Chronological changes in plasma levobupivacaine concentrations after bilateral modified-thoracoabdominal nerve block through perichondrial approach

Katsuhiro Aikawa, MD, PhD, Yuka Uchinami, MD, PhD Yuji Morimoto, MD, PhD

Department of Anesthesiology and Critical Care Medicine, Hokkaido University Hospital, Sapporo, Japan

Address correspondence to:

Katsuhiro Aikawa, MD, PhD, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Hospital, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan (katsuhiro.aikawa@med.hokudai.ac.jp)

Phone/Fax: +81-11-706-7861

ORCID: Katsuhiro Aikawa http://orcid.org/0000-0003-0871-3956

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All authors contributed to the study conception and design. Material preparation, data collection

and analysis were performed by Katsuhiro Aikawa, and Yuka Uchinami. The first draft of the manuscript was written by Katsuhiro Aikawa and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest:

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Abstract

The local anesthetic (LA) systemic toxicity of trunk blocks is a major concern. Recently, modified-thoracoabdominal nerve block through perichondrial approach (M-TAPA) has attracted attention; however, plasma LA level is unknown. We tested whether the peak plasma LA concentration following M-TAPA, using 25 mL of 0.25% levobupivacaine mixed with epinephrine on each side, would be below the toxic level (2.6 μg/mL). We recruited 10 patients undergoing abdominal surgery with planned M-TAPA between November 2021 and February 2022. In all patients, 25 mL of 0.25% levobupivacaine mixed with 1:200,000 epinephrine was administered on each side. Blood samples were obtained at 10, 20, 30, 45, 60, and 120 min after the block. The highest individual peak and mean peak plasma LA concentration were 1.03 and 0.73 μg/mL, respectively. We could not capture the peak in five patients; however, the highest concentration in all patients were significantly lower than the toxic level. A negative correlation between the peak level and body weight was observed. Our results indicated that the plasma LA concentration following M-TAPA using total of 50 mL of 0.25% levobupivacaine with epinephrine remains below the toxic level. Further research is required due to the small sample size of this study.

Introduction

The elevation of plasma local anesthetic (LA) concentration and subsequent LA systemic toxicity (LAST) of regional anesthetic techniques are major concerns [1]. Especially, substantial attention has been gathered on the trunk blocks due to the property that LA spreads along the broad neurovascular plane, which can lead to rapid absorption [2]. Therefore, a number of studies have been conducted to clarify the chronological plasma LA concentration and estimate the risk of LAST [3, 4].

In 2019, Tulgar et al. [5] introduced the modified-thoracoabdominal nerve block through perichondrial approach (M-TAPA), which has attracted increasing attention [6-8]. Given its broad sensory coverage, LA may spread broadly and reach the toxic levels. However, the plasma LA concentration has not been investigated. Previous studies have reported that a mixture of epinephrine decreases the peak levobupivacaine concentration (C_{max}) and prolongs the time to peak (T_{max}), which could help prevent LAST [4]. Therefore, we conducted a single-arm, exploratory study to test the hypothesis that the peak plasma LA concentration following M-TAPA, using 25 mL of 0.25% levobupivacaine with epinephrine on each side, would be below the toxic level (2.6 μg/mL) [9].

Methods

This study was approved by the Institutional Review Board of Hokkaido University Hospital (IRB No. 021–0021, approval date: September 6, 2021) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study was registered in the UMIN Clinical Trial Registry prior to patient enrollment (UMIN000045406). Ten patients (age ≥20 years) undergoing abdominal surgery with planned M-TAPA were recruited after obtaining written informed consent. The exclusion criteria were as follows: American Society of Anesthesiologists Physical Status ≥3, allergy to LA, body weight ≤50 kg, liver/kidney dysfunction, pregnancy, and serum albumin ≤3 g/dL.

Anesthetic management was performed according to our institutional practices. In the operation room, all patients were monitored for noninvasive blood pressure, electrocardiography, and peripheral oxygen saturation. After tracheal intubation, the radial arterial line was secured. Subsequently, bilateral M-TAPA was performed by a single anesthesiologist (KA), as previously described [5, 6], using 25 mL of 0.25% levobupivacaine with 1:200,000 epinephrine on each side. We note that the needle tip was positioned between the posterior aspect of the 9th or 10th level of the costal cartilage and the origin of the transversus abdominis muscle, based on Tulgar's original report [10]. However, in this study, a precise postoperative pinprick test was challenging as the patients who underwent colectomy had many gauze dressings on the abdomen. Since we have

confirmed that our procedure successfully leads to sensory loss around the umbilicus in all patients in a previous study [6], we adopted a brief pinprick test around the umbilicus to evaluate block success postoperatively.

A 2 mL blood sample was collected from the arterial line at each time point, i.e., 10, 20, 30, 45, 60, and 120 min, after the block completion and promptly centrifuged (1500 *g*, 10 min at 4 °C). A 0.6 mL of plasma was stored at -20 °C until measurement. The plasma levobupivacaine concentration was measured using liquid chromatography-tandem mass spectrometry with the electrospray ionization technique, using praziquantel as the internal standard [11]. All samples were prepared using deproteination with acetonitrile. Chromatographic separation was achieved with two mobile phases ([A] 5 mM ammonium acetate buffer [pH adjusted to 5.6 with acetic acid] and [B] acetonitrile; A:B = 65:35). The calibration curves were linear between 0.5 and 2,000 ng/mL with $1/\chi 2$ weighting ($R^2 \geq 0.98$).

The primary outcome was the plasma levobupivacaine concentrations in each time points. The sample size was determined based on previous studies [3, 4]. As the secondary outcome, the correlation between C_{max} and patient age, height, and weight, and adverse events occurring within 12 hours after M-TAPA were tested. Statistical analysis was performed using JMP Pro 16 software (SAS Institute, Japan).

Results

We enrolled 10 patients who underwent laparoscopic surgeries between November 2021 and February 2022. All samples were successfully collected and measured. The patient demographic data and measurement results are listed in Table 1. We confirmed decreased or no painful sensation in all cases postoperatively. The highest individual peak plasma concentration was 1.03 μg/mL at 60 min (Figure 1). The mean C_{max} and T_{max} were 0.73 (95% confidence interval [CI]: 0.60 to 0.85) μg/mL and 85.5 (95% CI: 59.2 to 111.8) min, respectively. The plasma levobupivacaine levels remained below the toxic level within 120 min after M-TAPA; however, we could not capture the peak in 5 patients (Figure 1). Figure 2a shows the mean plasma concentration with the corresponding standard deviation for each time point. There were no correlation between C_{max} and age, or height. However, a negative correlation was identified between patient body weight ($R = -0.66$ [95% CI: -0.91 to -0.05], $p = 0.039$; Figure 2b). Additionally, no symptoms associated with LAST were identified by within 12 hours.

Discussion

The main finding of this study is that the plasma levobupivacaine concentration following M-TAPA, using 25 mL of 0.25% levobupivacaine with epinephrine on each side, remains below the toxic level. A significant variability was observed in the individual C_{max} and T_{max}, which is consistent with plasma LA concentration after fascial plane blocks in previous studies [3, 4]. To the best of our knowledge, this is the first study to investigate the chronological changes in plasma LA concentrations following M-TAPA.

Recently, Ciftci [12] and Sawada et al. [7] conducted cadaveric studies and demonstrated dye spread on the transversus abdominis plane (TAP) along the costal arch. Therefore, TAP block may be appropriate for a comparison of pharmacodynamics. Corvetto et al. [4] measured the plasma concentration of LA after a unilateral TAP block using 20 mL of 0.25% levobupivacaine with epinephrine, which was 0.36 μg/mL. Subsequently, they revealed the calculated peak as 0.84 μg/mL at 25 min when the same injectate was administered bilaterally [13]. Given that we administered 10 mL larger volume of 0.25% levobupivacaine in this study, our data suggest that the C_{max} after M-TAPA would be lower and the absorption speed could be slower than that after TAP block.

The C_{max} could be influenced by the spread of LA on the neurovascular plane. Corvetto et al. [4] studied the sensory coverage of the TAP block and observed that the Th9 to Th12 dermatomes

were covered. In contrast, our previous study demonstrated that M-TAPA reliably provides Th8 to Th10 dermatomal coverage [6]. Although M-TAPA can provide wide sensory coverage, these results related to C_{max} and dermatomal area could indicate that the spread of LA is more limited than that of the TAP block. An investigation of the correlation between C_{max} and sensory coverage would be interesting.

In the present study, we could not determine the C_{max} in 5 out of 10 cases. This was unexpected, as a previous study of the TAP block using epinephrine reported a T_{max} of 41.4 (95% CI: 26.4 to 60.3) min [4]. Although the C_{max} of the TAP block could be similar to or higher than that of M-TAPA, we have safely used the TAP block in our daily practice for a decade. Moreover, based on the results of previous studies [3, 4, 14], it is difficult to imagine a scenario in which plasma concentrations suddenly increase more than twofold after 120 minutes. Given our results and associate references, M-TAPA could be a safe procedure, however, it is difficult to denying the occurrence of toxic blood concentrations after M-TAPA based solely on this evidence.

Epinephrine constricts the vessels and retards the absorption of LA into the circulation, thereby decreasing the peak concentration and prolonging the time to peak, which could help prevent LAST [4]. Recently, Güngör et al. [8] reported that M-TAPA provided superior analgesia to local infiltration analgesia in patients undergoing laparoscopic cholecystectomy. They performed M-TAPA at the end of the surgery, using a total of 40 mL of 0.25% bupivacaine. Although they did

not report any LAST symptoms, adding epinephrine would be safer and preferable.

Our data indicated that the plasma levobupivacaine concentration within 120 min following M-TAPA remained below the toxic level; however, cumulative experience and careful observations are required. Turner et al. [3] reported a patient with a plasma concentration below the known toxic threshold who developed mild LAST symptoms.

This study has several limitations. First, the sample size was small, similar to other plasma LA concentration studies. Second, the data obtained should be interpreted as approximations since the blood samples were collected at scheduled time points. Moreover, we could not determine the plasma levobupivacaine concentration after 120 min. Third, this study included only laparoscopic surgery; therefore, investigation of the laparotomy may be needed. Finally, in this study, we only performed the pinprick test around the umbilicus to evaluate block success.

Conclusions

Our results showed that the plasma levobupivacaine concentration after bilateral M-TAPA was lower than the known toxic threshold when used with epinephrine. A negative correlation was observed between the patient's body weight and peak LA concentration. Our results will contribute to patient safety measures; however, further investigation is needed because of the small sample size of this study.

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Tables

Table 1. Patient demographic data and measurements

No.	Age	Height (cm)	Weight (kg)	Surgery	Levobupivacaine dose (mg/kg)	Peak plasma concentration (μg/mL)	Time to peak (min)
1	40s	153	54	Colectomy	2.3	1.03	60
2	60s	168	66	Colectomy	1.9	0.78	45
3	20s	166	68	Gynecological	1.8	0.45	120
4	30s	163	68	Gynecological	1.8	0.65	120
5	70s	172	58	Colectomy	2.2	0.96	120
6	60s	164	75	Colectomy	1.7	0.56	120
7	40s	153	53	Colectomy	2.4	0.72	45
8	30s	161	72	Gynecological	1.7	0.75	120
9	80s	164	66	Colectomy	1.9	0.7	45
10	40s	152	65	Gynecological	1.9	0.65	60

Figure Legends

Figure 1: Chronological changes in the plasma levobupivacaine concentration in all patients

Figure 2: a Chronological changes in the mean plasma levobupivadcaine concentration. **b** the correlation between body weight and peak levobupivacaine concentration

Figures

Figure 1

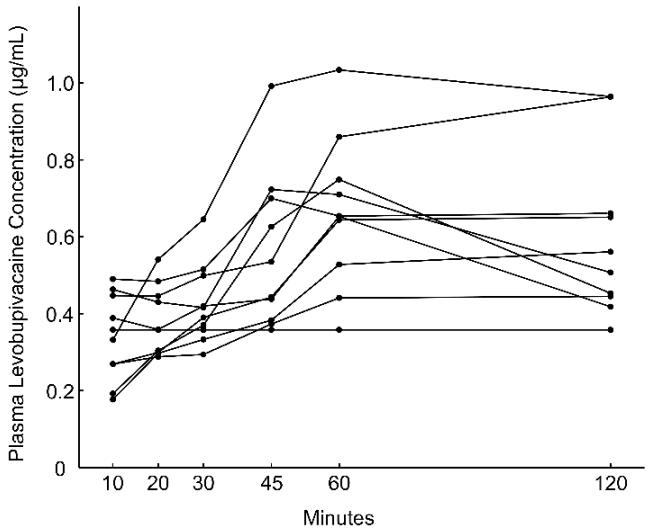

Figure 2