Laparoscopic Gastrectomy Using External Oblique Intercostal Block Versus Wound Infiltration: A Trial Protocol

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Objective: A novel external oblique intercostal block (EOIB) might have analgesic effects on T6–10 and be indicated for laparoscopic gastrectomy. However, EOIB effects on postoperative pain are unknown. We aim to generate evidence to support such EOIB application. We will compare the efficacy of EOIB and wound infiltration (WI) in a single-center, single-blind, randomized controlled trial.
Methods: We will assess plasma concentrations of levobupivacaine after EOIB, its pharmacokinetics, and the pinprick test in patients randomly assigned to receive EOIB or WI before laparoscopic or robot-assisted gastric distal or total gastrectomy. The EOIB and WI will start after general anesthesia induction with 20 and 40 mL of 0.25% levobupivacaine per side, respectively, before skin closure. The outcomes will be numeric rating scale (NRS) scores at 12 h postoperatively (primary) and postoperative NRS scores at 2, 24, and 48 h; fentanyl application; QoR-15 scores on postoperative days 1, 2, and 7; and World Health Organization Disability Assessment Schedule 2.0 scores at 3 months (secondary).
Conclusions: We hope that our study will provide evidence to support EOIB application in laparoscopic surgery. Plasma concentrations will help determine levobupivacaine pharmacokinetics, which if similar to conventional nerve blocks, will indicate EOIB's safety.

Key words: external oblique intercostal block, laparoscopic gastrectomy, wound infiltration

INTRODUCTION

Analgesic methods for upper abdominal surgery have changed over time. Epidural analgesia has been conventionally considered the gold standard for perioperative analgesia; however, its use is decreasing owing to enhanced recovery after surgery and the postoperative use of antithrombotic therapy [1, 2]. Although regional analgesia is an important approach to reduce postoperative pain, there are no analgesic guidelines specific to laparoscopic gastrectomy for malignant gastric tumor, and specific peripheral nerve blocks are not strongly recommended in the enhanced recovery after surgery (ERAS) protocol [3]. Subcostal transverse abdominal plane block, considered effective for upper abdominal surgery, has limited analgesic spread to T6–7 because the semilunar line prevents local anesthetic diffusion [4, 5].

External oblique intercostal block (EOIB), a nerve block reported by Elsharkawy in 2021 [6], has an efficacy range of T6–10 and is indicated for upper abdominal procedures. The results of a cadaver study have revealed that EOIB could be effective in the anterior and lateral cutaneous branches [6]. This block can easily identify landmarks and be performed under ultrasound guidance due to its superficial puncture depth compared with conventional techniques (such as rectus sheath and transverse abdominal plane blocks) [6, 7]. Furthermore, needle and catheter insertion sites are distant from the surgical site. However, the effects of EOIB have not been prospectively investigated. Additionally, plasma concentrations and the pharmacokinetics of local anesthetics have not yet been determined, although high plasma concentrations of local anesthetics are likely owing to their spread into the intercostal muscles [8].

The duration of analgesia provided by wound infiltration (WI) is limited, and its effects are controversial [9, 10]. Nonetheless, WI is a simple and inexpensive approach that provides adequate somatic blockade [11] and is recommended in the guidelines of one postoperative analgesic protocol [12].

Therefore, we designed a randomized controlled trial to compare the efficacy of EOIB and WI. We will also measure plasma concentrations of levobupivacaine after EOIB and investigate its pharmacokinetics.

MATERIALS AND METHODS

Aim

This proposed randomized controlled trial will determine the safety and effectiveness of EOIB compared with WI, as well as the plasma concentrations and pharmacokinetics of levobupivacaine after EOIB.

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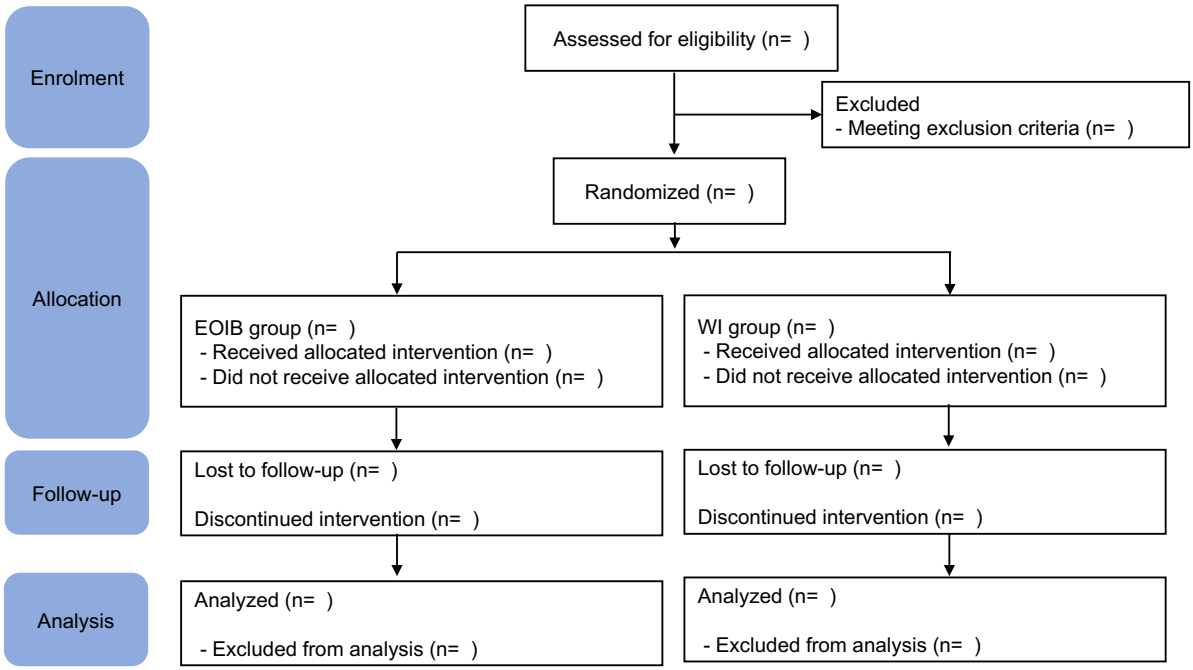

Fig. 1 **G**astrectomy using **E**xternal **O**blique **I**ntercostal block versus woun**D** (GEOID) flow diagram
EOIB: external oblique intercostal block; WI: wound infiltration

Design

Study setting

Participants will be recruited from the Department of Surgery at Nara Medical University Hospital (Kashihara, Japan).

Eligibility criteria

Patients (aged 20–85 years) classified as American Society of Anesthesiologists Performance Status 1 to 2, scheduled for robot-assisted or laparoscopic gastrectomy, who provide written informed consent, will be eligible for inclusion. Exclusion criteria will comprise emergency surgery, preoperative opioid administration, allergies to local anesthetics, inability to provide informed consent, coagulation disorders (prothrombin time-international normalized ratio > 1.25, activated partial thromboplastin time > 35 s, platelet count < 10.0 $\times 10^4/\mu L$), weight < 34 kg, preoperative antithrombotic therapy without an adequate withdrawal duration according to the Japanese guidelines, or judged inappropriate to participate in the study by the investigators. **Fig. 1** shows the flow diagram.

Intervention description

Anesthesia, muscle relaxants and other administered agents

All participants will receive general anesthesia with 1.5–2 mg/kg of propofol, 0.9 mg/kg of rocuronium, fentanyl, and remifentanil for induction and will be maintained with sevoflurane, remifentanil, and fentanyl. Sevoflurane will be administered in order to achieve bispectral Index of 40–60. Remifentanil and fentanyl will be adjusted to achieve High Frequency Variability Index (Mdoloris Medical Systems, Loos, France) of 50–70. Rocuronium will be administered to maintain deep muscle relaxation during surgery using train-of-four monitoring. Remifentanil will be administered at the discretion of the anesthesiologist. Fentanyl (2–4 μg/kg), acetaminophen (1 g or 15 $mg \cdot kg^{-1}$ if the body weight is < 50 kg), and ondansetron (4 mg) will be administered intravenously before the end of surgery. The patient will be extubated only when the train-of-four ratio is > 100%, with sufficient reversal by sugammadex.

EOIB group

Ultrasound-guided EOIB will be performed using a 6–13 MHz EDGE II linear probe (Fujifilm Sonosite, Tokyo, Japan) after inducing general anesthesia in the supine position. The probe will be placed in the sagittal plane between the midclavicular and anterior axillary lines, at the level of the 6th rib. This will be identified by counting from the 10th rib at the level of the lower costal margin or counting down from the 1st rib under the clavicle with ultrasound guidance. The skin entry point of the needle will be between the 6th and 7th ribs, with the needle directed cephalad to caudad. We will place the tip of the needle in the EOI plane and confirm correct placement using hydrodissection with saline. Thereafter, a needle tip will be advanced toward caudally as in the original procedure [6], then 20 mL of 0.25% levobupivacaine per side (total 40 mL) will be injected to provide local anesthesia.

WI group

The surgeons will perform WI in the peritoneum, fascia, and subcutaneous tissue at each port site using a 22-gauge short needle to administer (40 mL of 0.25%) levobupivacaine before skin closure [13].

Discontinuation of interventions

The investigator will withdraw patients from the

			Study period						
	Before operation		**Operative day**			**Postoperative day**			
	Enrollment	**Allocation**	**Post allocation**						
	Preoperative	0day	during operation	2 hours after operation	12 hours after operation	Day 1	Day 2	Day 7	3 months after operation (by mail)
Timepoint*	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7
Enrollment:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
Interventions:									
EOIB			X						
WI			X						
Blood sampling			X						
Assessments:									
NRS				X	X	X	X		
Pinprick test				X		X			
QoR-15		X				X	X	X	
Postoperative fentanyl consumption								X	
WHODAS2.0		X							X

Table 1 Participant timelines
*Timepoints (t): $-t_1$, one day before surgery; t_0, day when patients provided informed consent and entered the operating room; t_1, t_2, and t_3, during, 2 and 12 h after surgery, respectively; t_4, t_5, t_6, t_7: POD 1, 2, 7, and 90, respectively (by post)

study if the following conditions are met: refusal to participate or consent withdrawal; deemed ineligible after enrollment; operative procedure is converted to open surgery; fatal complications requiring intensive care after surgery such as massive intraoperative bleeding or anaphylactic shock, or an investigator judges that the further participation might be detrimental to the patient.

Outcomes

The primary endpoint will be the numeric rating scale (NRS) scores at 12 h after surgery. The secondary endpoints will be NRS scores at 2 h after surgery and on postoperative day (POD) 1 and 2; postoperative fentanyl consumption; variation in Quality of Recovery (QoR)-15 scores from preoperative baseline to POD 1, 2, and 7; and variation in World Health Organization Disability Assessment Scale 2.0 (WHODAS 2.0) scores between baseline and 3 months after surgery. We will measure plasma concentrations of levobupivacaine at 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 30, 45, 60, 90, and 120 minutes after EOIB to determine the exploratory endpoint. We will also assess pinprick sensation of the T4–11 region as test scores of 0 (loss), 1 (decreased), or 2 (normal). Scores of 0 or 1 will be defined as effective [14]. Ward nurses will evaluate all outcomes for POD 0, while outcomes for POD 1 and 2 will be assessed blindly by the non-study-affiliated acute pain service team in our institution. Pinprick test will be evaluated by the co-investigator who is unaware of the patient's trial allocation.

Participant timeline

All outcomes will be evaluated and data will be collected according to the participant timeline (**Table 1**).

Sample size

No reference data are available for EOIB because it is a novel anesthetic method. Therefore, we assumed that the analgesic effect of EOIB compared with that of WI would be a mean improvement (reduction) of 1 in NRS, with a standard deviation (SD) of 0.9, referring to the results of a previous study on WI in gastrectomy due to gastric cancer [15]. The evidence for the change of 1 in the NRS as a minimal clinically important difference (MCID) was extrapolated from a report indicating that a change of 10 in the 100 mm pain visual analog scale would be the MCID in postoperative acute pain [16]. Assuming a significance level of 5% (two-sided) and 80% power, 14 patients per group will be needed for comparisons using unpaired t-tests. Assuming a dropout rate of about 10%, we will randomly assign a total of 32 patients to one of two groups.

Recruitment

If the team providing care considers the patient eligible for this study, they can refer the patient to

the study researcher. Written informed consent will be required from all patients before inclusion in the study. Each participant will be informed that their participation would be voluntary, and they will be able to withdraw from the study at any time. Patients will be selected and randomly assigned to the groups scheduled for laparoscopic or robot-assisted gastrectomy under general anesthesia.

Allocation

The **G**astrectomy using **E**xternal **O**blique **I**ntercostal block versus woun**D** (GEOID) study will be a single-center, single-blind, randomized controlled trial. Patients will be randomly assigned in a 1:1 ratio to the intervention (EOIB) or control (WI) groups. The groups will be stratified by block randomization using GraphPad QuickCalcs (https://www.graphpad.com) and the adjustment factors of surgical technique (robot-assisted or laparoscopic) and resection site (total or pyloric gastrectomy. An investigator who is not directly involved in this trial will randomize the group allocation of participants who have provided written informed consent. The anesthesiologist and surgeon will be informed of the allocated group on the day of surgery. Intraoperative adherence will be maintained because the interventions are included in the surgical procedure.

Blinding

Only the participants will be blinded because it is impossible for the anesthesiologists and surgeons. The participants will not be unblinded during the trial.

Data collection and management

The results will be collected by the investigators or outcome assessors using case report form (CRF). The investigator will collect arterial blood samples at the specified time points. The concentration of levobupivacaine will be examined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan). The WHODAS 2.0 scores will be posted to participants 3 months after surgery and returned to the investigators when completed. If the questionnaire is not returned on the specified date, an investigator will tell the participant by telephone to post a reply. All information in the study protocol will be collected by the investigator during the study period and recorded on the CRFs that will be stored at the Nara Medical University data center.

Statistical methods

Differences in the primary endpoint between the groups will be assessed using unpaired t-tests or Wilcoxon rank-sum test when appropriate. We will estimate the means and 95% confidence intervals (Cis) of each group, and differences between them. Each secondary endpoint will be calculated as means with 95% Cis and if necessary, as medians for the control group. Changes in the endpoint that differ between the groups will also be estimated as means with 95% Cis.

Plasma levobupivacaine concentrations will be summarized as means with 95% Cis per time point. Maximum plasma concentrations (C_{max}), maximum concentration time (T_{max}), and other parameters will be directly determined from measured values and mean C_{max} and T_{max} values will be calculated for each patient. Furthermore, variations in plasma concentrations in each participant will be described using spaghetti plots or other figures. The results of pinprick tests will be summarized using a heat map or other graphs. We will analyze all endpoint subgroups such as the surgical duration and oral medications to identify factors that might be useful in determining future investigations and treatment strategies. Figures and tables will be prepared as needed to supplement and interpret the analytical results.

We do not expect to miss data, because most will be collected during and immediately after surgery. We do not plan imputation if data do become lost.

Monitoring

To improve the accuracy of data collection, a committee of staff who are not involved in this study will monitor data from the first patient and at specified time points. The committee will deliver the results to the principal investigator. No interim analyses will be planned. We will define adverse events as the administration of a drug or the use of a medical device that could be detrimental to health. The investigators will report to the Data and Safety Monitoring Board (DSMB) and the Minister of Health, Labour, and Welfare within the established submission period if a serious adverse event occurs. We did not establish a coordinating center or trial steering committee, because this trial will be conducted at a single center. We organized the DSMB according to Japan's Clinical Trials Act (Act No. April 16 14, 2017). The DSMB constitutes members who are independent of investigators with experience in evaluating clinical trials. The DSMB will deliberate on the direction of this trial if unpredicted serious adverse events occur. This study will not be audited. However, an audit will be considered if the monitoring reveals serious violations of relevant laws and regulations or deviations from the protocol.

Ethics and dissemination

Ethics approval and consent to participate

The Nara Medical University Certified Review Board (Approval Number: CRB5200002) approved the study protocol. Written informed consent will be obtained from all patients before inclusion in the study, and each will be informed that their participation will be voluntary and that they may withdraw from the study at any time.

Protocol amendments

If the protocol requires changing, all revisions and their rationales will be reported to the approved Clinical Research Review Committee for review and approval. The principal investigator will then review the explanatory records of the patients.

Confidentiality

All collected data will be stored anonymously on a computer not connected to the Internet at Nara Medical University. Only investigators will be able to access the data. Appointed staff will be able to temporarily access the data during monitoring.

Access to data

The datasets used and/or analyzed during the study will not be available to the public but will be available from the corresponding author upon reasonable request.

Dissemination policy

Research results will be published in peer-reviewed journals, presented at national and international conferences, and distributed to participating physicians and participants.

DISCUSSION

We consider that EOIB would be a simple and effective approach to manage pain after upper abdominal surgery. However, only few studies have investigated this novel nerve block We believe that this trial will provide evidence for the effects of EOIB on laparoscopic surgery. Plasma concentrations of levobupivacaine will help in assessing the pharmacokinetics after EOIB. We can then compare the pharmacokinetics after EOIB with those after conventional nerve blocks, which are traditionally well-performed and investigated. If the pharmacokinetics are similar to conventional nerve blocks, EOIB can be performed as safely as possible. If the results of this study provide evidence of efficacy and pharmacokinetics, this study will help to select a better nerve block for upper abdominal surgery.

On the contrary, if significant differences are not found between the groups, WI may become the more popular method of analgesia for gastrectomy in gastric cancer because it is a simple and inexpensive approach. New findings might emerge through discussion and validation.

Abbreviations

CRF: case report form
DSMB: Data and Safety Monitoring Board
EOIB: external oblique intercostal block
NRS: Numerical Rating Scale
WI: wound infiltration

ANCILLARY AND POST-TRIAL CARE

No post-trial care will be provided in this protocol. The investigators will have insurance to compensate participants should any harm arise that is related to the trial.

AUTHORS' CONTRIBUTIONS

TS, the principal investigator, contributed to the design of the study protocol, the drafting of the manuscript, obtaining the grant, and the collection of data. NT contributed to the conception of the study idea, the design of the study protocol, and the collection of data. YK and TY contributed to the collection of data. MK helped obtain funding and contributed to data acquisition. YK, TY, MI, and MK contributed substantially to the development and acquisition of the protocol. SS and KA substantially contributed to the design of the study protocol and provided information for proper operation. NO provided statistical expertise in the protocol. All authors critically reviewed the protocol, substantially revised the manuscript, and approved the final manuscript. The investigators will obtain written informed consent from the participants the day before surgery and record it in an electronic medical chart.

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Competing interests

The authors declare that they have no competing interests.

Maruishi Pharmaceutical Corporation (Osaka, Japan), which produces and distributes levobupivacaine in Japan, provided our hospital with nonfinancial support by measuring plasma levobupivacaine concentrations in patient samples without compensation. Blood samples will be collected from all patients after obtaining their written informed consent. The company is not involved in this study in any other capacity.

Protocol version

GEOID protocol v. 1.1 (25 June 2022).

Trial registration

Japan Registry of Clinical Trials, jRCTs051220096. Registered on 16 September 2022.

REFERENCES

1) Chin KJ, McDonnell JG, Carvalho B, Sharkey A, Pawa A, Gadsden J. Essentials of our current understanding: Abdominal wall blocks. Reg Anesth Pain Med 2017; 42: 133-183.
2) Cook TM, Counsell D, Wildsmith JAW, Royal College of Anaesthetists Third National Audit Project. Major complications of central neuraxial block: Report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth 2009; 102: 179-190.
3) Feldheiser A, Aziz O, Baldini G, Cox BPBW, Fearon KCH, Feldman LS, *et al*. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. Acta Anaesthesiol Scand 2016; 60: 289-334.
4) Børglum J, Maschmann C, Belhage B, Jensen K. Ultrasound-guided bilateral dual transversus abdominis plane block: A new four-point approach. Acta Anaesthesiol Scand 2011; 55: 658-663.
5) Sondekoppam RV, Brookes J, Morris L, Johnson M, Ganapathy S. Injectate spread following ultrasound-guided lateral to medial approach for dual transversus abdominis plane blocks. Acta Anaesthesiol Scand 2015;59: 369-376.

6) Elsharkawy H, Kolli S, Soliman LM, Seif J, Drake RL, Mariano ER, *et al*. The external oblique intercostal block: Anatomic evaluation and case series. Pain Med 2021; 22: 2436–2442.
7) Coşarcan SK, Erçelen Ö. The analgesic contribution of external oblique intercostal block: Case reports of 3 different surgeries and 3 spectacular effects. Medicine 2022; 101: e30435.
8) Moore DC, Bush WH, Scurlock JE. Intercostal nerve block: A roentgenographic anatomic study of technique and absorption in humans. Anesth Analg 1980; 59: 815–825.
9) Tam T, Harkins G, Wegrzyniak L, Ehrgood S, Kunselman A, Davies M. Infiltration of bupivacaine local anesthetic to trocar insertion sites after laparoscopy: A randomized, double-blind, stratified, and controlled trial. J Minim Invasive Gynecol 2014; 21: 1015–1021.
10) Skjelsager A, Ruhnau B, Kistorp TK, Kridina I, Hvarness H, Mathiesen O, *et al*. Transversus abdominis plane block or subcutaneous wound infiltration after open radical prostatectomy: A randomized study. Acta Anaesthesiol Scand 2013; 57: 502–508.
11) Møiniche S, Jørgensen H, Wetterslev J, Dahl JB. Local anesthetic infiltration for postoperative pain relief after laparoscopy: A qualitative and quantitative systematic review of intraperitoneal, port-site infiltration and mesosalpinx block. Anesth Analg 2000; 90: 899–912.
12) Macfater H, Xia W, Srinivasa S, Hill AG, Van De Velde M, Joshi GP, *et al*. Evidence-based management of postoperative pain in adults undergoing laparoscopic sleeve gastrectomy. World J Surg 2019; 43: 1571–1580.
13) Joshi GP, Janis JE, Haas EM, Ramshaw BJ, Nihira MA, Dunkin BJ. Surgical site infiltration for abdominal surgery: A novel neuroanatomical-based approach. Plast Reconstr Surg Glob Open 2016; 4: e1181.
14) Tamura T, Kitamura K, Yokota S, Ito S, Shibata Y, Nishiwaki K. Spread of Quadratus Lumborum Block to the Paravertebral Space Via Intramuscular Injection: A Volunteer Study. Reg Anesth Pain Med 2018; 43: 372–377.
15) Zhu Z, Chen B, Ye W, Wang S, Xu G, Pan Z, *et al*. Clinical significance of wound infiltration with ropivacaine for elderly patients in china underwent total laparoscopic radical gastrectomy: A retrospective cohort study. Medicine 2019; 98: e15115.
16) Myles PS, Myles DB, Galagher W, Boyd D, Chew C, MacDonald N, *et al*. Measuring acute postoperative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state. Br J Anaesth 2017; 118: 424–429.