Original Article

Comparison of Plasma Levobupivacaine Concentrations Following Single-Shot Thoracic Paravertebral and Retrolaminar Blocks

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ABSTRACT

Introduction: Retrolaminar blocks (RLBs) are effective, easy to perform, and safer than paravertebral blocks (PVBs). However, the pharmacokinetics of RLBs is not well understood. We compared changes in the plasma concentrations of levobupivacaine following a single-shot thoracic PVB or RLB.

Methods: The study protocol was approved by the ethics committee of Tokyo National Medical Center (R 15-135), and the trial was registered in the UMIN Clinical Trials Registry (UMIN000021759). The primary outcome was comparison of plasma levobupivacaine concentrations following single-shot thoracic PVB and RLB. A total of 46 women undergoing partial mastectomy were randomly allocated to receive either a thoracic PVB or RLB. In both groups, 2 mg kg^{-1} levobupivacaine (0.5%) was administered, and blood samples were collected at 5, 10, 20, 60, and 120 min after the injection.

Results: Forty-two patients were analyzed for plasma levobupivacaine concentration, and 30 patients were assessed for pain. The maximum plasma concentration and time to reach the maximum concentration were determined using nonlinear regression analysis and were 1.32 μg ml^{-1} and 9 min in the thoracic PVB group, respectively, and 1.47 μg ml^{-1} and 5.5 min in the RLB group, respectively. The intraoperative opioid consumption did not differ between groups, but the time to the first request for analgesics was significantly shorter for the RLB group ($p = 0.0318$).

Conclusions: The plasma concentration of levobupivacaine peaked earlier in the RLB group than in the thoracic PVB group. Therefore, local anesthetic toxicity should be avoided when performing RLB.

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KEYWORDS: mastectomy, segmental, nerve block, pain, postoperative

Introduction

A paravertebral block (PVB) causes analgesia without postoperative nausea and vomiting and can reduce the development of chronic pain. Despite these advantages, recent reports[1–4)] emphasized the risk of serious complications of PVB, such as local anesthetic toxicity, epidural or intrathecal spread of local anesthetics, and pneumothorax.

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By contrast, a retrolaminar block (RLB), which is a modified PVB, is considered a simpler and easier technique[5, 6] and is associated with fewer serious complications. Mechanical complications and analgesic effects have been evaluated in several studies, but the plasma concentrations of local anesthetics have not been fully investigated.

Knowledge of the pharmacokinetics of the local anesthetics used for RLB is important to understand the potential risk of systemic toxicity. However, currently available data are scarce. Furthermore, an understanding of the pharmacokinetics of each type of block is important to avoid fatal local anesthetic toxicity.

In this study, we compared the pharmacokinetics of levobupivacaine and analgesic efficacy after a single-shot RLB or thoracic PVB (TPVB) in patients undergoing breast surgery.

Materials and Methods

The study protocol was approved by the ethics committee of Tokyo National Medical Center (R15-135), and the trial was registered in the UMIN Clinical Trials Registry (UMIN000021759). Written informed consent was obtained from all patients. The inclusion criteria included adult women with an American Society of Anesthesiologists physical status of 1-2 and who were scheduled to undergo unilateral partial mastectomy with sentinel lymph node biopsy. The exclusion criteria were patients with a known allergy to local anesthetics or a history of renal or hepatic dysfunction. The primary outcome was the comparison of plasma levobupivacaine concentrations following single-shot TPVB and RLB. The secondary outcome comprised the analgesic efficacy of TPVB and RLB, the intraoperative consumption of remifentanil and fentanyl, and the incidence of postoperative nausea and vomiting.

No premedication was given to the patients. Intravenous access was secured, and standard noninvasive monitoring devices were attached to measure blood pressure, continuous electrocardiography, and pulse oximetry. To facilitate tracheal intubation, general anesthesia was induced with 2-3 mg kg^{-1} propofol and 3-4 μg ml^{-1} fentanyl with 0.6-0.9 mg kg^{-1} rocuronium. Anesthesia was maintained with propofol and remifentanil, and body temperature and bispectral index (Medtronic, Dublin, Ireland) were continuously monitored. Immediately after inducing anesthesia, an experienced anesthetist performed a TPVB or RLB by using a 22 G 80 mm Tuohy needle (Hakko, Tokyo, Japan) in lateral position. Patients were randomly allocated to either the TPVB or RLB group and were injected accordingly with 2 mg kg^{-1} levobupivacaine (0.5%). TPVB was performed using the in-plane method at the fourth thoracic vertebra (T4) by using an ultrasound device (EDGE™, SonoSite, Bothell, WA, USA) with a 6-15 MHz linear probe. Probes were placed horizontally to the ribs, and transverse processes and pleural membranes were identified. The needle was advanced parallel to the ribs. When the needle reached the PV space, a small amount of 0.9% saline was administered. After confirming that the pleura was pushed down, local anesthetic was administered. RLB was performed according to the previously reported blind method,[7] and a needle was inserted 1.5 cm from the midline next to the T4 spinous process and advanced at an approximately 45° angle to the skin in the cranial direction until contact was made with the vertebral lamina. Levobupivacaine was injected after a negative aspiration test of air, blood, and cerebrospinal fluid.

After the injection of the study drug, venous blood samples were obtained at 5, 10, 20, 60, and 120 min. Plasma was separated immediately by centrifugation at 4 ℃, and the plasma samples were subsequently frozen and stored until the plasma levobupivacaine concentrations were measured using high-performance liquid chromatography (Accela; Thermo Fisher Scientific Co., Ltd., Kanagawa, Japan) and liquid chromatography-mass spectrometry with a triple-stage quadrupole mass spectrometer (TSQ Quantum Ultra; Thermo Fisher Scientific Co., Ltd.).

The pain level was assessed according to a numerical rating scale (NRS) at 1 h after surgery and 6 h after the block. Furthermore, nonsteroidal anti-inflammatory drugs were given if the NRS score was more than four. Patients and nurses who performed pain assessment were blinded to the treatment group assignment throughout the study. Kaplan-Meier curves were used to estimate the time to the first request for analgesics within 6 h after surgery, and the log-rank test was used to determine the significance. The other data were analyzed using descriptive statistics, unpaired t-tests, Mann-Whitney U-test, and chi-square test. Descriptive data are presented as the mean (SD) when normally distributed or as the median (range, minimum-maximum) when not normally distributed.

The G*Power 3 program was used to determine the necessary sample size with no pilot study, and the results indicated that 40 patients were needed to perform a 2-way analysis of variance with an effect size of 0.25 and a statistical power of 0.8. Levobupivacaine concentrations were

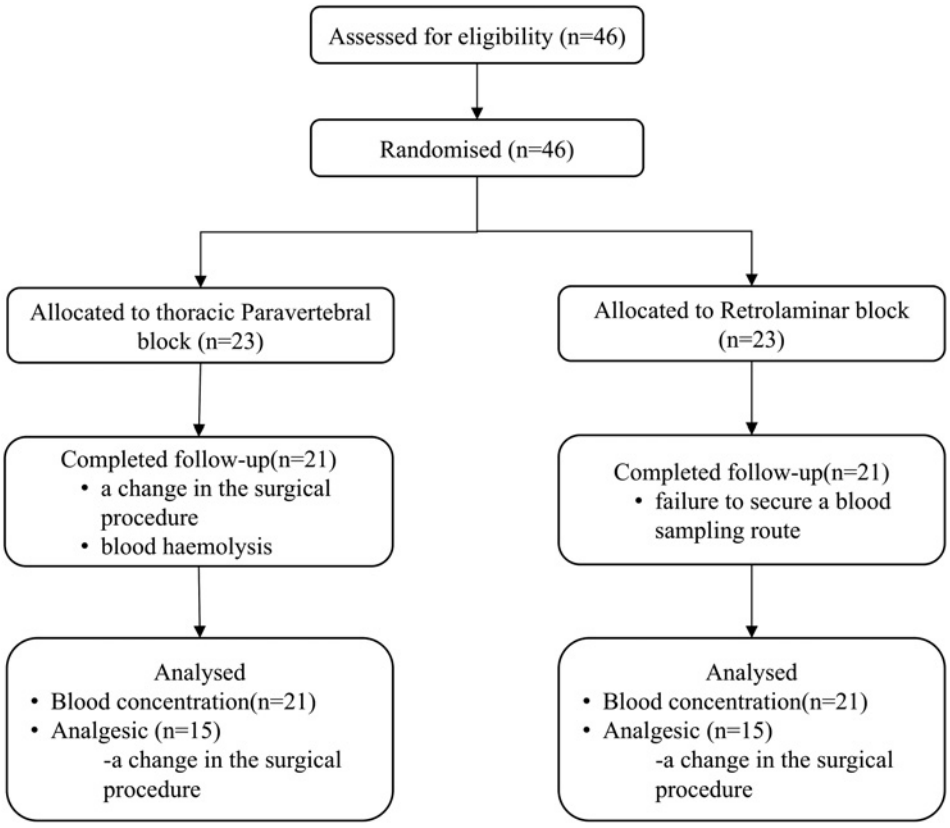

Fig. 1 CONSORT flow diagram

measured within and between groups by using a two-way analysis of variance with a Bonferroni post-hoc correction for multiple comparisons. The baseline and surgical characteristics between the groups were compared using a t-test or Mann-Whitney U-test as appropriate. To determine the maximum plasma concentration (Cmax) and time to reach Cmax (Tmax) in each group, a nonlinear regression analysis was performed using a two-compartment model of measured plasma concentrations. All statistical analyses, including the curve fittings and resampling simulations, were performed using the GraphPad Prism version 6.0 software package (GraphPad Software, San Diego, CA, USA). A probability of less than 5% was considered statistically significant.

Results

A total of 46 patients were enrolled, and 4 patients were excluded because of an unexpected change in the surgical procedure, blood sample hemolysis, or failure to secure a blood sampling route; the data of the remaining 42 patients were then analyzed (Fig. 1). Table 1 shows the baseline characteristics. No clinically significant changes in blood pressure, heart rate, or electrocardiography occurred, and no adverse events occurred in either group during the study period.

The mean (SD) plasma levobupivacaine concentrations at 5, 10, 20, 60, and 120 min after TPVB were 1.163 (0.259), 1.293 (0.271), 1.135 (0.203), 0.685 (0.128), and 0.493 (0.115) μg ml^{-1}, respectively; after RLB, the corresponding values were 1.415 (0.358), 1.289 (0.313), 0.953 (0.244), 0.587 (0.144), and 0.424 (0.124) μg ml^{-1}, respectively (Fig. 2). The concentrations were significantly different between the groups at only 5 min after each block. However, the mean Cmax did not differ significantly between the TPVB and RLB groups (1.293 vs. 1.415 μg ml^{-1}).

Nonlinear regression analysis showed that the Cmax and Tmax were 1.294 μg ml^{-1} and 9.5 min in the TPVB group, respectively, and 1.421 μg ml^{-1} and 5.5 min in the RLB group, respectively (Fig. 3). The correlations of determination (R^2) were 0.86 and 0.83 in the TPVB group and RLB group, respectively.

A total of 30 patients were assessed for pain after excluding 12 patients because of a change in the surgical procedure. The NRS scores did not differ significantly between groups at 1 h after surgery or at 6 h after the peripheral nerve block. Furthermore, the intraoperative

Table 1 Baseline characteristics of patients receiving either TPVB or RLB.

	TPVB (n = 21)	RLB (n = 21)	p
Age; years	49.4 (8.3)	51.6 (10.2)	0.54
Height; cm	160.0 (5.1)	157.9 (6.0)	0.20
Weight; kg	54.0 (7.8)	51.9 (6.1)	0.26
Body mass index; kg m^2	21.1 (2.9)	20.9 (2.6)	0.67
ASA I/II	15/6	15/6	1.00
Duration of anesthesia; min	160.9 (6.3)	167.9 (8.6)	0.52
Duration of surgery; min	115.0 (6.4)	127.5 (8.6)	0.25
Levobupivacaine dose; mg	107.5 (15.5)	103.5 (12.5)	0.28

Values are mean (SD) or number
ASA: American Society of Anesthesiologists; SD: standard deviation

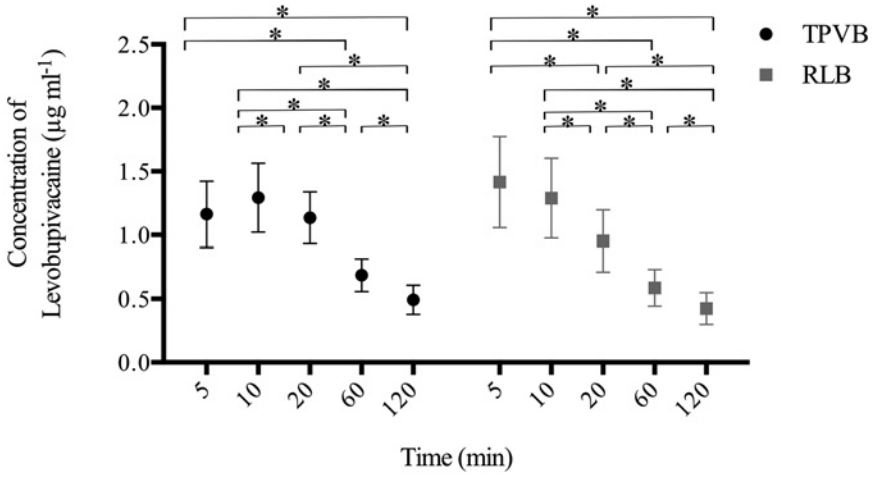

Fig. 2 Mean concentrations of levobupivacaine in each group at 5, 10, 20, 60, and 120 min after administration.
*p < 0.05, comparisons within groups.

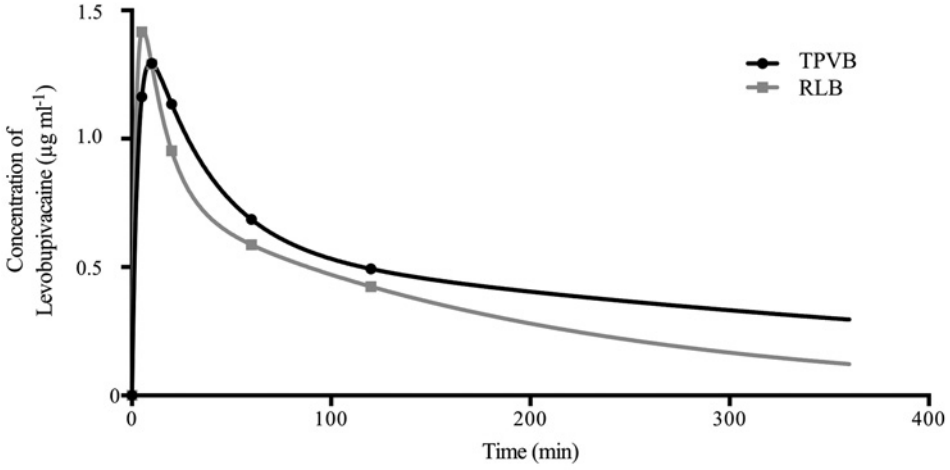

Fig. 3 Nonlinear regression analysis showing the difference in time to the mean peak plasma concentration of local anesthetic in patients receiving TPVB or RLB.

Table 2 Pain assessment, intraoperative doses of fentanyl or remifentanil, and number of postoperative nausea and vomiting incidences after either TPVB or RLB. IQR [range] or mean (SD).

	TPVB (n = 15)	RLB (n = 15)	p
Numerical rating score after surgery	0.0 (0.0 – 0.0 [0.0 – 1.0])	0.0 (0.0 – 0.0 [0.0 – 4.0])	0.473
Numerical rating score 60 min after surgery	1.0 (0.0 – 4.0 [0.0 – 5.0])	3.0 (2.0 – 4.0 [0.0 – 6.0])	0.089
Numerical rating score 6 h after block	1.0 (1.0 – 2.0 [0.0 – 5.0])	2.0 (1.0 – 3.0 [1.0 – 3.0])	0.2
Fentanyl dose; μg	213 (29.7)	206.7 (17.6)	0.46
Remifentanil dose; μg	605 (211)	613.5 (200)	0.91
Postoperative nausea and vomiting	2	1	1

IQR: interquartile range; SD: standard deviation

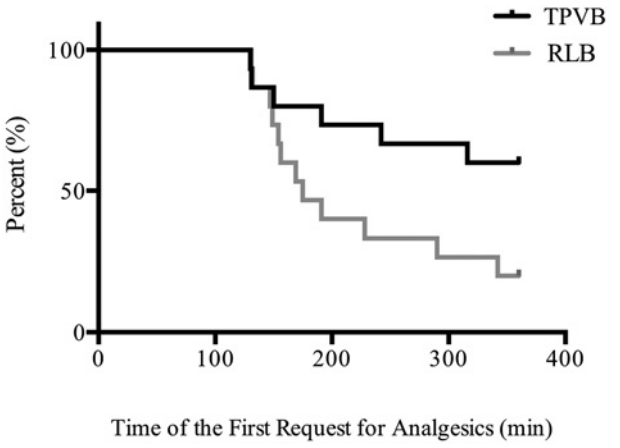

Fig. 4 Kaplan-Meier curves showing the time to the first request for analgesics within 6 h after surgery.

doses of fentanyl or remifentanil and the incidences of postoperative nausea and vomiting did not differ significantly between the groups (Table 2). No patient in either group developed clinically serious side effects.

The Kaplan-Meier estimate of the time to the first request for analgesics was 175 min (95% confidence interval [CI], 147-290) in the RLB group and 360 min (95% CI, 150-360) in the TPVB group (Fig. 4). Comparisons by log-rank test showed that the time to the first request for analgesics was significantly shorter in the RLB group than in the TPVB group ($p = 0.0318$).

Discussion

A deep understanding of the effects of the administration route and pharmacokinetics of local anesthetics is necessary to achieve an effective peripheral nerve block. We compared two techniques, namely, TPVB and RLB, and found that the plasma concentration of the local anesthetic rapidly reached the Cmax after the RLB procedure. Furthermore, postoperative analgesic efficacy was significantly lower in the RLB group than in the TPVB group. This observation is consistent with the short duration of the analgesic effect of RLB estimated by the Kaplan-Meier method.

A previous study[8] of TPVB using 2 mg kg^{-1} ropivacaine reported that the arterial blood Cmax and Tmax were 2.47 μg ml^{-1} and 7.5 min, respectively, and that the venous blood Cmax was 1.6 μg ml^{-1}. The results of the present study indicate that the Cmax and Tmax of the levobupivacaine concentration after TPVB were comparable. On the contrary, in the RLB group, the Cmax and Tmax were 1.421 μg ml^{-1} and 5.5 min, respectively, thus indicating that the Cmax was higher and that the Tmax was earlier than those in the TPVB group.

The difference between both Tmax and Cmax in the TPVB and RLB groups was attributed to three factors. First, in TPVB, local anesthetic is administered to the PV space. Given that the administration site of RLB is not a compartment like the PV space, the local anesthetic contact area in RLB may be larger than that in TPVB. Accordingly, levobupivacaine is rapidly absorbed.[9] Second, local anesthetics are readily absorbed into the bloodstream because the posterior external vertebral venous plexus is distributed in the lamina.[10] Third, a portion of the local anesthetic was administered into the erector spinae muscle. When a local anesthetic is administered intramuscularly, it is rapidly absorbed depending on its characteristics because muscles have a relatively high blood flow.[11] In the present study, there was little difference in the characteristics of the local anesthetic administered between the two groups. Therefore, no difference in plasma concentration due to hypertonicity, osmolality, and volume of local anesthetics was observed.

The onset of systemic toxicity parallels the plasma concentration of a local anesthetic.[12] Electroencephalography was not performed in the present study because the patients received general anesthesia. Given that there was

no apparent circulatory collapse or arrhythmia, we considered that the local anesthetic concentration did not reach a toxic range. Both groups in this study received a single 2 mg kg^{-1} dose of long-acting levobupivacaine. The venous concentration of levobupivacaine that causes central nervous system toxicity in healthy people was reported to be 2.62 μg ml^{-1}.[13] In the present study, the maximum venous plasma concentration 5 min after RLB was 1.991 μg ml^{-1}. Therefore, the levobupivacaine plasma concentration measured in this study was within the safe range.

The analgesic effect evaluated on the basis of the amount of fentanyl or remifentanil administered during surgery was equivalent in both groups. However, the analgesic effect of the blocks was different after surgery. The Kaplan-Meier curve showed a significant difference between groups in the time to the first request for analgesics. Previous reports[14] showed that RLB does not spread to the PV space unless the volume of anesthetic exceeds 30 ml. Furthermore, other studies reported[15] a lower analgesic efficacy in RLB. In the original[7] and previous reports[16] of RLB, local anesthetic was continuously administered via an inserted catheter, thus suggesting that the duration of the analgesic effect of RLB is short.

Various modified RLB methods have been reported, but the procedure is not yet fully established. Therefore, the effect of RLB, the absorption of the local anesthetic, and the plasma concentration may differ according to the puncture technique or injection site. Although RLB is considered to have fewer mechanical complications than TPVB, the plasma concentration can increase more rapidly after RLB than after TPVB. Other techniques, including ultrasound-guided RLB[17] and erector spinae plane block,[18] have also been reported. When selecting the most appropriate nerve block, it is important to consider the injection site, analgesic effect range, volume, and local anesthetic dose.

This study has some limitations. Similar to a previous study,[15] the venous plasma concentrations were measured only at 5, 10, 20, 60, and 120 min following each block. Therefore, the changes in plasma levobupivacaine concentration may not have been fully characterized. The pharmacokinetic parameters in the absorption process were also not analyzed. It is possible that the arterial plasma levobupivacaine concentration peaked before 5 min in the RLB group. The range of the analgesic effect could not be evaluated for either block because of the need for compressive wound dressing after surgery. The number of cases was also insufficient to evaluate the analgesic efficacy; therefore, further studies are needed.

In conclusion, the plasma concentrations of levobupivacaine after RLB were similar to those after TPVB, but the variation in concentration after 5 min was substantial. The plasma concentration of levobupivacaine peaked earlier in the RLB group than in the TPVB group; therefore, local anesthetic toxicity should be avoided when performing RLB.

Authors' contributions: R.O. designed the study and wrote the first draft of the paper.

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Conflicts of interest: The Anesthesiology Department of Toho University received a donation from Edwards Life Science in 2017. Edwards Life Science is a company that specializes in cardiovascular monitoring and treatment but not regional anesthesia or pharmacological interventions. This donation did not affect the design or performance of the study, the creation of the manuscript, or the decision to submit the manuscript to the journal.

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