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SHORT COMMUNICATION

Effects of adding epinephrine on the early systemic absorption kinetics of local anesthetics in abdominal truncal blocks

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Abstract We evaluated the pharmacokinetics of ropivacaine following rectus sheath block (RSB) and transversus abdominis plane (TAP) block with or without epinephrine. A total of 26 adult patients undergoing lower abdominal surgery with RSB (=RSB trial) and another 26 adult patients undergoing open prostatectomy with TAP block (=TAP trial) were enrolled. Patients were randomly assigned to receive either a mixture of 0.75 % ropivacaine 13.2 mL with 1 % plain lidocaine 6.8 mL (TAP-E(−) and RSB-E(−) groups) or a mixture of 0.75 % ropivacaine 13.2 mL and 1 % lidocaine containing adrenaline (1:100,000) 6.8 mL (TAP-E(+) and RSB-E(+) groups) under general anesthesia. The serum concentrations of ropivacaine were measured using gas chromatography with mass spectrometry. The peak concentration was significantly lower and time to peak concentration was significantly longer in the TAP-E(+) group than in the TAP-E(−) group ($P < 0.05$ and <0.01, respectively), while there were no significant differences in these parameters between the RSB-E(+) and RSB-E(−) groups. These results indicate that epinephrine attenuates the early phase of local anesthetic absorption from the injected site in TAP blocks, but not RSB.

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With the development of ultrasound imaging techniques which enabled precise target identification, peripheral nerve blocks in the trunk, including rectus sheath block (RSB) and transversus abdominis plane (TAP) block, are increasingly used for perioperative analgesia during abdominal surgery [1, 2]. These compartmental blocks usually require a large amount of local anesthetic to increase the spread of injectate corresponding to incisional segments [3]. Therefore, even at dilute concentrations, regional blocks may cause potential serious systemic toxicity [2]. Generally, ropivacaine has seen more widespread use in regional blocks due to its long duration of action and improved safety profile in terms of cardiac and neurological toxicity [4]. Several studies have demonstrated rapid absorption of local anesthetics into systemic circulation following truncal blocks in hypervascular target tissues [5–8]. In neuraxial blocks, epinephrine is often added to local anesthetic solutions to prolong the duration of analgesia, improve the onset time, and reduce the peak plasma level, consequently preventing systemic and local anesthetic toxicity [9, 10]; however, few clinical investigations have demonstrated beneficial pharmacological profiles after adding epinephrine to ropivacaine for peripheral nerve blocks [6, 11, 12]. In this study, we evaluated the pharmacokinetics of ropivacaine administered with lidocaine with and without adrenaline following RSB and TAP block.

The study protocol was approved by our hospital ethics committee, and written informed consent was obtained from all patients. A total of 26 adult patients undergoing elective colorectal surgery with midline incisions were

enrolled in the RSB trial. Another 26 patients undergoing elective open retropubic prostatectomy were enrolled in the TAP block trial. In each trial, the patients were randomly assigned to two groups: RSB trial 0.5 % ropivacaine without epinephrine (RSB-E(−) group $n = 13$) or with epinephrine (RSB-E(+) group $n = 13$); TAP block trial 0.5 % ropivacaine without (TAP-E(−) group $n = 13$) or with epinephrine (TAP-E(+) group $n = 13$). Following induction of general anesthesia and tracheal intubation, bilateral RSB at the umbilical level or bilateral posterior TAP block at the mid-axillary line was performed following ultrasound-guided techniques using a portable ultrasound unit equipped with a 6- to 12-MHz linear probe. With real-time imaging of the rectus abdominis muscle or transversus abdominis muscle, a 20-gauge Toughy needle was inserted using the in-plane approach. A total of 10 mL of a local anesthetic solution was injected into each side, and every 2- to 3-mL syringe was aspirated during injection, so as to prevent inadvertent intravascular injection. The distribution of the local anesthetic was also monitored. All patients were administered a mixture of 0.75 % ropivacaine 13.2 mL with 1 % plain lidocaine 6.8 mL (TAP-E(−) and RSB-E(−) groups) or a mixture of 0.75 % ropivacaine 13.2 mL and 1 % lidocaine containing adrenaline (1:100,000) 6.8 mL (TAP-E(+) and RSB-E(+) groups). Blood samples (3 mL) were drawn from a radial artery catheter before and 15, 30, 45, 60, 90, 120, and 180 min after completion of the nerve block, and centrifuged to separate the plasma, which was stored at −20 °C until the assay. Plasma ropivacaine concentrations were analyzed using gas chromatography with mass spectrometry, as previously described by Björk et al. [13]. The limit of determination for ropivacaine was 10 ng/mL. The intra-assay coefficient of variation varied from 3.7 % at 500 ng/mL to 3.1 % at 1,000 ng/mL. The pharmacokinetic parameters Cmax, Tmax, t1/2, CL, and Vd were calculated and fitted using a computer program (Moment Analysis Program: Graduate School of Pharmaceutical Sciences, Kyoto University). A sample size of at least 12 patients per group was needed for a power of 80 % based on previous studies [14], and we expected a difference in C_{max} of approximately 0.7 μg/mL and a difference in T_{max} of approximately 10 min. The statistical analysis was performed using the paired t test.

The patient characteristics did not differ between the groups in either trial. The time course of the serum ropivacaine concentrations after RSB was similar in the RSB-E(+) and RSB-E(−) groups. The changes in the plasma ropivacaine concentrations after TAP block are shown in Fig. 1a. The peak concentration (C_{max}) in the TAP-E(−) group was significantly higher than that observed in the TAP-E(+) group. In addition, the time to peak concentration (T_{max}) in the TAP-E(−) group was significantly shorter than that observed in the TAP-E(+) group (Table 1). There were no significant differences in C_{max}, T_{max}, or other pharmacokinetic parameters between the RSB-E(+) and RSB-E(−) groups (Table 1; Fig. 1b).

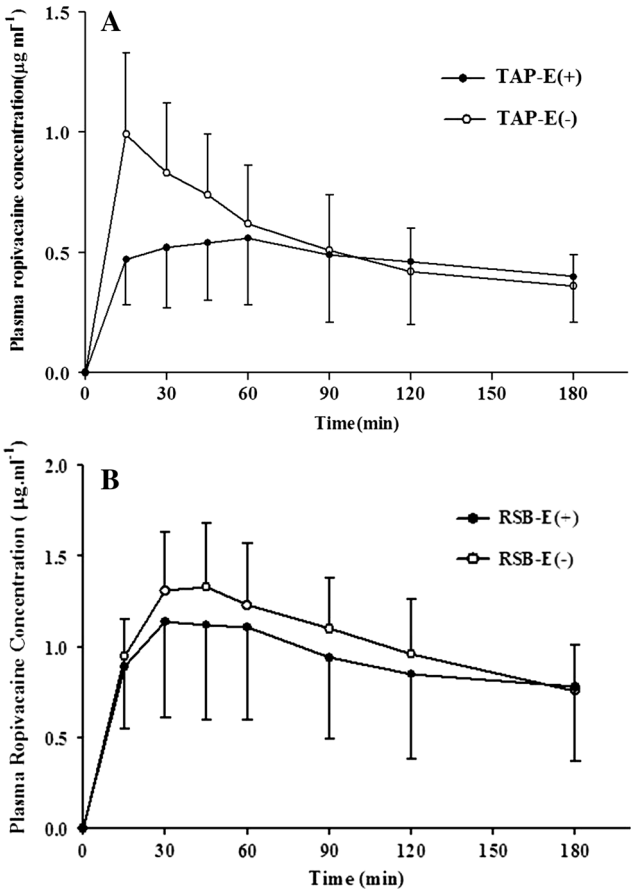

Fig. 1 Plasma concentration of ropivacaine following **a** bilateral transversus abdominis plane block and **b** bilateral rectus sheath block. Nerve block was performed with a mixture of 0.75 % ropivacaine 13.2 mL with 1 % plain lidocaine 6.8 mL (TAP-E(−) and RSB-E(−) groups) or with a mixture of 0.75 % ropivacaine 13.2 mL with 1 % lidocaine containing epinephrine (1:100,000) 6.8 mL (TAP-E(+) and RSB-E(+) groups). Values are the mean ± SD of 13 experiments

No patients exhibited any serious adverse reactions, such as systemic or local anesthetic toxicity or epinephrine-induced adverse cardiovascular effects in either block group.

This is the first report to investigate the effects of epinephrine on the pharmacokinetics of ropivacaine following abdominal wall blocks. In the TAP-block group, the systemic absorption of ropivacaine was significantly attenuated following the addition of epinephrine (3.3 μg/mL), as the C_{max} was reduced and the T_{max} was delayed. In contrast, the ropivacaine pharmacokinetics following RSB were not affected by the addition of epinephrine. The C_{max} and T_{max} are related to the first phase of absorption of local anesthetics [15]. Therefore, they may be affected by the

Table 1 Mean pharmacokinetic parameters calculated for the study population after rectus sheath block (RSB trial) and transverses abdominis plane block (TAP trial) with 0.5 % ropivacaine 20 mL with or without epinephrine

	RSB trial		TAP trial	
	E+ group	E− group	E+ group	E− group
C_{max} (μg mL^{-1})	1.27 ± 0.54	1.39 ± 0.33	0.63 ± 0.27*	1.01 ± 0.33
T_{max} (min)	43.0 ± 27.7	36.9 ± 9.9	43.9 ± 24.1**	18.5 ± 6.6
$t_{1/2}$ (h)	3.5 ± 1.5	2.6 ± 0.9	3.0 ± 0.7	2.3 ± 0.9
CL (L/h)	21.8 ± 16.2	22.8 ± 10.3	49.5 ± 36.3	41.4 ± 14.2
Vd (L)	100.3 ± 40.9	92.3 ± 29.1	186.5 ± 80.2*	124.6 ± 47.6

Data are given as Mean ± SD ($n = 13$ per group)

C_{max} Maximum concentration, T_{max} time to reach C_{max}; $t_{1/2}$ terminal elimination half-life, *CL* total body clearance, *Vd* volume of distribution

* $P < 0.05$ compared with TAP group 0.5 Epi(−)

** $P < 0.01$ compared with TAP group 0.5 Epi(−)

vascular density (hyper or hypo), local anesthetic properties, adjuvants (vasoconstrictors), and the substantial area for absorption of the injectate [16–18]. In terms of anatomy, the differences in vascular density between target regions for RSB and TAP blocks are notably significant. The target layer for TAP block for local anesthetic injection is between the internal oblique and transversus abdominis muscles. This neurovascular plane resembles the intercostal region, exhibiting hypervascular perfusion with intercostal or subcostal arteries. Indeed, several reports [7, 8] have shown that the T_{max} in a TAP block is similar to that observed in an intercostal nerve block [5]. In contrast, the target layer for RSB is between the rectus abdominis muscle and posterior sheath, which is a bilaminar, fibrous, and aponeurotic extension of the lateral abdominal muscles. Therefore, the difference in the effects of epinephrine on the systemic absorption of ropivacaine between RSB and TAP block are primarily due to anatomical differences between the injected sites. In contrast, the C_{max} in the RSB-E(−) group was markedly higher than that observed in the TAP-E(−) group. This may be due to the wider spread of local anesthetic solutions in RSB, compared to that seen in TAP block, resulting from the easy dissection of the layer between the rectus abdominis and posterior sheath, which may increase the total amount of absorption.

In this study, the two trials were independent, and the spread of the local anesthetic could not be measured or controlled, even under US guidance.

Several in vitro and in vivo studies have indicated the vasoconstrictive properties of ropivacaine over a wide range of concentrations [6, 19, 20]. In particular, it is well known that ropivacaine can induce vasoconstriction at low concentrations [17, 21]. Gherardini et al. [19] showed a biphasic response with contraction at low concentrations (1.5×10^{-5}–1.5×10^{-3} M) and the release of contraction at high concentrations (1.5×10^{-3} M) in isolated human arteries in vitro. Therefore, the inhibitory effects of epinephrine on the systemic absorption of ropivacaine may be obscured in hypovascular sites, such as RSB sites, in which ropivacaine per se has already induced vasoconstriction. Indeed, in clinical studies, no beneficial effects have been observed following the addition of epinephrine to ropivacaine in peripheral nerve blocks such as ulnar nerve blocks [20] and femoral nerve blocks [22]. In contrast, the addition of epinephrine prolongs the T_{max} and reduces the C_{max} of the plasma ropivacaine concentration in epidural blocks [23], caudal blocks in children [24], and thoracic paravertebral blocks [6].

The limitations of this study include the fact that we used a mixed ropivacaine solution diluted with pharmaceutically formulated 1 % lidocaine containing epinephrine. Gherardini et al. [19]. demonstrated that ropivacaine does not constrict human mammary artery preparation more strongly than lidocaine at the low concentrations (3×10^{-4} to 10^{-3} M) used in this study. Therefore, lidocaine may also attenuate local anesthetic absorption in the systemic circulation.

In conclusion, we found that epinephrine attenuates the early phase of ropivacine absorption from the injected site in TAP blocks, but not in RSB. This difference appears to depend on the vascular density, or blood flow, of the injected site. Adding epinephrine to the local anesthetic solution may be beneficial for TAP blocks, but not RSB.

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