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Chronological changes in plasma levobupivacaine concentrations after bilateral modified-

thoracoabdominal nerve block through perichondrial approach

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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 $0.73 \mu g/mL$, 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.

1 Introduction

2 The elevation of plasma local anesthetic (LA) concentration and subsequent LA systemic 3 toxicity (LAST) of regional anesthetic techniques are major concerns [1]. Especially, substantial 4 attention has been gathered on the trunk blocks due to the property that LA spreads along the 5 broad neurovascular plane, which can lead to rapid absorption [2]. Therefore, a number of studies 6 have been conducted to clarify the chronological plasma LA concentration and estimate the risk 7 of LAST [3, 4]. 8 In 2019, Tulgar et al. [5] introduced the modified-thoracoabdominal nerve block through 9 perichondrial approach (M-TAPA), which has attracted increasing attention [6-8]. Given its broad 10 sensory coverage, LA may spread broadly and reach the toxic levels. However, the plasma LA 11 concentration has not been investigated. Previous studies have reported that a mixture of 12 epinephrine decreases the peak levolupivacaine concentration (C_{max}) and prolongs the time to 13 peak (T_{max}), which could help prevent LAST [4]. Therefore, we conducted a single-arm, 14 exploratory study to test the hypothesis that the peak plasma LA concentration following M-TAPA, 15 using 25 mL of 0.25% levobupivacaine with epinephrine on each side, would be below the toxic

16 level (2.6 μ g/mL) [9].

17 Methods

18 This study was approved by the Institutional Review Board of Hokkaido University Hospital 19 (IRB No. 021-0021, approval date: September 6, 2021) and conducted in accordance with the 20 ethical principles outlined in the Declaration of Helsinki. The study was registered in the UMIN 21 Clinical Trial Registry prior to patient enrollment (UMIN000045406). Ten patients (age ≥20 22 years) undergoing abdominal surgery with planned M-TAPA were recruited after obtaining 23 written informed consent. The exclusion criteria were as follows: American Society of 24 Anesthesiologists Physical Status \geq 3, allergy to LA, body weight \leq 50 kg, liver/kidney dysfunction, 25 pregnancy, and serum albumin ≤ 3 g/dL. 26 Anesthetic management was performed according to our institutional practices. In the 27 operation room, all patients were monitored for noninvasive blood pressure, electrocardiography, 28 and peripheral oxygen saturation. After tracheal intubation, the radial arterial line was secured. 29 Subsequently, bilateral M-TAPA was performed by a single anesthesiologist (KA), as previously 30 described [5, 6], using 25 mL of 0.25% levobupivacaine with 1:200,000 epinephrine on each side. 31 We note that the needle tip was positioned between the posterior aspect of the 9th or 10th level of 32 the costal cartilage and the origin of the transversus abdominis muscle, based on Tulgar's original

- 33 report [10]. However, in this study, a precise postoperative pinprick test was challenging as the
- 34 patients who underwent colectomy had many gauze dressings on the abdomen. Since we have

35 confirmed that our procedure successfully leads to sensory loss around the umbilicus in all 36 patients in a previous study [6], we adopted a brief pinprick test around the umbilicus to evaluate 37 block success postoperatively. 38 A 2 mL blood sample was collected from the arterial line at each time point, i.e., 10, 20, 30, 39 45, 60, and 120 min, after the block completion and promptly centrifuged (1500 g, 10 min at 4 $^{\circ}$ C). 40 A 0.6 mL of plasma was stored at -20 °C until measurement. The plasma levobupivacaine 41 concentration was measured using liquid chromatography-tandem mass spectrometry with the 42 electrospray ionization technique, using praziquantel as the internal standard [11]. All samples 43 were prepared using deproteination with acetonitrile. Chromatographic separation was achieved 44 with two mobile phases ([A] 5 mM ammonium acetate buffer [pH adjusted to 5.6 with acetic acid] 45 and [B] acetonitrile; A:B = 65:35). The calibration curves were linear between 0.5 and 2,000 46 ng/mL with $1/\chi^2$ weighting (R² \ge 0.98). 47 The primary outcome was the plasma levobupivacaine concentrations in each time points. The 48 sample size was determined based on previous studies [3, 4]. As the secondary outcome, the 49 correlation between C_{max} and patient age, height, and weight, and adverse events occurring within 50 12 hours after M-TAPA were tested. Statistical analysis was performed using JMP Pro 16 software

51 (SAS Institute, Japan).

52 **Results**

53 We enrolled 10 patients who underwent laparoscopic surgeries between November 2021 and 54 February 2022. All samples were successfully collected and measured. The patient demographic 55 data and measurement results are listed in Table 1. We confirmed decreased or no painful 56 sensation in all cases postoperatively. The highest individual peak plasma concentration was 1.03 57 μ g/mL at 60 min (Figure 1). The mean C_{max} and T_{max} were 0.73 (95% confidence interval [CI]: 0.60 58 to 0.85) µg/mL and 85.5 (95% CI: 59.2 to 111.8) min, respectively. The plasma levobupivacaine 59 levels remained below the toxic level within 120 min after M-TAPA; however, we could not 60 capture the peak in 5 patients (Figure 1). Figure 2a shows the mean plasma concentration with 61 the corresponding standard deviation for each time point. There were no correlation between Cmax 62 and age, or height. However, a negative correlation was identified between patient body weight 63 (R = -0.66 [95% CI: -0.91 to -0.05], p = 0.039; Figure 2b). Additionally, no symptoms associated 64 with LAST were identified by within 12 hours.

65 **Discussion**

The main finding of this study is that the plasma levobupivacaine concentration following M-66 TAPA, using 25 mL of 0.25% levobupivacaine with epinephrine on each side, remains below the 67 68 toxic level. A significant variability was observed in the individual C_{max} and T_{max}, which is 69 consistent with plasma LA concentration after fascial plane blocks in previous studies [3, 4]. To 70 the best of our knowledge, this is the first study to investigate the chronological changes in plasma 71 LA concentrations following M-TAPA. 72 Recently, Ciftci [12] and Sawada et al. [7] conducted cadaveric studies and demonstrated dye 73 spread on the transversus abdominis plane (TAP) along the costal arch. Therefore, TAP block may 74 be appropriate for a comparison of pharmacodynamics. Corvetto et al. [4] measured the plasma 75 concentration of LA after a unilateral TAP block using 20 mL of 0.25% levobupivacaine with 76 epinephrine, which was 0.36 μ g/mL. Subsequently, they revealed the calculated peak as 0.84 77 µg/mL at 25 min when the same injectate was administered bilaterally [13]. Given that we 78 administered 10 mL larger volume of 0.25% levobupivacaine in this study, our data suggest that 79 the C_{max} after M-TAPA would be lower and the absorption speed could be slower than that after 80 TAP block.



83	were covered. In contrast, our previous study demonstrated that M-TAPA reliably provides Th8
84	to Th10 dermatomal coverage [6]. Although M-TAPA can provide wide sensory coverage, these
85	results related to C_{max} and dermatomal area could indicate that the spread of LA is more limited
86	than that of the TAP block. An investigation of the correlation between C_{max} and sensory coverage
87	would be interesting.
88	In the present study, we could not determine the C_{max} in 5 out of 10 cases. This was unexpected,
89	as a previous study of the TAP block using epinephrine reported a T_{max} of 41.4 (95% CI: 26.4 to
90	60.3) min [4]. Although the C_{max} of the TAP block could be similar to or higher than that of M-
91	TAPA, we have safely used the TAP block in our daily practice for a decade. Moreover, based on
92	the results of previous studies [3, 4, 14], it is difficult to imagine a scenario in which plasma
93	concentrations suddenly increase more than twofold after 120 minutes. Given our results and
94	associate references, M-TAPA could be a safe procedure, however, it is difficult to denying the
95	occurrence of toxic blood concentrations after M-TAPA based solely on this evidence.
96	Epinephrine constricts the vessels and retards the absorption of LA into the circulation, thereby
97	decreasing the peak concentration and prolonging the time to peak, which could help prevent
98	LAST [4]. Recently, Güngör et al. [8] reported that M-TAPA provided superior analgesia to local
99	infiltration analgesia in patients undergoing laparoscopic cholecystectomy. They performed M-

100 TAPA at the end of the surgery, using a total of 40 mL of 0.25% bupivacaine. Although they did

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

102	Our data indicated that the plasma levobupivacaine concentration within 120 min following
103	M-TAPA remained below the toxic level; however, cumulative experience and careful
104	observations are required. Turner et al. [3] reported a patient with a plasma concentration below
105	the known toxic threshold who developed mild LAST symptoms.
106	This study has several limitations. First, the sample size was small, similar to other plasma LA
107	concentration studies. Second, the data obtained should be interpreted as approximations since
108	the blood samples were collected at scheduled time points. Moreover, we could not determine the
109	plasma levobupivacaine concentration after 120 min. Third, this study included only laparoscopic
110	surgery; therefore, investigation of the laparotomy may be needed. Finally, in this study, we only

111 performed the pinprick test around the umbilicus to evaluate block success.

112 **Conclusions**

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

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Tables

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

Table 1. Patient demographic data and measurements

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





