperative complications (*P*=0.029). The detailed grading of severity and a list of individual complications are provided as **online appendix (A, B)**.
Hospital stay was 7 (IQR 4.5;12) days for patients with EDA and 5 (IQR 4;8) days in the PCA group (*P*=0.434). Three patients from the EDA group were readmitted after discharge (PCA: 0; *P*=0.247).

Perioperative fluid management, vasopressor requirements and perioperative pain

Perioperative fluid management was similar between the groups. EDA and PCA patients received 1604±962ml *vs.* 1575±851ml balanced crystalloids (*P*=0.861) and 817±429ml *vs.* 664±294ml colloids (*P*=0.051). Weight gain on POD1 compared to preoperatively was 1.45±0.32kg in the EDA group and 2.28±0.56kg in the PCA group (*P*=0.191). Significantly more patients with EDA needed vasopressor treatment during surgery and until POD 1, while no single patient required vasopressors after POD 3 (**Figure 2**). Pain was overall well controlled by both modalities and no significant differences were noted at any time point (**Figure 3**).

Subgroup analysis

A tendency to more major complications was observed in the EDA group (15 vs. 5, *P*=0.213). As major complications have a significant impact on primary and

secondary outcome measures, a *post hoc* analysis was performed excluding patients with major complications. Fifty EDA patients were compared with 52 PCA patients. Medical recovery and high dependency stay were significantly shorter in the PCA group (P=0.050 and P=0.010), respectively, while hospital stay was similar (**Figure 4**). The ERAS® protocol was modified during the study period and the first 26 consecutive patients were not treated within the complete pathway as mentioned in the methods section. The second subgroup analysis included therefore only patients with full ERAS® pathway and having no major complication. Again, the PCA group had significantly shorter medical recovery (P=0.019) and stay in the high dependency unit (P<0.001) compared with patients having EDA (**online appendix C**).

Discussion

This present study shows that epidurals rather *impede recovery* after laparoscopic colorectal resections without delivering superior pain relief or other benefits. A major drawback identified was transitory hemodynamic instability requiring vasopressor treatment in a significant proportion of EDA patients. So the hypothesis was not verified and *enhanced recovery* pathways should not recommend the use of epidurals for laparoscopic colorectal resections.

Main finding of the present study was a trend for longer medical recovery in EDA patients that became significant in the analyzed subgroups. One explanation might be the transitory hemodynamic instability due to sympathetic blockage in patients with EDA as confirmed by our reports and by others[8, 31, 32]. This also explains the observed longer stay in the high dependency unit. Overall length of stay was not significantly changed. Hospital stay relies on various factors, which may modify to a certain extent the effect of perioperative care and different analgesic regimens in particular[24]. Logistic and economic resources differ between countries and institutions and socio-cultural differences cannot be neglected; comparison of hospital stay can therefore be misleading. Medical recovery is the more specific endpoint that tends to occur about 2 days before discharge as shown by our group and by others[25]. Actually, only Levy et al. reported significantly shorter hospital stay in patients with PCA[16], while several other randomized studies comparing EDA *vs*. PCA for laparoscopic colorectal resections did not find any difference[9-11]. Small patient samples however limit those trials. Levy reported further extremely short postoperative stays of 2.7 days only in patients with PCA[16]. Proven benefits of EDA for major and especially open procedures (e.g. superior pain relief, reduction of cardiopulmonary complications, faster bowel recovery)[8] are probably minor and

irrelevant for minimal-invasive procedures with very short stays[14, 16]; this being said, minor drawbacks like pruritus and especially transitory hypotension become problematic and may increase stay at a high dependency unit and slow down recovery as shown in the present study and observed by others [8, 9, 16, 31, 32].

Colon and rectal surgery differ considerably in terms of technique, surgical trauma and early outcomes. The most recent ERAS® recommendations were therefore issued separately for the two entities[4, 5]. While the available data from the present study and previous ones appears to be sufficient to abandon EDA for laparoscopic *colon* resections, evidence is insufficient to for *rectal* resections as the collectives in the respective randomized trials are too small[9, 10, 16].

EDA failed in 12% of the patients in our study and was removed in 28% patients after anticipated POD 2. These “deviations” disfavor the EDA group on the one hand but reflect clinical realities on the other hand[8, 33]. Further, epidural analgesia can be performed at different thoracic levels, and combination and concentration of medications vary considerably. The results of our study can therefore not be uncritically generalized to other settings. However, the institutional technique applied in the present study and the reported success rates were in line with recent publications and might therefore still be of interest for many institutions [8, 20, 33]. Several interesting alternatives for perioperative pain management have been suggested meanwhile and favorable results have been reported in particular for laparoscopic transverse abdominus plane blocks, wound infiltration, systemic steroids and systemic lidocaine [17, 18].

Several limitations need to be addressed. Both groups were well matched by means of randomization. However, EDA patients experienced more overall and major complications than patients with PCA. These were mainly unrelated

complications entailing a potential bias disfavoring the EDA group. Therefore, patients with major complications were excluded in a *post hoc* subgroup analysis because of an obvious impact on outcome. Postoperative pain management is embedded in a global care scheme and the impact of EDA or other modalities on recovery, pain relief and length of stay needs to be interpreted in this context. As mentioned in the methods section, the enhanced recovery pathway was adapted during the study period. In order to avoid the bias of various perioperative care pathways and unbalanced major complications, a second subgroup analysis was performed with all consecutive patients within the full ERAS® pathway and without major complications. The interesting point was that both subgroup analyses confirmed the results of the main analysis according to the intention-to-treat principle, and resulted in significantly reduced times for medical recovery and high dependency stay in PCA patients.

In conclusion, the present study suggests that epidurals decrease blood pressure in about one third of patients who therefore require transitory hemodynamic support and a prolonged stay in a high dependency unit. Thus, EDA impedes recovery after laparoscopic colorectal resections without providing superior pain relief or reduced complications when compared with morphine-based PCA. Hospital stay remains unchanged. EDA should therefore not be a mandatory item of ERAS® pathways in laparoscopic surgery. The most recent ERAS® recommendations already considered the new evidence[4, 5], and modern alternatives to morphine-based regimens deserve future investigations.

Acknowledgements: Special thanks to our dedicated ERAS nurse Valérie Addor and to our study nurse Giustina Mariotti who were responsible for data collection and management. We acknowledge further all junior and senior members of the anesthesia and surgical team who were implicated in patients' recruitment and follow-up.

Conflict of interest: The authors declare no conflict of interest.

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Table 1 Demographic and surgical details comparing patients with epidural *vs.* patient-controlled analgesia.

	EDA N=65	**PCA N=57**	***P***
Age (years)	63.1±15.1	61.2±17.8	0.529
Male gender (%)	37 (57%)	34 (60%)	0.854
BMI (kg/m^2)	25.9±5.1	25.5±4.2	0.980
ASA I/II/III	6/49/10	7/41/9	0.853
Charlson	3.2±3.3	3.2±3.8	0.822
Malignant/benign disease	43/22	37/20	0.518
Type of surgery			0.904
Left/sigmoid colectomy	30 (46%)	27 (47%)	
Right/ileocecal resection	18 (28%)	13 (23%)	
Rectum/(sub)total	10 (15%)	11 (19%)	
Other	7 (11%)	6 (11%)	
Conversion, No. of (%)	12 (19%)	8 (14%)	0.625
OR time (min)	239±107	235±104	0.832
Estimated blood loss (ml)	232±217	169 ±152	0.095

Mean values ± standard deviation or no. of patients (%).

EDA – epidural analgesia, PCA – patient-controlled opioid-based analgesia, BMI – body mass index, ASA - American Society of Anesthetists, OR time – operation room time.

Online appendix A Postoperative complications by severity.

	EDA **N=65**	**PCA** **N=57**	***P***
No. of patients (%) with			
Any complication	35 (54%)	19 (33%)	0.029
Grade I	4	4	
Grade II	16	10	
Grade III a/b	2 / 9	0 / 2	
Grade IV a/b	0 / 2	3 / 0	
Grade V (mortality)	2	0	
Major complications (≥III)	15 (23%)	5 (9%)	0.213
Reoperation	9 (14%)	4 (7%)	0.254

Postoperative complications were graded by severity according to the Dindo-Clavien classification [26]. Complications grade III-V were summarized as major morbidity.

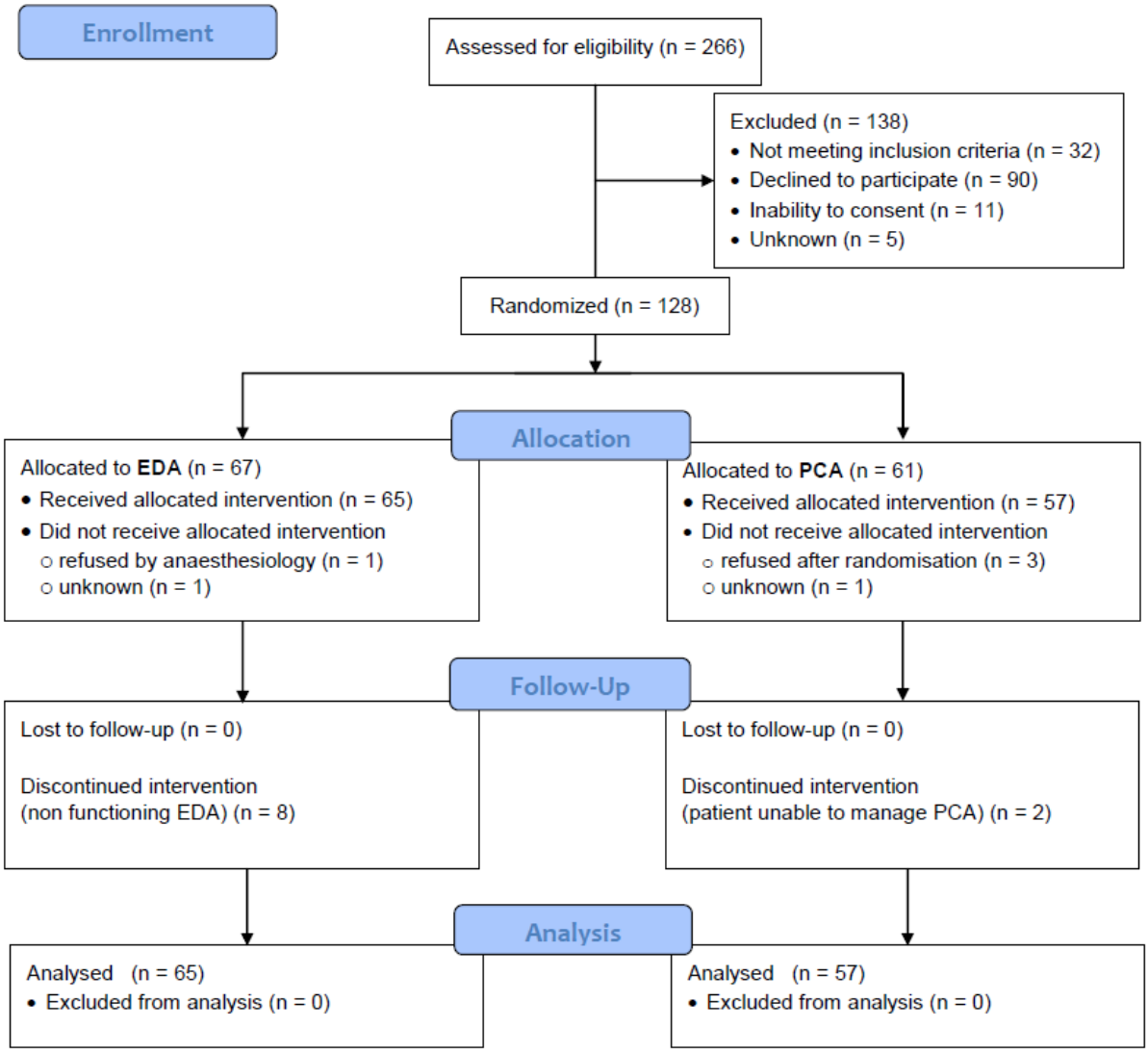
EDA – epidural analgesia, PCA – patient-controlled opioid-based analgesia**.**

Online appendix B List of surgical and medical complications.

	EDA N=65	PCA N=57
Surgical	21	10
Anastomotic leak	4	1
Bleeding	0	1
Surgical site infection	2	0
Ileus	13	5
Other	2	3
Medical	14	9
Pulmonary	1	1
Cardiac	1	0
Renal	3	2
Urinary retention	11	7
Other	3	5

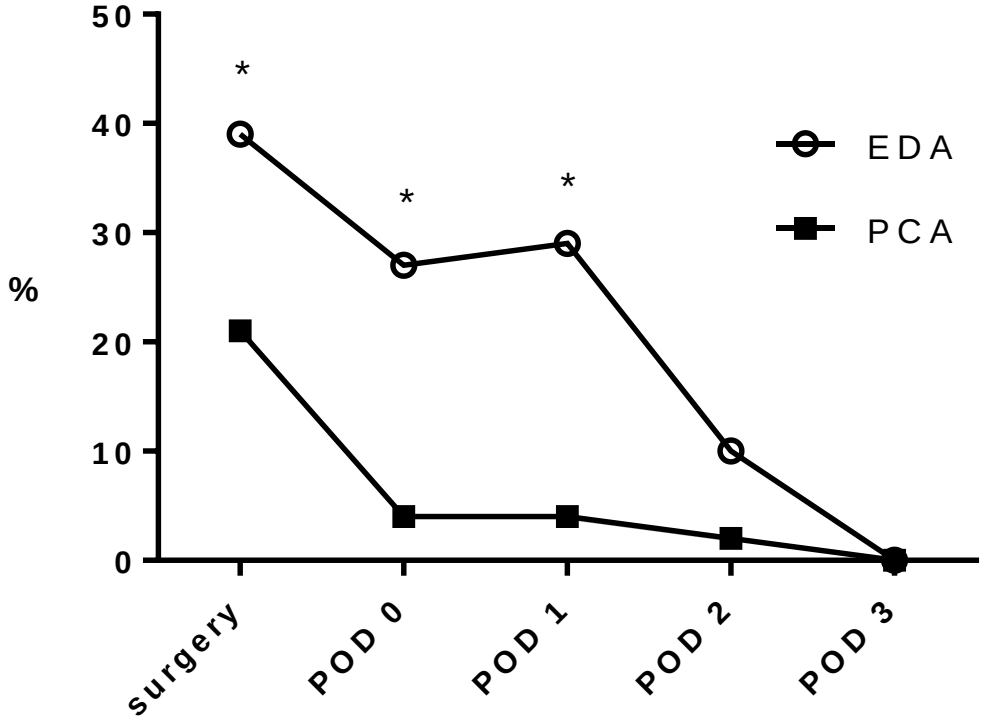
The most frequent postoperative complications are summarized for patients with epidural analgesia (EDA) and patient-controlled opioid-based analgesia (PCA).

Figure 1 Study flow chart.



CONSORT diagram. Randomized controlled trial comparing epidural analgesia (EDA) *versus* patient-controlled opioid-based analgesia (PCA) for laparoscopic colorectal surgery.

Figure 2 Perioperative vasopressor requirements.

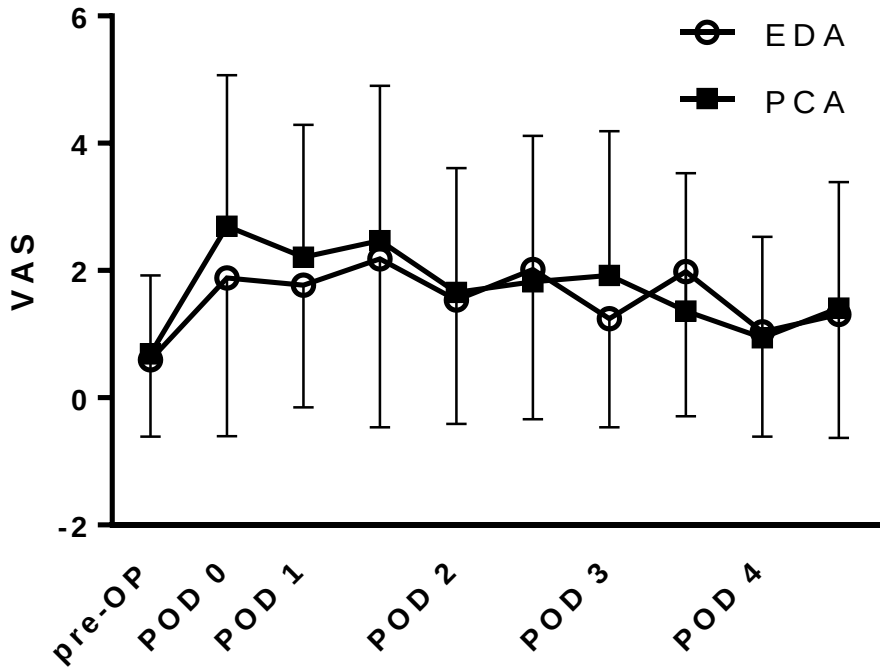


Percentage of patients in the EDA (white circles) and PCA group (black rectangles), respectively, requiring vasopressor treatment during and after laparoscopic colorectal surgery.

EDA – epidural analgesia, PCA – patient-controlled opioid-based analgesia**.**

* indicates statistical significance (P<0.05).

Figure 3 Perioperative pain scores.



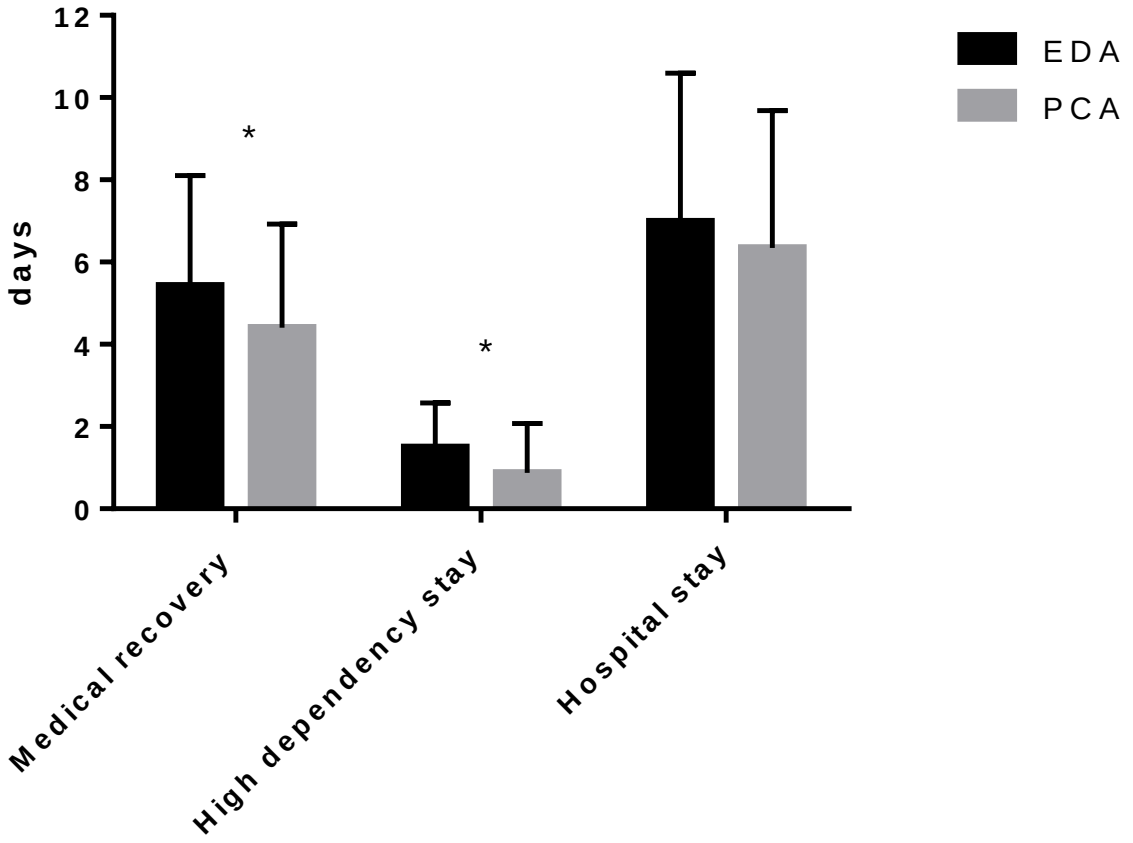
Pain was assessed by use of a visual analogue scale (VAS) from 0-10 before surgery, the evening after surgery and twice daily thereafter until postoperative day (POD) 4 for patients with EDA (white circles) and PCA (black rectangles), respectively.

EDA – epidural analgesia, PCA – patient-controlled opioid-based analgesia**.**

* indicates statistical significance (P<0.05).

Data expressed as mean±SD.

Figure 4 Subgroup analysis excluding patients with major complications.



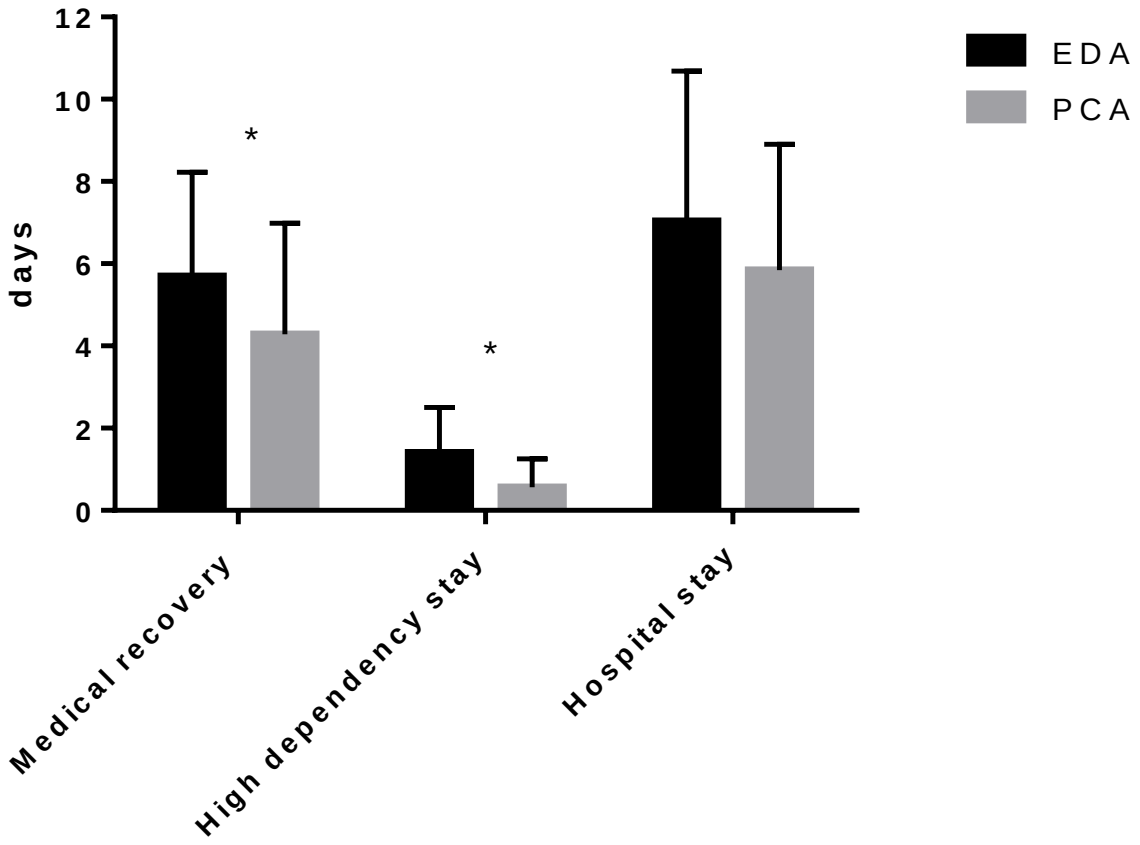
A *Post hoc* subgroup analysis included all patients without major complications: 50 EDA patients *vs.* 52 PCA patients were compared with regards to medical recovery, and length of stay in a high dependency unit and in hospital, respectively.

EDA – epidural analgesia, PCA – patient-controlled opioid-based analgesia**.**

* indicates statistical significance (P<0.05).

Data expressed as mean±SD.

Online appendix C Subgroup analysis: patients with full ERAS® pathway and having no major complications.



Patients within the full ERAS® pathway and without major complications (40 EDA *vs.* 40 PCA) were compared concerning medical recovery, high dependency and hospital stay.

EDA – epidural analgesia, PCA – patient-controlled opioid-based analgesia**.**

* indicates statistical significance (P<0.05).

Data expressed as mean±SD.