Effects of Programmed Intermittent Thoracic Paravertebral Bolus of Levobupivacaine on the Spread of Sensory Block: A Randomized, Controlled, Double-Blind Study

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thoracic paravertebral space, TPVS

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ABSTRACT

Background and Objectives:

This randomized, controlled, double-blind trial compared the effectiveness of levobupivacaine delivery of a programmed intermittent paravertebral bolus with a continuous paravertebral infusion.

Methods:

Thirty-two consecutively enrolled patients who underwent unilateral video-assisted thoracic surgery were randomized to receive either a programmed intermittent paravertebral bolus of 10 mL of 0.2% levobupivacaine every 2 h (Bolus group, n=16) or a continuous paravertebral infusion of 0.2% levobupivacaine at 5 mL/h (Infusion group, n=16) after the operation. Postoperatively, after injection of 20 mL of 0.25% levobupivacaine through the paravertebral catheter, a mechanical infusion pump was set depending on the assigned group. The primary efficacy outcome was the number of anesthetized dermatomes 24 h after the initial bolus of levobupivacaine. The secondary efficacy outcomes included the number of anesthetized dermatomes at other time points, pain at rest and coughing, additional analgesic use and patient acceptance of the analgesic technique. Arterial levobupivacaine concentration was measured to ensure safety. $P < 0.05$ was considered statistically significant.

Results:

The mean [95% confidence interval] number of anesthetized dermatomes 24h after the initial bolus of levobupivacaine was significantly larger among subjects receiving programmed intermittent bolus (n=16) compared with those receiving continuous infusion (n=16; 6.8 [5.7-7.9]

vs 3.1 [2.0-4.2]; $p < 0.001$). The arterial levobupivacaine concentration did not reach a toxic level.

Conclusions:

The programmed intermittent paravertebral bolus of levobupivacaine provided a wider dermatomal spread of sensory block than continuous paravertebral infusion with an identical hourly dose of levobupivacaine.

Clinical Trial Registration:

UMIN Clinical Trials Registry identification number UMIN000022532

INTRODUCTION

Thoracic paravertebral block provides unilateral multi-segmental sensory blockade by a bolus injection of a large amount of local anesthetic [1-3]. Bolus injection of a local anesthetic followed by continuous infusion is the standard technique of thoracic paravertebral block for post-thoracotomy analgesia [4-6]. However, the range of anesthetized dermatomes becomes gradually narrower when the local anesthetic is administered at a constant rate [7]. Although the addition of a bolus injection of local anesthetic to continuous infusion or repeated bolus injections can maintain the range of anesthetized dermatomes of thoracic paravertebral block in theory, the effect of repeated intermittent thoracic paravertebral injection of the local anesthetic on the time-dependent change in the number of anesthetized dermatomes has not been elucidated. In this randomized, controlled, double-blind trial, we compared the effectiveness of levobupivacaine delivery by a programmed intermittent paravertebral bolus with levobupivacaine delivery by continuous paravertebral infusion in patients undergoing unilateral video-assisted thoracic surgery. We hypothesized that programmed intermittent paravertebral bolus of levobupivacaine would maintain wider sensory block compared with continuous paravertebral levobupivacaine infusion. The primary efficacy outcome was the number of anesthetized dermatomes 24 h after the initial bolus of levobupivacaine.

METHODS

Patients and design

The Research Ethics Committee of Nagasaki University Hospital approved the protocol of this study (Approval number 15111602). This study was prospectively registered in the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm; registration number: UMIN000022532, May 30, 2016). We conducted the present study at Nagasaki University Hospital in Nagasaki Japan, and enrolled patients between May 31, 2016 and January 5, 2017. Written informed consent was obtained from patients. Patients with American Society of Anesthesiologists physical status classification I-III who were scheduled to undergo elective video-assisted unilateral lung lobectomy or pulmonary segmentectomy were recruited. Exclusion criteria were as follows: age < 20 or > 80 years; prior thoracotomy on the ipsilateral side; body mass index > 30 kg/m^2; body weight < 40 kg; allergy or contraindication to drugs used in the present study; hepatic or renal failure; history of chronic opioid use; pre-existing neuropathy; infection at the injection site; bronchial asthma; and inability to communicate lucidly.

Thirty-two consecutively enrolled patients were randomly allocated into one of two groups and received either continuous thoracic paravertebral infusion of 0.2% levobupivacaine at 5 mL/h (Infusion group) or intermittent thoracic paravertebral bolus injection of 0.2% levobupivacaine 10 mL every 2 h (Bolus group) for 50 h postoperatively. Block randomization (block size of 4) stratified by sex on a 1:1 basis between the Infusion group and Bolus group using a computer-generated randomization schedule was performed by an anesthesiologist (I.T.) who did not participate in either the nerve block procedure or postoperative evaluation. The unblinded anesthesiologist set up the portable, programmable, battery-powered mechanical infusion pump (CADD-Solis Ambulatory Infusion Pump, Smiths Medical, St. Paul, MN).

Outcomes were evaluated by anesthesiologists who were blinded to the treatment allocation. Patients, nurses, observers, and the statistician were blinded to patient allocation throughout the study period.

Technique for thoracic paravertebral block and postoperative pain management

No patients received premedication. Standard monitoring including intra-arterial blood pressure monitoring was established. General anesthesia was induced with remifentanil 0.5 μg/kg/min and propofol 1 mg/kg. Rocuronium 0.6-0.9 mg/kg was given to facilitate double lumen endobronchial tube intubation. Anesthesia was maintained with sevoflurane 1.0-1.5% and remifentanil 0.05-0.5 μg/kg/min. Blood pressure and heart rate were maintained within 20% of their respective baseline values.

After anesthesia induction, a thoracic paravertebral catheter was placed under ultrasound guidance using an ultrasound machine (S-Nerve, FUJIFILM Medical Inc., Tokyo, Japan) equipped with a high-frequency linear transducer (HFL 38x; FUJIFILM Medical) with the patient in a lateral decubitus position and the side to be blocked uppermost. Two anesthesiologists (K.H. and H.M.) who are skilled in ultrasound-guided nerve blocks, performed all procedures. After a standard aseptic technique, the transducer within a sterile sheath was placed on the patient in a transverse and partial oblique position to the vertebral column, parallel to the rib at the fifth intercostal space, to obtain a view of the internal intercostal membrane and the lateral apex of the thoracic paravertebral space (TPVS). If the procedure was difficult at the fifth intercostal level, we achieved thoracic paravertebral catheter placement at the fourth or sixth intercostal level. A 17-G Tuohy needle (E17I-95; Hakko CO., LTD, Tokyo, Japan) was inserted in plane with the transducer in a lateral-to-medial direction under ultrasound guidance [7,8]. After the needle tip was advanced beyond the internal intercostal membrane, 10 mL of normal saline

was injected to confirm the appropriate position of the needle tip and dilate the TPVS. Subsequently, a closed-end 19G epidural catheter with two side holes at 3 and 6 mm from the catheter tip directed 180 degrees opposite (Hakko) was threaded into the TPVS 3-5 cm beyond the needle tip. Then, the transducer was rotated to image the sagittal view of the TPVS to estimate the appropriate catheter tip position into the TPVS by injecting a mixture of 3 mL normal saline with 0.5 mL of air through the catheter [7,9]. If a hyperechoic flash by the air-saline mixture was not observed in the TPVS, the catheter was withdrawn by 0.5 cm and the same amount of the mixture was re-injected. If a hyperechoic flash was not observed when the catheter length within the TPVS was 3 cm, the catheter was removed and reinserted [7]. After the catheter tip position was confirmed to be in the TPVS, to exclude intravascular migration of the catheter tip, we performed the negative aspiration test followed by injection of 2% lidocaine with 1:200,000 epinephrine 3 mL [10,11]. Finally, the catheter was secured to the skin with a suture.

Twenty milliliters of mepivacaine 1% was injected through the paravertebral catheter before the surgery for intraoperative analgesia. A 40-100 mm skin incision was placed on the axillary line in the fourth or fifth intercostal space. One to three thoracoscopic ports were placed between the fourth to eighth intercostal spaces. A chest tube was placed through one of the port incisions at the end of the surgery. The patients received intravenous droperidol 1.25 mg to prevent postoperative nausea and vomiting, fentanyl 5 μg/kg i.v. incrementally and flurbiprofen axetil 50 mg i.v. approximately 60 min prior to the end of surgery. Acetaminophen 15 mg/kg (maximum 1000 mg) i.v. was administered approximately 30 min before the end of surgery. With the patient placed in the supine position after surgery, after the catheter tip position and appropriate paravertebral injectate spread [12,13] were confirmed by postoperative routine chest roentgenogram with 10 mL of radiopaque dye (Omnipaque 240; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan)

injected through the paravertebral catheter, levobupivacaine 0.25% 20 mL was incrementally injected through the thoracic paravertebral catheter. After emergence from general anesthesia, the patient was treated with sugammadex 2 mg/kg to antagonize the neuromuscular blocking effect of rocuronium and the trachea was extubated.

In the Bolus group, after the initial bolus injection of 0.25% levobupivacaine 20 mL, a bolus injection of 0.2% levobupivacaine 10 mL was administered every 2 h up to 50 h postoperatively. In the Infusion group, immediately after the initial bolus injection of 0.25% levobupivacaine 20 mL, continuous thoracic paravertebral levobupivacaine infusion of 0.2% levobupivacaine at 5 mL/h was initiated up to 50 h postoperatively. Patient-controlled intravenous fentanyl administration (bolus dose, 10 μg/mL fentanyl 0.5 μg/kg, with a 10-min lockout interval and with no background infusion) was initiated immediately after extubation. Acetaminophen 15 mg/kg (maximum dose 1000 mg) i.v. was started 6 h after the end of surgery and repeated 3 times at 6 h intervals. Oral administration of loxoprofen (60 mg three times daily) was initiated on the morning of the first postoperative day until the end of this study. If pain control was insufficient, patients were given diclofenac suppository 25 mg as required. Thoracic paravertebral levobupivacaine and patient-controlled intravenous fentanyl were administered using CADD-Solis Ambulatory Infusion Pumps (Smiths Medical). Ward nurses who did not participate in this study confirmed the appropriate functioning of the two mechanical infusion pumps.

Measurement of plasma levobupivacaine concentration

Arterial blood samples were obtained immediately before the initial bolus of levobupivacaine through the thoracic paravertebral catheter, and 0.5, 1, 6.5, 12.5, and 24.5 h after the first administration of levobupivacaine. To avoid overlooking the influence of the latest programmed

levobupivacaine bolus injection on the plasma levobupivacaine concentration, we selected 6.5, 12.5 and 24.5 h (30 min after the latest bolus injection) as sampling time points instead of 6, 12 and 24 h, respectively. Plasma was separated immediately by centrifugation of blood samples at 4°C. Plasma samples were frozen and stored until measurement of the levobupivacaine concentration. The plasma concentration of levobupivacaine was measured using liquid chromatography (LC)-tandem mass spectrometry (MS/MS) with an electrospray ionization technique. LC was performed with the Accela^{TM} High Speed LC System (Thermo Fisher Scientific K.K, Kanagawa, Japan), and MS/MS was carried out with the TSQ Quantum Ultra^{TM} Triple Quadrupole Mass Spectrometer (Thermo Fisher Scientific). Praziquantel was used as the internal standard, and all samples were prepared using the deproteination method with acetonitrile. The chromatographic separation was achieved on a XBridge C_{18} column 2.1*100mm (Nihon Waters K.K, Tokyo, Japan) with two mobile phases (A: 5 mM ammonium acetate buffer [pH adjusted to 5.2 with acetic acid], B: acetonitrile; A: B = 62:38). The chromatographic analysis time was 6.5 min per sample. The calibration curves in various biological matrixes were linear between 0.5 and 2000 ng/mL with 1 X^{-2} weighting ($r \geq 0.99$).

Study parameters and statistical analysis

The primary efficacy outcome was the number of anesthetized dermatomes 24 h after the initial thoracic paravertebral levobupivacaine injection. Secondary efficacy outcomes included the number of anesthetized dermatomes at other time points, pain at rest, pain at coughing, numbers of intravenous patient-controlled fentanyl administrations and diclofenac suppository administrations, and patient satisfaction rating. As safety outcomes, we examined the incidences of nausea, vomiting and hypotension, and the time-dependent change in serum levobupivacaine concentration. The evaluation of anesthetized dermatomes was performed using an ice pack in a

standardized fashion at each time point by anesthesiologists who were blinded to the patient allocation. The area starting at the T4 dermatome between the anterior axillary line and midclavicular line was tested, first in the cranial direction and then in the caudal direction. If required, cervical and high thoracic dermatomes were tested at the upper extremity and the neck, and lumbar dermatomes were tested at the lower extremity. The dermatome at which the patient perceived less or no sensation to the cold stimulus compared with that of the contralateral side was registered as an anesthetized dermatome. The pain scores were collected at each time point by anesthesiologists who were blinded to the patient allocation. The pain score was evaluated with an 11-point numerical rating scale (0 = no pain, 10 = the worst imaginable pain). Patients were asked to rank their satisfaction with postoperative pain management at 24 and 48 h after the initial thoracic paravertebral levobupivacaine injection according to the following scale: 1 = very unsatisfactory, 2 = unsatisfactory, 3 = neutral, 4 = satisfactory, and 5 = very satisfactory [14]. The records of postoperative fentanyl consumption were extracted from the internal memory of the CADD-Solis Ambulatory Infusion Pump and managed with the CADD™-Solis Medication Safety Software (Smiths Medical).

In the pilot study, the difference in the mean number of anesthetized dermatomes 24 h after the initial thoracic paravertebral levobupivacaine injection between the Bolus group (n = 9, 6.7 segments) and Infusion group (n = 13, 3.7 segments) was 3.0 with standard deviations of 2.4 in the Bolus group and 0.8 in the Infusion group. A sample size of 11 patients per group was the minimum calculated number needed to provide a statistical power of 0.95 and a significance level of 0.05 using the two-sided Welch's t-test. Because we expected a dropout rate of 30%, 16 patients per group were enrolled in the present study. Patients who underwent randomization and

184 received the assigned intervention were included in the efficacy analyses on the basis of an
185 intention-to-treat principle.

186 The number of anesthetized dermatomes after the initial thoracic paravertebral
187 levobupivacaine injection were analyzed using a linear mixed effect model with an unstructured
188 residual covariance matrix for measurements within patient and with interventions (Bolus group
189 or Infusion group), time point, and interaction between interventions and time point as fixed
190 effects and sex as a covariate. Secondary efficacy outcomes other than the number of
191 anesthetized dermatomes and safety outcomes are presented as the median [interquartile range]
192 or n (%). Baseline and perioperative characteristics are summarized as frequencies for
193 categorical data and mean ± standard deviation for continuous data.

194 All tests were two-sided, and $P < 0.05$ was considered statistically significant. All statistical
195 analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Thirty-two consecutively enrolled patients were randomized, and all patients received their allocated interventions. Contrast agent spread was adequate after injection into the TPVS in all subjects, and no catheters were repositioned or re-inserted after contrast agent injection. No patients were excluded during the follow-up period; hence, 32 patients were included in the final analysis (Fig. 1). The baseline and perioperative characteristics were comparable between the Bolus and Infusion groups (Table 1). Blood samples from one patient in the Bolus group and one patient in the Infusion group were inadequately preserved. Therefore, arterial levobupivacaine concentration was evaluated using blood samples from 15 patients in each group.

Figure 2 shows the time course of the number of anesthetized dermatomes after the initial thoracic paravertebral levobupivacaine bolus. The number of anesthetized dermatomes 24 h after the initial thoracic paravertebral levobupivacaine bolus (point estimate [95% confidence interval]) was larger in the Bolus group (6.8 [5.7-7.9]) than in the Infusion group (3.1 [2.0-4.2]) ($p < 0.001$) (Table 2). The number of anesthetized dermatomes at 6, 12, and 48 h after the initial bolus of levobupivacaine were also significantly larger in the Bolus group (Table 2). No significant differences other than the number of anesthetized dermatomes were observed in the secondary efficacy outcomes (Table 3). No patient required post-operative anti-emetics. There were no complications related to thoracic paravertebral block.

Figure 3 shows the levobupivacaine concentration during programmed intermittent thoracic paravertebral injection or continuous thoracic paravertebral infusion for 24 h after the initial thoracic paravertebral levobupivacaine bolus. The plasma concentration of levobupivacaine showed no significant differences between the two groups. The highest levobupivacaine

218 concentration observed in our study was 1.368 μg/mL in the Bolus group at 24 h, which did not
219 reach a toxic level.

DISCUSSION

We demonstrated that programmed intermittent thoracic paravertebral bolus injection of levobupivacaine provides a wider region of anesthetized dermatomes than continuous infusion with an identical hourly dose of levobupivacaine. However, no analgesic differences were observed. In previous studies, repeated bolus injection of a local anesthetic into the TPVS was achieved manually [15,16], and the effect of repeated intermittent bolus in terms of analgesic effect for post-thoracotomy analgesia is controversial. Furthermore, anesthetized dermatomes have not been elucidated in those previous studies. Recently, infusion pumps capable of delivering programmed intermittent boluses have become available [17,18], facilitating the administration of a repeated or programmed intermittent bolus regimen to nerves for postoperative analgesia. Several factors are related to the programming of intermittent bolus, such as the concentration, volume and type of local anesthetic, interval between bolus injections, and infusion speed during each injection [17]. When a patient-controlled local anesthetic injection regimen is included, a further detailed program can be available [18]. Even in labor epidural analgesia in which the advantage of the programmed intermittent epidural bolus technique has been well elucidated, the optimal regimen is still not known and varies significantly among previous studies [18,19]. Although further study is required to determine the appropriate programmed intermittent bolus regimen of thoracic paravertebral block to achieve better post-thoracotomy analgesia, the results of the present study can theoretically be beneficial for reducing postoperative pain after other surgical procedures with a larger incision.

Recently, various types of ultrasound-guided techniques to approach the TPVS have been developed [20]. For example, the paralaminar in-plane approach provided wider sensory block and superior analgesia than intercostal the approach when 20 mL of 0.5% ropivacaine was injected at

243 the start and end of surgery, followed by continuous infusion of 0.2% ropivacaine at 5 mL/h [21].
244 In one of the previous studies involving repeated bolus injection of a local anesthetic into the
245 TPVS, a landmark-based technique was used [15]. In another study, a catheter was placed under
246 direct vision by the operating surgeon [16]. Taken together, the approach to the TPVS needs to be
247 considered in addition to the programmed intermittent thoracic paravertebral bolus regimen to
248 obtain better analgesia.

249 One concern during programmed intermittent thoracic paravertebral bolus for postoperative
250 analgesia is a sharp increase in the plasma concentration of the local anesthetic that presumably
251 occurs after each intermittent bolus, which results in local anesthetic systemic toxicity. Although
252 not taking into consideration the site of injection, the maximum dose for a single dose and total
253 dose in a 24 h period of levobupivacaine was proposed as 150 mg and 400 mg, respectively [22]. In
254 the present study, the initial bolus dose and cumulative dose (first 24 h) of levobupivacaine were
255 50 mg and 290 mg, respectively. In a previous report, an initial bolus of 0.5% levobupivacaine
256 20 mL followed by repeated bolus of 0.5% levobupivacaine 15 mL every 6 h (400 mg/day) [16] did
257 not cause local anesthetic systemic toxicity. Although the programmed intermittent bolus
258 regimen used in the present study did not cause systemic local anesthetic toxicity or hypotension,
259 we should keep in mind that the programmable infusion pump can inject local anesthetic solution
260 automatically in the absence of medical staff and without checking the patient's status.

261 The safe range of the plasma levobupivacaine concentration during continuous peripheral
262 nerve blocks has not been established [23]. At an arterial concentration of 2.51 μg/mL [24] or 1.99
263 μg/mL [25] or less, no central nervous or cardiovascular toxicity was reported. The venous plasma
264 levobupivacaine concentration that induces neurological symptoms was 2.62 μg/mL in a study
265 on human volunteers [26]. In the present study, the maximum levobupivacaine concentration was

1.368 μg/mL at 24 h after the initial bolus injection of paravertebral levobupivacaine (Fig. 3B). Judging from a previous report [27], the levobupivacaine concentration might not have reached its steady state during the first 24 h of this study. However, it seems unlikely that the plasma levobupivacaine concentration reached the estimated toxic level (2 μg/mL or higher) at the end of the study period. Taken together, the programmed intermittent thoracic paravertebral bolus of levobupivacaine regimen used in the present study can be considered safe with sufficient margin.

This prospective study has several limitations. First, we did not assess if the anesthetized dermatomes covered the surgical incision. Although we placed the thoracic paravertebral catheter close to the thoracotomy incision site (4th to 6th intercostal space), some incision sites might not have been anesthetized in some patients even in the Bolus group. This could have influenced the result that programmed intermittent bolus did not provide a better analgesic effect than continuous infusion in this study and explained the controversial results of previous studies [15,16]. In theory, programmed intermittent bolus would provide better postoperative analgesia because a significantly larger number of anesthetized dermatomes would be obtained. As we strived to prove the hypothesis that the number of anesthetized dermatomes is larger when the programmed intermittent bolus is applied to thoracic paravertebral block, the power of this study might be insufficient to reveal the difference in opioid consumption or pain between the two groups. In fact, the Infusion group tended to have greater postoperative fentanyl consumption. Further studies are warranted to determine whether a programmed intermittent bolus regimen provides superior analgesia with sufficient sample size.

Second, we measured the arterial levobupivacaine concentration up to 24 h after the initial levobupivacaine injection although it might have been better to continue the measurements up to 48 h or longer. Because the radial artery catheter was no longer required clinically beyond

postoperative day 1 and the levobupivacaine concentration was not the primary outcome measure, we did not keep the arterial catheter in place only for blood sampling in consideration of the patients' comfort and safety.

CONCLUSION

In conclusion, the programmed intermittent thoracic paravertebral bolus of levobupivacaine provided a wider dermatomal spread of sensory block than continuous paravertebral infusion with an identical hourly dose of levobupivacaine.

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Figure Legends

Figure 1:

CONSORT flow diagram.

Figure 2:

Time course of the number of anesthetized dermatomes after the initial paravertebral bolus injection of 0.25% levobupivacaine 20 mL in patients receiving programmed intermittent bolus injection with 0.2% levobupivacaine 10 mL every 2 h (red circle), or continuous infusion with 0.2% levobupivacaine 5 mL/h (blue square), respectively. Data are expressed as mean ± standard deviation.

Figure 3:

Time-dependent change in the plasma concentration of levobupivacaine during programmed intermittent bolus injection of 0.2% levobupivacaine 10 mL every 2 h (red dotted line), or continuous infusion of 0.2% levobupivacaine 5 mL/h (blue line), respectively, after the initial bolus injection of 0.25% levobupivacaine 20 mL. (A) Plasma concentration of levobupivacaine. Data are shown as mean ± standard deviation. (B) Plots of the plasma concentration of levobupivacaine in each patient.

Table 1. Baseline and perioperative characteristics of the study patients

	Bolus group (n = 16)	Infusion group (n = 16)
Age (yr)	68 (7)	72 (7)
Gender (M/F)	10/6	10/6
Height (cm)	161 (8)	161 (9)
Weight (kg)	57 (9)	59 (12)
Body mass index (kg/m^2)	22 (2)	23 (3)
American Society of Anesthesiologists physical status classification (I/II/III)	2/14/0	1/15/0
Duration of anesthesia (min)	307 (57)	314 (57)
Duration of surgery (min)	202 (58)	209 (55)
Intraoperative remifentanil (μg/kg/min)	0.21 (0.04)	0.21 (0.03)

Data are presented as mean (standard deviation), or n.

Table 2. Time course of the estimated number of anesthetized dermatomes in patients receiving initial paravertebral bolus injection of 0.25% levobupivacaine 20 mL followed by programmed intermittent bolus injection with 0.2% levobupivacaine 10 mL every 2 h (Bolus group), or by continuous infusion with 0.2% levobupivacaine 5 mL/h (Infusion group).

Time after initial levobupivacaine bolus [h]	Bolus group	Infusion group	Difference (Bolus - Infusion)	P value
	Estimate (95% confidence interval)	Estimate (95% confidence interval)	Estimate (95% confidence interval)	
1	6.0 (4.9 - 7.0)	4.9 (3.9 - 6.0)	1.1 (-0.4 - 2.5)	0.153
6	5.7 (4.7 - 6.6)	3.5 (2.6 - 4.5)	2.1 (0.8 - 3.4)	0.002
12	5.4 (4.3 - 6.4)	3.4 (2.4 - 4.4)	1.9 (0.5 - 3.3)	0.009
24	6.8 (5.7 - 7.9)	3.1 (2.0 - 4.2)	3.7 (2.2 - 5.2)	< 0.001
48	6.5 (5.3 - 7.6)	2.6 (1.4 - 3.8)	3.9 (2.3 - 5.6)	< 0.001

Data are expressed as point estimate (95% confidence interval).

Table 3. Postoperative patient data except for the number of anesthetized dermatomes during thoracic paravertebral levobupivacaine administration (approximately 48 h postoperatively)

Parameters	Bolus group (n = 16)	Infusion group (n = 16)	P-value
Pain at rest after initial bolus of thoracic paravertebral levobupivacaine (numerical rating scale) *			
0.5 h	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.59
1 h	1.5 [0.0-6.0]	0.0 [0.0-2.5]	0.49
6 h	0.5 [0.0-2.5]	0.5 [0.0-2.5]	0.98
12 h	0.0 [0.0-4.0]	0.5 [0.0-2.5]	0.93
24 h	1.0 [0.0-3.0]	1.0 [0.0-4.0]	0.55
48 h	0.0 [0.0-2.0]	0.0 [0.0-1.5]	0.73
Pain during coughing after initial bolus of thoracic paravertebral levobupivacaine (numerical rating scale) *			
0.5 h	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.57
1 h	5.0 [0.0-7.0]	1.5 [0.0-5.0]	0.44
6 h	2.5 [0.5-5.0]	2.0 [0.0-5.0]	0.67
12 h	2.5 [1.0-7.0]	3.5 [1.5-4.5]	0.91
24 h	4.0 [2.5-6.0]	4.0 [2.0-6.0]	0.58
48 h	3.5 [2.5-6.0]	2.0 [1.0-3.0]	0.09
Number of intravenous patient-controlled analgesia fentanyl uses			
0-12 h	2.0 [0.0-2.5]	0.5 [0.0-2.5]	0.38
12-24 h	0.0 [0.0-2.0]	1.0 [0.0-2.0]	0.65
24-36 h	0.0 [0.0-1.0]	1.0 [0.0-2.0]	0.23
36-48 h	0.0 [0.0-1.0]	1.0 [0.0-2.5]	0.15
all	2.5 [0.5-7.5]	5.5 [3.0-7.0]	0.36
Number of diclofenac suppository uses			
0-24 h	3 (18.8)	1 (6.3)	0.60
24-48 h	1 (6.3)	2 (12.5)	> 0.99
all	4 (25)	3 (18.8)	> 0.99
Patient satisfaction **			
0-24 h	5 [5-5]	4.5 [4-5]	0.14
24-48 h	5 [5-5]	5 [4-5]	0.24
Nausea	7 (43.8)	6 (37.5)	> 0.99

Vomiting	3 (18.8)	2 (12.5)	> 0.99
Hypotension	0 (0.0)	0 (0.0)	-

Data are presented as the median [interquartile range] or n (%).

* Patients were asked to assess the level of pain on a scale of 0 to 10 (0 = no pain, 10 = the worst imaginable pain).

** Patients were asked to rank their satisfaction on postoperative pain management according to the following scale: 1 = very unsatisfactory, 2 = unsatisfactory, 3 = neutral, 4 = satisfactory, and 5 = very satisfactory.

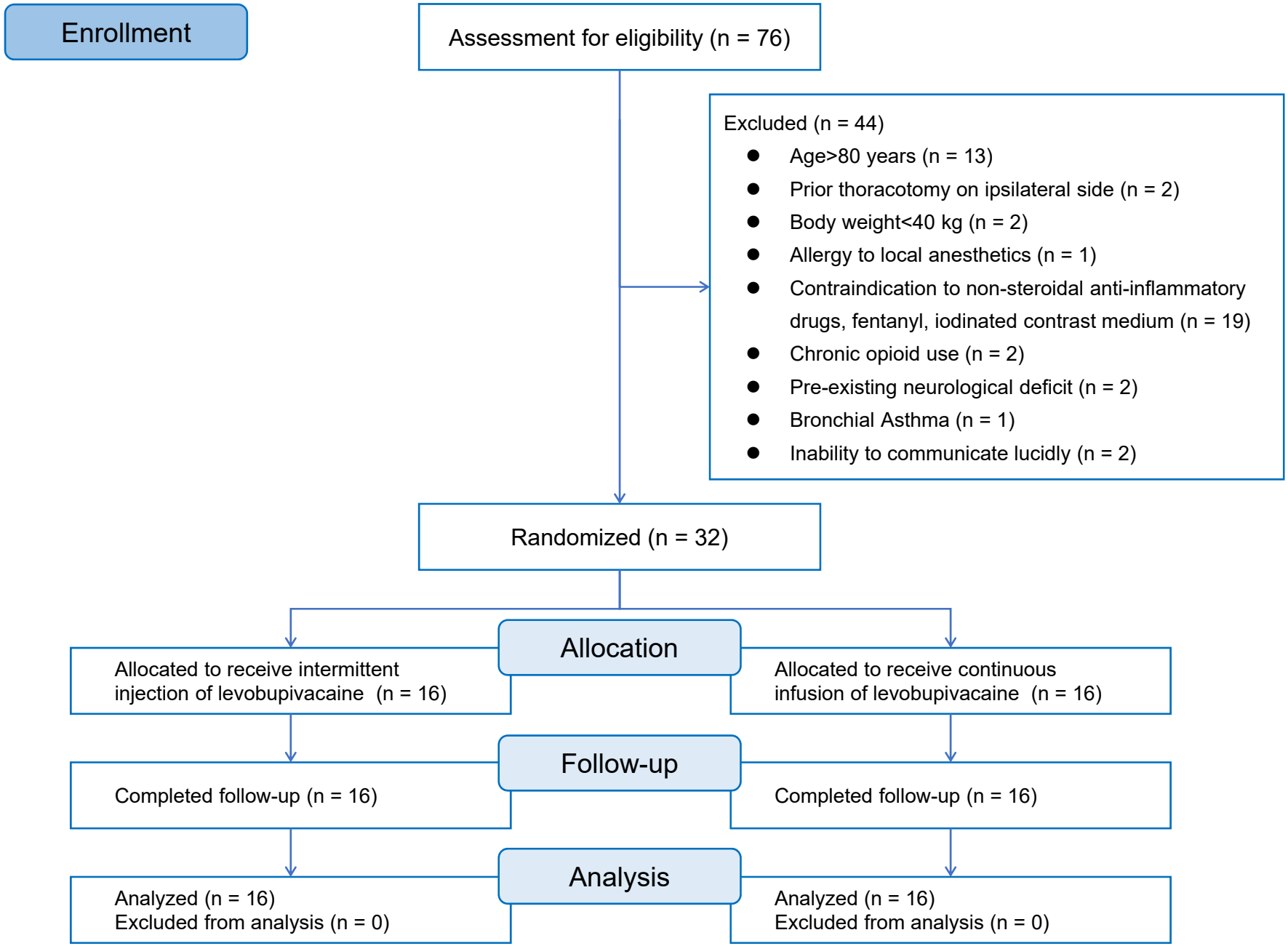
Enrollment
Assessment for eligibility (n = 76)
Excluded (n = 44)
Age>80 years (n = 13)
Prior thoracotomy on ipsilateral side (n = 2)
Body weight<40 kg (n = 2)
Allergy to local anesthetics (n = 1)
Contraindication to non-steroidal anti-inflammatory drugs, fentanyl, iodinated contrast medium (n = 19)
Chronic opioid use (n = 2)
Pre-existing neurological deficit (n = 2)
Bronchial Asthma (n = 1)
Inability to communicate lucidly (n = 2)
Randomized (n = 32)
Allocation
Allocated to receive intermittent injection of levobupivacaine (n = 16)
Allocated to receive continuous infusion of levobupivacaine (n = 16)
Follow-up
Completed follow-up (n = 16)
Completed follow-up (n = 16)
Analysis
Analyzed (n = 16)
Excluded from analysis (n = 0)
Analyzed (n = 16)
Excluded from analysis (n = 0)

Fig. 1

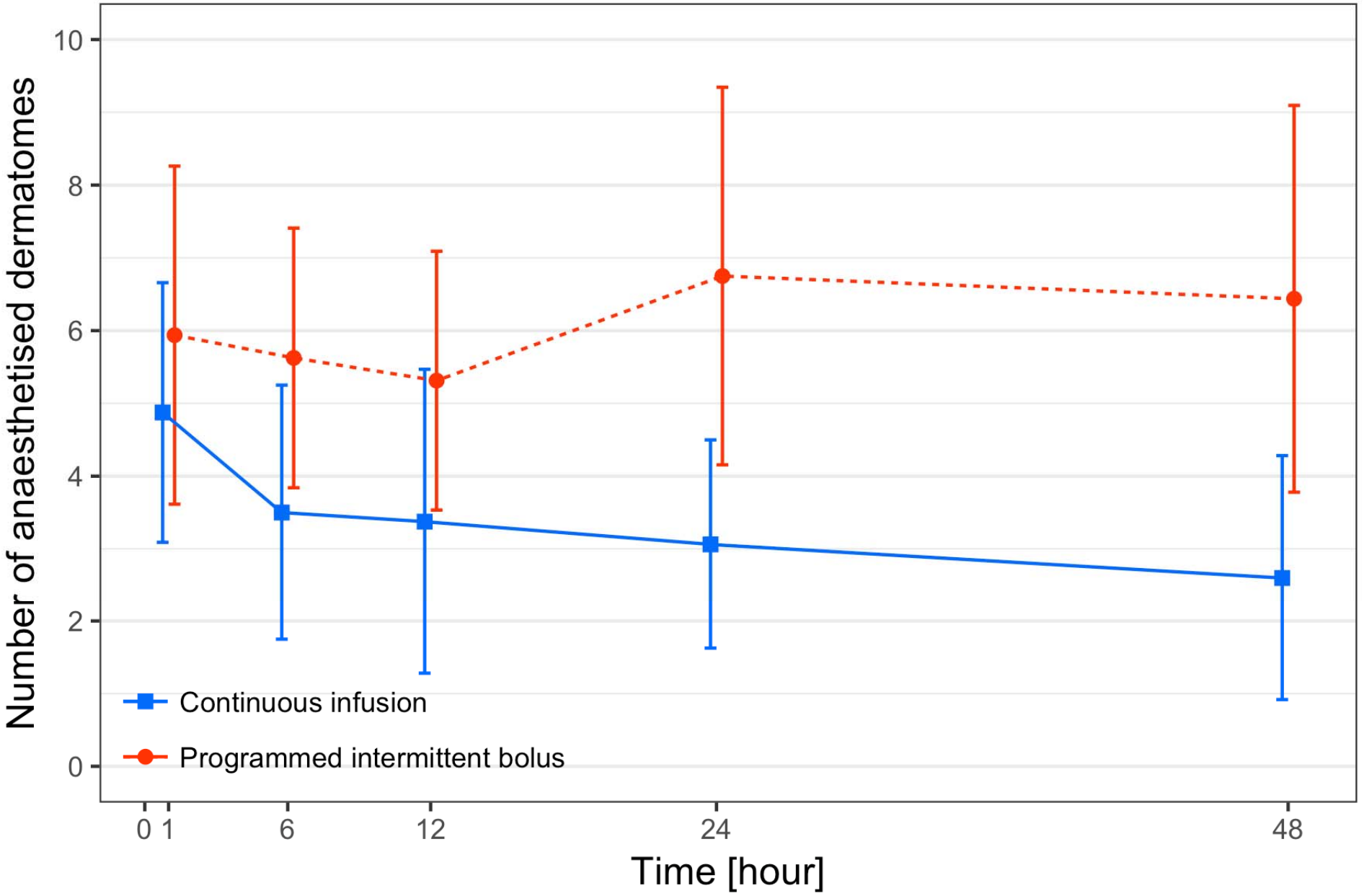
Number of anaesthetised dermatomes
10
8
6
4
2
0
Continuous infusion
Programmed intermittent bolus
0 1
6
12
24
48
Time [hour]

Fig. 2

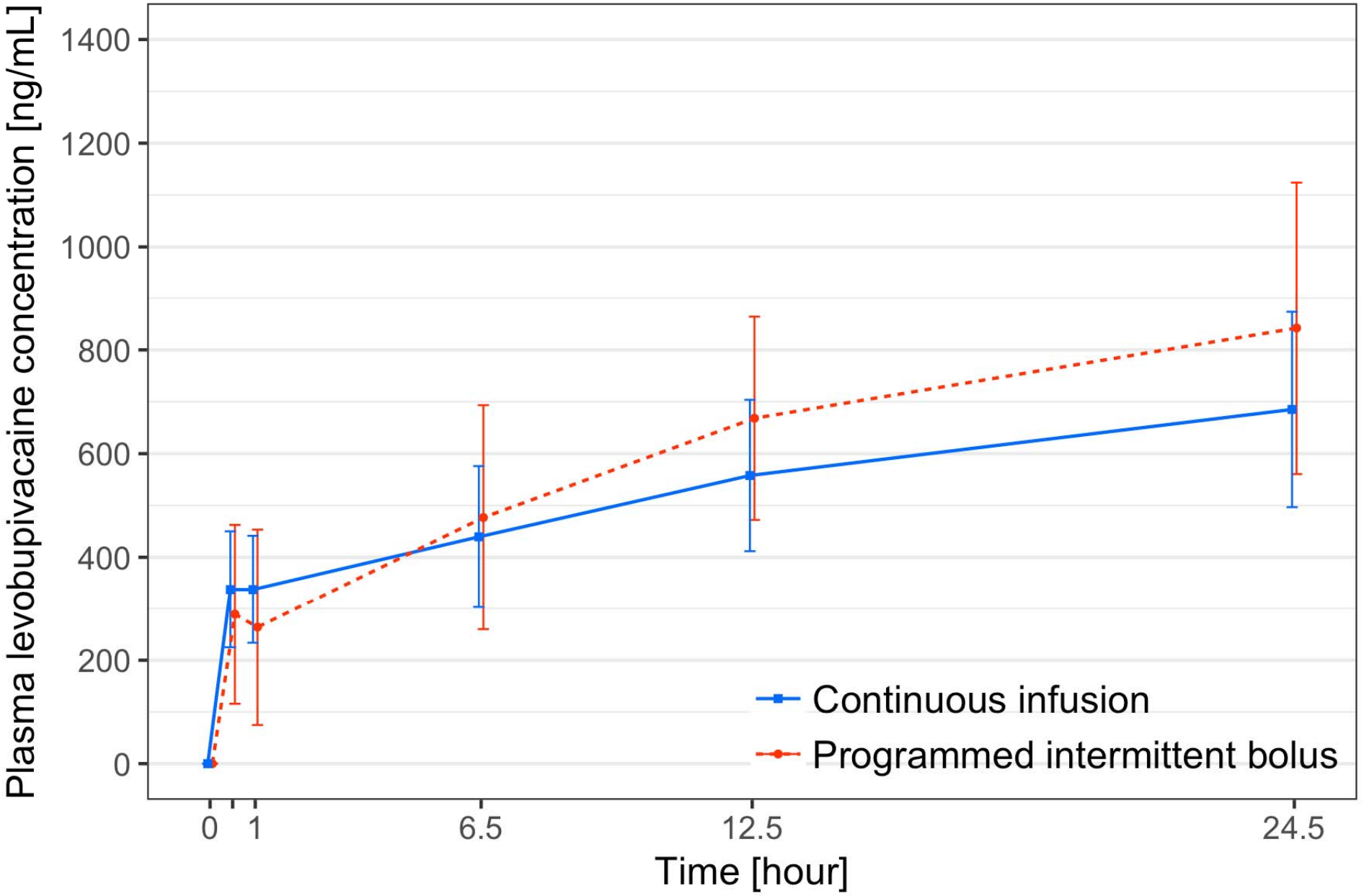
Plasma levobupivacaine concentration [ng/mL]
1400
1200
1000
800
600
400
200
0
0
1
6.5
12.5
24.5
Time [hour]
Continuous infusion
Programmed intermittent bolus

Fig. 3A

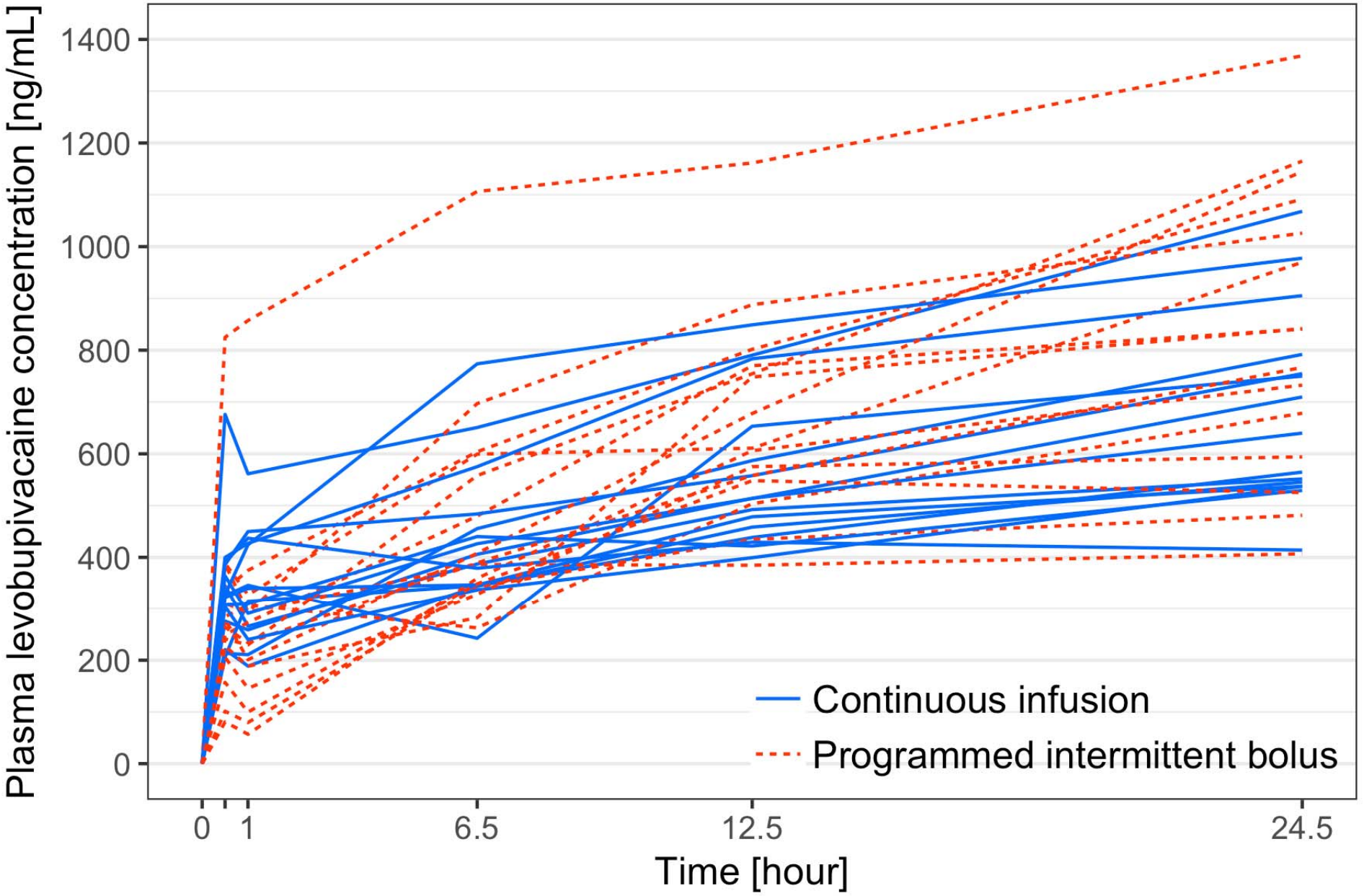
Plasma levobupivacaine concentration [ng/mL]
1400
1200
1000
800
600
400
200
0
0
1
6.5
12.5
24.5
Time [hour]
Continuous infusion
Programmed intermittent bolus

Fig. 3B