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Clinical Study Protocol

Randomized Controlled Trial of Epidural versus Patient-controlled Intravenous Analgesia for Postoperative Pain Control after Laparoscopic Gastrectomy

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Although epidural analgesia (EDA) is considered standard postoperative analgesia for open gastrectomy, it has been unclear whether EDA has benefits in laparoscopic gastrectomy (LG) because postoperative pain after a laparoscopic procedure is significantly reduced. We are conducting a two-arm, single-center, prospective randomized non-inferiority trial to evaluate the postoperative pain relief of patient-controlled intravenous analgesia (PCIA) compared to EDA. A total of 132 patients undergoing LG will be randomized to EDA and PCIA groups (n = 64 each) for postoperative pain control. The primary endpoint is postoperative pain at 24 h after surgery. This study will clarify the optimal pain management after LG.

Key words: laparoscopic gastrectomy, epidural analgesia, patient-controlled intravenous analgesia, pain relief

Enhanced recovery after surgery (ERAS) protocols are composed of multimodal perioperative care, and they have proven valuable in reducing complications, shortening the postoperative length of hospital stays, and costs [1,2]. Epidural analgesia (EDA) is considered an indispensable procedure after open abdominal surgery in ERAS protocols since EDA has been shown to provide superior pain relief and decreased the rate of postoperative complications after abdominal surgery [3,4].

In recent years, laparoscopic gastrectomy for gastric cancer has become a standard procedure. It has been reported that the laparoscopic approach is associated with a reduction in postoperative pain and opioid consumption, lower morbidity, faster recovery and shorter postoperative length of hospital stays compared to open surgery [5-8]. Although EDA is an excellent pain relief modality, the role of EDA in laparoscopic surgery is unclear. Several clinical studies showed that the use of EDA slowed down the recovery after laparoscopic colorectal surgery [9-11]. Moreover, the use of EDA requires an invasive and specialized technique for catheter placement and has the potential to cause severe complications such as epidural hematoma or abscess [12]. It was also reported that one-third of EDA might not function adequately because of catheter misplacement or deviation or an inadequate dose [13].

In postoperative pain control, multimodal analgesia has been recommended because it provides excellent pain relief with minimized adverse events related to analgesia [14]. Patient-controlled intravenous analgesia (PCIA) plays an important role in multimodal analgesia concepts, and is a safe, less-invasive and effective anal-

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gesia using a peripheral vein.

We are conducting a prospective, randomized controlled trial to evaluate the pain relief efficacy of PCIA compared to that of EDA after laparoscopic gastrectomy (LG).

Methods

Study design. This is a two-arm, single-center, prospective randomized non-inferiority trial to evaluate the postoperative pain relief provided by PCIA compared to that of EDA following laparoscopic gastrectomy. This trial is being conducted at the Okayama University Hospital. A total of 132 eligible patients undergoing laparoscopic gastrectomy have been randomized to the EDA and PCIA groups (n = 64 each) for postoperative pain control (Fig. 1).

Ethical Consideration

This study is being conducted in compliance with the principles of the Declaration of Helsinki, and this protocol has been approved by the Institutional Review Board of the Okayama University Hospital (No. 1705-004). This trial is registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000027643).

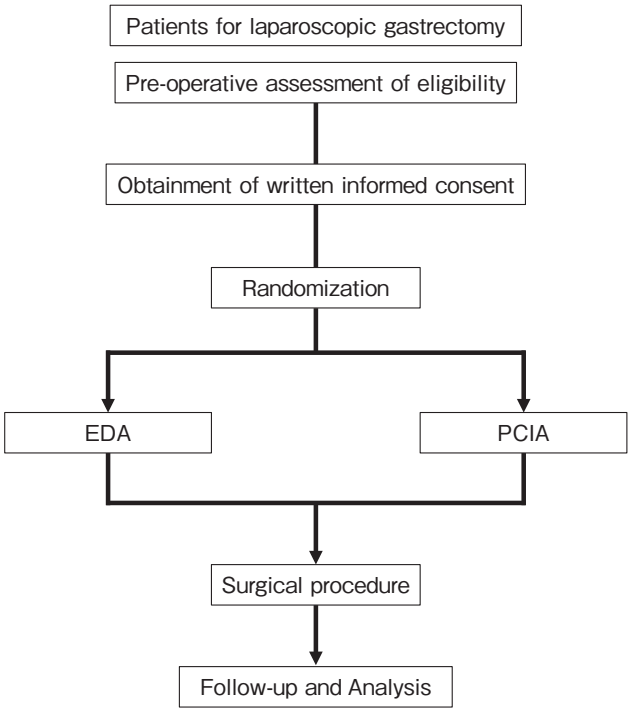

Fig. 1 Trial flowchart. EDA, epidural analgesia; PCIA, patient-controlled intravenous analgesia.

Endpoints

The primary endpoint is postoperative pain at rest 24 h after surgery, which is assessed using a numerical rating scale (NRS) [15]. The patients' NRS pain scores are graded from 0 (no pain) to 10 (imaginable worst pain), and self-reported by the patients and recorded by the nursing staff. Secondary endpoints include the achievement day of discharge criteria, the length of the postoperative hospital stay, postoperative complications, postoperative pain on days 2, 3, 4 after surgery, additional doses of analgesics, adverse events related to analgesia, and the patient's satisfaction. The achievement day of discharge criteria is used to assess the recovery after surgery; this is considered a more specific outcome parameter than the length of postoperative hospital stays because social and logistic factors are not interfering. The criteria are defined as eating a normal diet, no complaints of pain, full mobilization comparable to that of the patient's preoperative status, and no complications for 24 h. All patients will be followed-up until a regular checkup at approx. 1 month after surgery.

Postoperative complications are graded using the Clavien-Dindo classification system [16]. The postoperative pain is assessed using a NRS at rest and movement, and routine evaluation twice daily starts the evening of the surgery day and is continued until postoperative day (POD) 4. The adverse events related to analgesia include sedation, postoperative nausea and vomiting, hypotension, and urinary retention. The patient's satisfaction is assessed using a 5-point Likert scale from very dissatisfied (1) to very satisfied (5). Safety related to the interventions is also being evaluated.

Eligibility Criteria

All of the patients who meet the eligibility criteria based on the inclusion and exclusion criteria, which are listed in Table 1, are being enrolled in this study from July 2017 to June 2019.

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria
(1) Patients who are scheduled to undergo LG including TG, DG, and PG
(2) Aged 20–80 years
(3) Patients who can provide written informed consent
Exclusion criteria
(1) ASA-PS ≥ 4
(2) Patients undergoing anticoagulant therapy
(3) Medical contraindication for EDA
(4) Abnormal anatomy of the spinal column
(5) Neoadjuvant chemotherapy
(6) Immunodeficiency
(7) Palliative surgery
(8) Emergency surgery
(9) Otherwise judged by the investigator as unsuitable for enrollment

ASA-PS, American Society of Anesthesiologists-Physical Status; DG, distal gastrectomy; EDA, epidural analgesia; LG, laparoscopic gastrectomy; PG, proximal gastrectomy; TG, total gastrectomy.

Randomization

After the patients' fulfillment of the eligibility criteria was confirmed, the patients receive verbal and written information about the study, and their written consent is obtained. After registration in the Data Center, each patient is randomly assigned to the EDA or PCIA group with the use of a computer-generated list. Allocation is performed by a stratified permuted block method. For medical and logistic reasons, blinding is not performed because it is not realistic for this study. The stratified factors are age, sex, American Society of Anesthesiologists (ASA) Physical Status classification, and surgical procedure.

Treatment Methods

Intervention. In all patients, the clinical path after LG in our institution will be used in order to standardize the perioperative treatment in two groups. In the EDA group, an epidural catheter is inserted at the thoracic level (Th8-10) before the induction of anesthesia using loss of resistance. The epidural space is confirmed by performing an absorption test and a 3-ml bolus of 1% lidocaine with epinephrine (dilution 1 : 100,000). A 5-ml bolus of 0.2% ropivacaine is started as soon as the epidural catheter is inserted, and a continuous infusion or bolus injection of 0.2% ropivacaine with fentanyl (1 μg/ml) is performed until the end of surgery depending on the anesthesiologist's decision based on the patient's vital signs.

In both the EDA and PCIA groups, the induction of general anesthesia is performed with propofol (target controlled infusion [TCI] 2-4 μg/ml), remifentanil (0.2-0.5 μg/kg/min), and rocuronium bromide (0.5-0.6 mg/kg) for muscle paralysis. Anesthesia is maintained with the total intravenous venous anesthesia (TIVA) technique using a propofol TCI and remifentanil infusion. Rocuronium bromide is used for muscle relaxation as needed. All cases will be extubated in the operating room if possible.

Postoperatively, EDA is maintained at a rate of 2 to 6 ml/h (target: NRS < 4) using an epidural patient-controlled analgesia (PCA) pump. A bolus of 3 ml is allowed every 15 min. In the PCIA group, intravenous fentanyl (10 μg/ml) is administered at 0-1 ml/h at the end of the surgery. A bolus of 1 ml is allowed every 15 min up to the maximal dose of 40 μg/h (target: NRS < 4).

Both interventions are planned to be discontinued on POD 2, but both can be continued until POD 7 if the analgesia team judges that a prolonged application is beneficial for the patient. All patients received celecoxib (200 mg × 2/day, oral) from POD 3 as baseline analgesia unless contraindicated. The pain score is assessed twice daily at rest and on mobilization or coughing by nursing staff. Additional analgesics including loxoprofen sodium hydrate (60 mg, oral), pentazocine (15 mg, intravenous), flurbiprofen axetil (50 mg, intravenous), and acetaminophen (1,000 mg, intravenous) are administered when the patient complains of pain (NRS > 3).

Adverse events. The adverse events related to PCIA and to EDA including sedation, postoperative nausea and vomiting, hypotension, and urinary retention are monitored during the patient's hospital stay. Moreover, severe complications such as epidural hematoma or abscess related to EDA are also monitored.

Statistical Consideration

Sample size. Based on retrospective data from our institution regarding laparoscopic gastrectomy for gastric cancer, the NRS scores (mean ± standard deviation) at rest 24 h after surgery were 2.11 ± 1.9 and 2.36 ± 1.8 in the EDA group and the PCIA group, respectively. In this study, a similar population is included (according to the eligibility criteria) compared

to the retrospective data. Therefore, the standard deviation of NRS scores in this study is estimated to be smaller than that of the retrospective data. We anticipate a 10% lower standard deviation compared to the retrospective data, and ensuring that at least 80% power with a one-sided alpha of 5% and a non-inferiority margin of 1 in terms of NRS score, 62 patients per each group are needed. To compensate for potential exclusions or withdrawals, we will include a total of 132 patients.

Statistical analysis. Student's T-test is used to analyze continuous variables. P-values < 0.05 are considered significant. The statistical analyses will be performed by using JMP 11.2 (SAS Institute, Cary, NC, USA).

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