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EFFICIENCY OF TAPERING PROGRAMMED INTERMITTENT EPIDURAL ANALGESIA IN VIDEO-ASSISTED THORACIC SURGERY: A DOUBLE-BLIND, PROSPECTIVE, RANDOMIZED STUDY

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ABSTRACT – *Objective:* Programmed intermittent epidural bolus (PIEB) is an effective analgesic method owing to the redistribution of the drug solution, which leads to a gradual improvement in postoperative pain over time. This study aimed to compare the postoperative analgesic effects of patient-controlled epidural analgesia (PCEA) with those of tapering PIEB (t-PIEB), in which the drug dosage is decreased over time, and continuous epidural infusion (CEI).

Materials and Methods: Patients undergoing video-assisted thoracoscopic surgery (VATS) with general and epidural anesthesia were randomized in a 1:1 ratio into the t-PIEB and CEI groups. Patients in the t-PIEB group received 3 mL of 0.2% ropivacaine from the pump every hour, whereas those patients in the CEI group received the same drug solution continuously at a rate of 3 mL/h. In both groups, a 2-mL bolus of 0.2% ropivacaine was administered postoperatively, with additional PCEA as needed. In the t-PIEB group, the dosage was gradually decreased to 2 mL/dose after 25 h and to 1 mL/dose after 49 h. The primary endpoint was the number of times the patient pressed the PCA button at 24, 48, and 72 h.

Results: No significant difference was observed in the frequency of PCA button pressing between the two groups during the observation period. The t-PIEB group had a significantly lower usage of ropivacaine.

Conclusions: Nt-PIEB could have analgesic effects comparable to those of CEI for postoperative pain following VATS with less medication use.

KEYWORDS: Ropivacaine, Patient-controlled epidural analgesia, Postoperative pain, Lung resection, Visual analog scale score.

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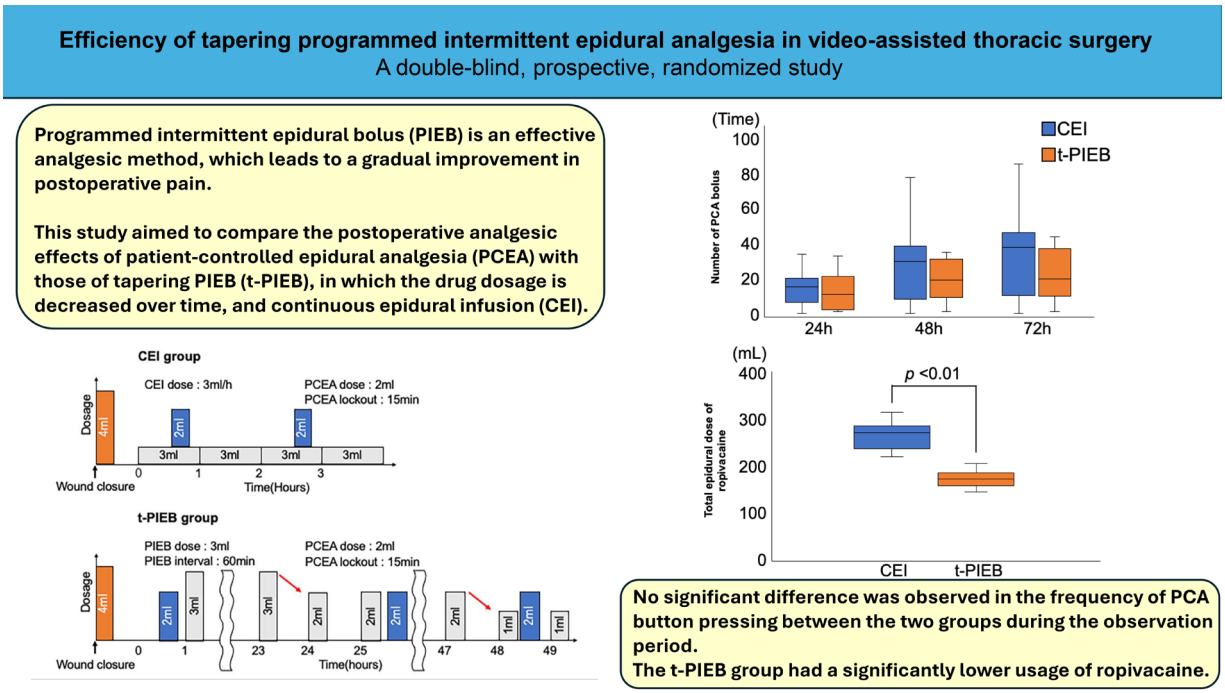
INTRODUCTION

Despite significant advances in radiation therapy, immunotherapy, and molecular targeted therapy, surgical resection remains the treatment of choice for patients with early-stage lung cancer[1]. Decades after extremely painful open chest surgeries, video-assisted thoracoscopic surgery



Graphical Abstract. Efficiency of tapering programmed intermittent epidural analgesia in video-assisted thoracic surgery.

(VATS) emerged in the early 1990s as a minimally invasive approach[1]. VATS lobectomy was defined by the following criteria: no rib-spreading; a maximum length of 8 cm of the access incision for removal of the lobectomy specimen; individual dissection of the vein, arteries, and airway for the lobe in question; and standard node sampling or dissection (identical to an open thoracotomy)[1]. Although postoperative pain is considered less severe than before, it remains one of the most painful surgical procedures. We believe that thoracic epidural analgesia is standard postoperative analgesia for VATS[2,3]. Postoperative analgesia methods, such as thoracic paravertebral block and intravenous patient-controlled analgesia, are available; however, unless there are contraindications, patients undergoing VATS are administered a thoracic epidural.

Programmed intermittent epidural bolus analgesia (PIEB) is an epidural analgesia method developed since the 2000s. This method, made possible by advances in medical equipment, automatically administers a bolus of a local anesthetic at predetermined intervals and doses. PIEB is more useful than the currently commonly used continuous epidural infusion analgesia (CEI) for postoperative analgesia of labor pain, gynecologic lower abdominal surgery, and total knee replacement surgery[4-6]. Bolus administration may provide higher-quality analgesia with fewer local anesthetics and different drug distribution than CEI.

However, it is unclear whether PIEB provides superior postoperative analgesia for VATS under general anesthesia or epidural anesthesia. Furthermore, postoperative pain decreases with time, and local anesthetics tailored to the pain are desirable[7]. We hypothesized that a reduction in local anesthetic dosage over time in addition to PIEB would provide higher-quality epidural analgesia with a minimal amount of drug solution. PIEB with dose tapering over time was defined as tapering PIEB (t-PIEB). In this study, we compared the analgesic effect of patient-controlled epidural analgesia (PCEA) at 24, 48, and 72 h postoperatively with that of t-PIEB and CEI and with the bolus frequency of PCEA. We also examined factors such as the visual analog scale (VAS) scores for postoperative pain and complications.

MATERIALS AND METHODS

Patients and study protocol

We conducted a randomized, double-blind clinical trial. This study was approved by the Human Research Ethics Committee of Hiroshima University (C2022-0008) and registered in the University Hospital Medical Information Network clinical trials database (UMIN000049027). Written informed consent was obtained from all patients, and the study adhered to the principles outlined in the Declaration of Helsinki.

This prospective, randomized, double-blind study enrolled 46 patients aged 18-79 years, classified as American Society of Anesthesiologists classes I-III, scheduled to undergo VATS between

October 2022 and October 2023. Patients who met at least one of the following criteria were excluded: (1) severe diabetes mellitus (HbA1c > 8.4), (2) the procedure was changed during surgery, (3) inadequate effect of epidural anesthesia at the end of anesthesia, and (4) deemed unsuitable by the investigator. The patients were randomized in a 1:1 ratio using a computer-generated distribution (Quick-Calcs, GraphPad Inc., La Jolla, CA, USA) to receive either t-PIEB or CEI.

Anesthesia

No premedication was administered before induction of anesthesia. Upon arrival in the operating room, patients were monitored using electrocardiography, pulse oximetry, and blood pressure measurement. Experienced anesthetists blinded to the study protocol performed epidural punctures. An epidural catheter was inserted in the left lateral decubitus position at the T4-T6 interspace before inducing general anesthesia. The epidural space was identified using the loss-of-resistance to saline technique with an 18-gauge Tuohy epidural needle. A closed-end, multi-orifice epidural catheter (Perifx FX, B. Braun, Aesculap, Tuttlingen, Germany) was advanced 5 cm, and 3 mL of 1% lidocaine was administered as the test dose.

After placement of the epidural catheter, general anesthesia was induced with intravenous fentanyl, remifentanil, propofol, and rocuronium and maintained with sevoflurane/desflurane, remifentanil, and rocuronium. The anesthesiologist in charge determined the volume of each drug solution. Fentanyl was limited to < 5 μg/kg because of its possible effect on postoperative pain. After intubation with a double-lumen tube for isolated single-lung ventilation, the patient was placed in the side-lying position and received an initial epidural loading dose of 4 mL bolus of 0.25% ropivacaine via the epidural catheter. Acetaminophen (1,000 mg or 15 mg/kg) was administered during wound closure for postoperative analgesia, and ondansetron was administered intravenously to prevent postoperative nausea and vomiting. At the end of the surgery, 4 mL of a 0.25% ropivacaine bolus was administered *via* an epidural catheter. Programmed epidural infusion using COOPDECH Amy (Daikeniki, Osaka, Japan) was prepared and attached to the patient by anesthesiologists who were not involved in the anesthetic management and the medical interview after surgery. To confirm whether epidural anesthesia provides adequate analgesic coverage, a block to cold sensation using a cooling gel pack was tested upon leaving the operating room. The drug solution used for epidural anesthesia was 0.2% ropivacaine in both groups, and the CEI group received continuous dosing at 3 mL/h. The t-PIEB group received a bolus

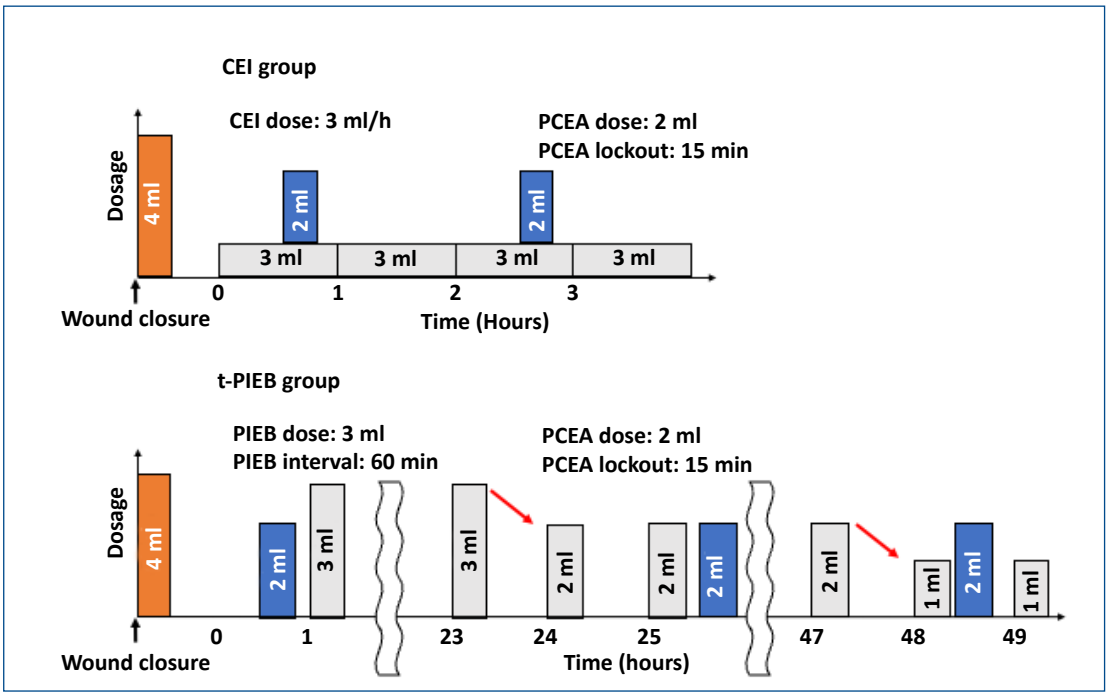


Figure 1. Pump settings in the CEI and t-PIEB groups. Both groups received an initial bolus dose of 4 mL of 0.25% ropivacaine epidurally to coincide with closure of the surgical incision. In the CEI group, local anesthetic was continuously administered at a dose of 3 mL/h. In the t-PIEB group, a bolus of 3 mL of local anesthetic was administered hourly. The bolus dose was tapered by 1 mL every 24 h. Both groups also received PCEA at a single dose of 2 mL and a lockout time of 15 min. CEI: continuous epidural infusion, t-PIEB: tapering programmed intermittent epidural bolus, PCEA: patient-controlled epidural analgesia.

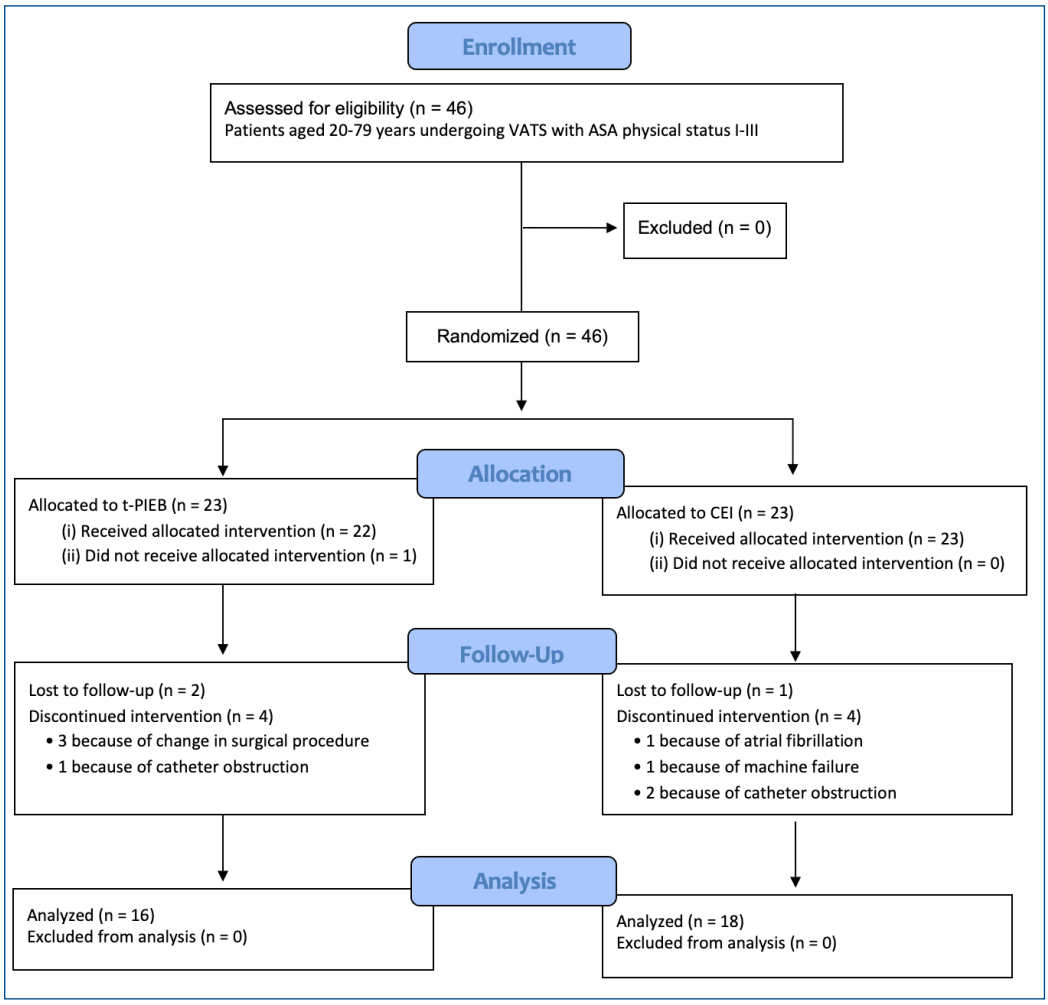


Figure 2. Participant flow diagram. Consolidated Standards of Reporting Trials (CONSORT) flow diagram indicating patient disposition. VATS: video-assisted thoracoscopic surgery; ASA PS: American Society of Anesthesiologists Physical Status; t-PIEB. tapering programmed intermittent epidural bolus; CEI: continuous epidural infusion.

dose of 3 mL every hour starting 1 h after COOPDECH Amy was connected. After 25 h, the bolus dose was reduced to 2 mL; after 49 h, it was further manually reduced to 1 mL. The PCEA dose was set to deliver a 2 mL bolus dose with a lockout interval of 15 min in both groups (Figure 1). Postoperatively, when epidural analgesia alone did not provide adequate pain relief, adjunctive analgesics were administered at the patient's discretion. Acetaminophen or flurbiprofen was administered based on the patient's renal and hepatic function. The patient began eating and taking oral analgesics and expectorants on the morning of the postoperative day (POD) 1. A thoracic drain was placed in all patients, and the attending physician reviewed the timing of removal.

Measurements

Postoperative patient evaluations were performed by anesthesiologists who were blinded to the treatment group. The primary endpoint was the number of times the PCA button was pressed at 24, 48, and 72 h. Secondary endpoints were total drug dose, VAS score at rest and during movement, number of additional analgesics, hypotension (≥ 20% decrease from preoperative blood pressure), and neurologic abnormalities.

Statistical analysis

T-his pilot study is expected to provide data for calculating the sample size for further trials with larger sample sizes. To account for the small number of dropouts, the target number of participants was set to 46. Non-normally distributed variables were reported as medians (Q1, Q3) and analyzed using the Mann-Whitney U test. Categorical variables are reported as numbers (%) and analyzed using the Chi-square or Fisher's exact test. Statistical analyses were performed using the GraphPad Prism 9.4.1 (GraphPad Software, San Diego, CA, USA). Statistical significance was set at p-value < 0.05.

Table I. Patient demographics.

	CEI (n = 18)	t-PIEB (n = 16)	*p*-value
Sex male/female	12/6	9/7	0.725
Years	72 (65, 74)	70 (67, 73)	0.765
Height, cm	163.0 (154.2, 168.7)	161.9 (151.8, 166.3)	0.993
Body weight, kg	58.2 (54.9, 64.5)	62.3 (54.8, 66.1)	0.766
ASA PS I/II/III	2/15/1	0 / 16 / 0	0.759
Anesthesia time, min	224 (186, 251)	205 (193, 225)	0.791
Surgery time, min	144 (111, 166)	130 (110, 150)	0.664
Bleeding volume, ml	41 (28, 87)	35 (29, 76)	0.627
Infusion volume, ml	1,325 (963, 1,500)	1,300 (1,038, 1,385)	0.791
Remifentanil usage, mg	1.6 (1.3, 2.0)	1.7 (1.2, 2.1)	0.885
Fentanyl usage, µg	100 (100, 188)	100 (100, 200)	0.428

Date is presented as median (Q1, Q3). CEI: continuous epidural infusion, t-PIEB: tapering programmed intermittent epidural bolus, ASA PS: American Society of Anesthesiologists physical status classification system.

RESULTS

During the study period, 46 patients who underwent VATS for lung cancer were recruited, and 23 patients each were assigned to the CEI and t-PIEB groups. Five and seven patients from the CEI and PIEB groups, respectively, were excluded from the analysis. The reasons for the exclusion included protocol deviations in five patients, such as a change in procedure, catheter obstruction, or mechanical trouble in four patients, and incomplete postoperative records in three patients. Overall, 34 patients completed the trial (Figure 2). Patient backgrounds are presented in Table I.

No significant difference was observed in the number of PCEA boluses at 24 h [median (Q1, Q3), 16 (8, 21) *vs.* 12 (4, 22), $p = 0.676$], 48 h [median (Q1, Q3), 29 (10, 37) *vs.* 20 (11, 30), $p = 0.522$], and 72 h [median (Q1, Q3), 37 (12, 44) *vs.* 20 (11, 36), $p = 0.469$] postoperatively between the two groups (Figure 3). The total drug doses at 72 h were significantly lower in the t-PIEB group [median (Q1, Q3), 271 mL (237, 285) *vs.* 173 mL (159, 187), $p < 0.001$] (Figure 4). No significant differences were observed in the VAS scores at rest or during movement, the numbers of additional adjunctive analgesics, incidence of hypotension, or neurologic abnormalities between the two groups during the observation period (Figure 5 and Table II).

DISCUSSION

This study compared the analgesic efficacy of CEI and t-PIEB as postoperative analgesic methods after VATS. No significant differences were obser-

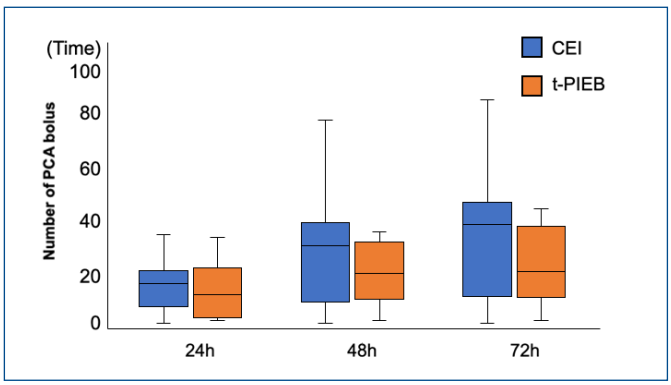


Figure 3. Number of times the patient pressed the PCEA button. Comparison of PCEA bolus frequencies at 24, 48, and 72 h postoperatively between the t-PIEB and CEI groups. Data are presented as medians (lines in the boxes) and Q1 and Q3 (bottom and top of the boxes, respectively), and the lower and upper outlier thresholds (the ends of the whiskers on the boxes). PCEA: Patient-controlled epidural analgesia; t-PIEB: tapering programmed intermittent epidural bolus; CEI: continuous epidural infusion.

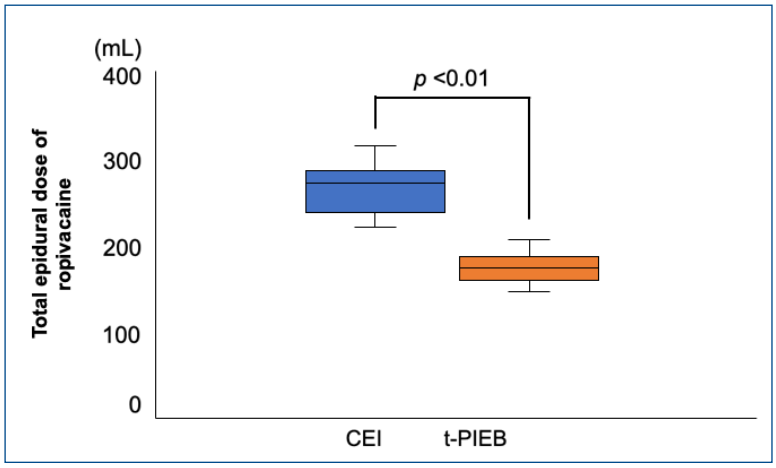


Figure 4. Total drug dose. Total drug doses at 72 h postoperatively were compared between the CEI and t-PIEB groups. Data are presented as medians (lines in the boxes) and Q1 and Q3 (bottom and top of the boxes, respectively). The lower and upper outlier thresholds (the ends of the whiskers on the boxes).
*Significant ($p < 0.05$) differences between the t-PIEB and CEI groups, as indicated by Mann-Whitney U tests. t-PIEB: tapering programmed intermittent epidural bolus; CEI: continuous epidural infusion.

ved in the number of PCA usages, VAS scores at rest or during movement, or the number of additional analgesics used in both groups postoperatively. There were no significant differences in the incidence of hypotension or neurological abnormalities. The total epidural dose of ropivacaine at 72 h was significantly lower in the t-PIEB group, and the dose was reduced according to the protocol.

The PIEB is a protocol for administering analgesics *via* an epidural catheter at predetermined intervals and is useful in managing pain during labor and delivery, cesarean section, and open gynecologic surgery[8-10]. The analgesic effect of epidural anesthesia is greatly influenced by the spread of the local anesthetic[11]. Previous scholars[12] have confirmed that intermittent administration provides a better spread of local anesthetics compared to continuous administration. In a report using a porcine model in which 1 mL of drug solution was administered into the epidural space, a comparison of a bolus group and a continuous 0.5 mL/h group showed significantly wider spread in the bolus group[13]. A study on labor pain showed that although the drug solutions varied in composition, the doses, whether continuous or intermittent, ranged from 5 to 12 mL/h, with superior analgesia and similar adverse events in the PIEB group[8]. In another previous study[14], a continuous-dose group receiving 5.1 mL/90 min (3.4 mL/h) of local anesthetic (2 mg ropivacaine and 2 µg fentanyl in 1 mL) was compared to an intermittent-dose group receiving 5.1 mL of the same drug solution every 90 min. Although no difference was observed in analge-

Table II. Postoperative values.

	CEI (n = 18)	t-PIEB (n = 16)	*p*-value
Additional analgesic, time			
0-24 h	2 (1, 2)	1 (1, 2)	0.694
24-48 h	0 (0, 0)	0 (0, 0)	0.318
48-72 h	0 (0, 0)	0 (0, 0)	0.471
Hypotension			
0-24 h	7	6	> 0.99
24-48 h	3	2	> 0.99
48-72 h	0	1	> 0.99
Neurological abnormalities	0	0	> 0.99

Data is presented as median (Q1, Q3). CEI: continuous epidural infusion, t-PIEB: tapering programmed intermittent epidural bolus.

sic efficacy, more PCEA use was observed in the CEI group, and more hypotension was observed in the PIEB group[14]. Drug composition and the mechanical setting of the dosage are important factors in PIEB. In our study, 3 mL of local anesthetic (2 mg of ropivacaine in 1 mL) was administered hourly. The present results indicate that the frequency of PCEA use varied considerably between the patients in both groups. In future larger studies, subgroup analysis based on sex or age may help identify the patient group suitable for t-PIEB.

Tapering has not been discussed extensively in previous studies and was performed as an experimental trial. At Hiroshima University Hospital, epidural catheters are jointly managed by the Department of Anesthesiology and the Postoperative Pain Management Team of the Nursing Department. For patients with an epidural catheter, the continuous dose of CEI was reduced from 3 mL/h to 1 mL/h the day before removal was scheduled, and the catheter was removed after confirming no worsening of pain. Postoperative pain is most intense on POD 0 and POD 1 and decreases over time[15]. The number of PCEA doses with PIEB was reported to be highest at 3-24 h after surgery and then reduced by less than 30% in open gynecological surgery[10]. In another study, the mean number of PCEA administrations was significantly lower in the PIEB group than in the CEI group at 24-36 h after thoracic surgery[14]. Based on these findings, we assumed that tapering the amount of drug administered every 24h would result in higher-quality drug administration. Even in the unlikely event of pain exacerbation due to the tapering, we assumed that the protocol would not harm the patient because the increased frequency of PCEA use would provide additional pain relief.

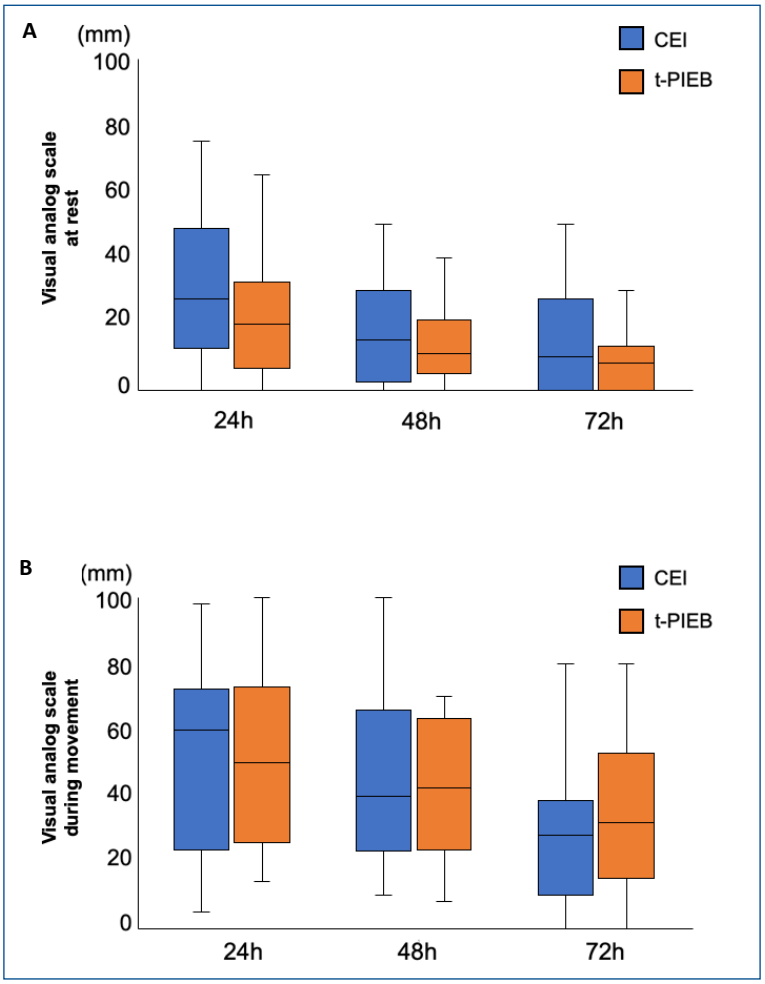


Figure 5. **A**, VAS score at rest. **B**, VAS score during movement. Comparison of VAS pain scores of pain at 24, 48, and 72 h after surgery between the t-PIEB and CEI groups. Data are presented as medians (lines in the boxes) and Q1 and Q3 (bottom and top of the boxes, respectively), and the lower and upper outlier thresholds (the ends of the whiskers on the boxes). VAS: visual analog scale; t-PIEB: tapering programmed intermittent epidural bolus; CEI: continuous epidural infusion; PCEA: patient-controlled epidural analgesia.

The PIEB can reduce workloads in the maintenance of epidural labor analgesia[16]. It also decreases the incidence of breakthrough pain and local anesthetic usage without increasing the incidence of side effects, such as nausea, vomiting, pruritus, and hypotension[17]. However, after thoracic surgery, hypotension occurred more frequently in the PIEB group than in the CEI group[14]. The causes of postoperative hypotension due to epidural anesthesia include sex, body mass index, bupivacaine concentration, and anesthesia duration[18]. For postoperative epidural analgesia, t-PIEB can prevent the occurrence of hypotension after surgery, which is problematic because it often leads to the temporary interruption of epidural analgesia and the need for adjunctive analgesics. Therefore, it is necessary to determine the optimal t-PIEB regimen for each type of surgery.

Limitations

This study has some limitations. First, the sample size was small, and only preliminary results were obtained. Since the study primarily focused on the feasibility and practicality of the method, it was not adequately powered to definitively measure the effects of the intervention or conduct a subgroup analysis. The validity of this protocol needs to be further validated in future larger studies. Secondly, this study included the patients who underwent VATS with a standardized postoperative regimen at a single institution. The possibility that PCEA can be used to treat pain outside the wound, such as shoulder pain, cannot be ruled out. Further studies are required to confirm the efficacy of the t-PIEB in other surgical fields. Third, the drug dosing protocol was not tapered in the CEI. If the drug dosing is tapered in CEI, differences may exist in the number of PCEA and VAS scores. A true efficacy between the CEI and t-PIEB protocols would similarly require dose titration in the CEI protocol. Further studies are needed to develop a drug administration protocol that provides adequate analgesic efficacy and fewer adverse effects.

CONCLUSIONS

No significant difference was observed in the number of PCEA boluses administered at 24, 48, and 72 h postoperatively between the t-PIEB and CEI groups. The t-PIEB can provide comparable analgesia at a lower total dose, making it a viable option for postoperative pain management.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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Authors' Contributions

Ayumu Matsumoto (data curation; formal analysis; investigation; methodology; resources; visualization; writing – original draft preparation).
Shiho Satomi (data curation; formal analysis; investigation; methodology; software; resources; visualization; writing – original draft).
Soshi Narasaki (investigation; resources; validation; writing – review and editing).
Satoshi Kamiya (investigation; resources; validation; writing – review and editing).
Hirotsugu Miyoshi (investigation; resources; validation; writing – review and editing).
Yasuo M. Tsutsumi (conceptualization; formal analysis; investigation; methodology).

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study was approved by the Human Research Ethics Committee of Hiroshima University with protocol number C2022-0008 on 24/10/2022 and was conducted following Helsinki Declaration and its latest amendments.

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Informed Consent

Written informed consent was obtained from all patients,and the study adhered to the principles outlined in the Declaration of Helsinki.

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