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ORIGINAL ARTICLE

Transversus abdominis plane block with 0.25 % levobupivacaine: a prospective, randomized, double-blinded clinical study

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Abstract
Purpose Because blood concentrations of local anesthetics sometimes reach toxic levels after transversus abdominis plane (TAP) block, reduction of the dose has been necessary to reduce the risk of systemic toxicity. We therefore investigated the effects of TAP block with 0.25 % levobupivacaine (100 mg) on postoperative pain and measured its plasma concentration after gynecological surgery.
Methods Forty women undergoing elective open gynecological surgery were randomized to receive bilateral TAP block with 20 ml 0.25 % levobupivacaine on each side (TAP group) or not (non-TAP group) before surgery. Postoperative pain was treated with intravenous patient-controlled analgesia by use of morphine. Patients were evaluated 3 and 24 h after the end of surgery. Visual analog scale (VAS) for pain at rest and with movement, and morphine consumption were recorded. Plasma concentrations of levobupivacaine after TAP block were measured.
Results Three hours after surgery, total morphine consumption was significantly lower in the TAP group (2.8 ± 1.6 mg) than in the non-TAP group (6.4 ± 4.8 mg, $P = 0.03$). There were no significant differences between VAS in the two groups. Mean plasma concentration of levobupivacaine peaked 10 min after TAP block (0.99 ± 0.43 μg/ml), and the highest concentration was 1.99 μg/ml.
Conclusion TAP block with 100 mg levobupivacaine is a safe and efficacious multimodal analgesic regimen for postoperative pain after open gynecological surgery.

Keywords Transversus abdominis plane (TAP) block · Levobupivacaine · Local anesthetic · Pharmacokinetics

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Introduction

Transversus abdominis plane (TAP) block has been shown to be effective for relieving postoperative pain after abdominal surgery, and is widely used as part of a multimodal analgesic regimen for lower abdominal surgery [1–4]. With regard to use of local anesthetics, the long-lasting local anesthetics levobupivacaine and ropivacaine, levo isomers with less systemic toxicity than the racemic compounds [5, 6], have frequently been used for TAP block [1, 4]. Although ropivacaine and levobupivacaine are used as low-toxicity local anesthetics, recent studies have shown that plasma concentrations of ropivacaine reach potentially toxic levels after bilateral injections of 20 ml 0.375–0.5 % ropivacaine (2.5–3 mg/kg), doses commonly used for TAP block [7–10]. Indeed, symptoms of systemic toxicity of 2.5 mg/kg ropivacaine have been reported, with mean peak plasma concentrations of 2.7 μg/ml [9].

Because, as far as we are aware, there has been only one study in which plasma concentrations of levobupivacaine were measured after TAP block [11], pharmacokinetic data after TAP block with levobupivacaine are lacking. However, the occurrence of convulsion after TAP block in which 0.375 % 40 ml (2.67 mg/kg) levobupivacaine was injected into a 56-kg parturient, has also recently been

reported [12]. Thus, TAP block with 2.67 mg/kg or more of levobupivacaine may also result in systemic toxicity, as was seen for TAP block with 2.5 mg/kg or more ropivacaine. Thus, reduction of the dose of levobupivacaine and ropivacaine for TAP block is required to reduce the risk of systemic toxicity.

Reduction of the dose of levobupivacaine would be safer from the perspective of toxicity after TAP block but might also reduce the analgesic potency of TAP block. The safety and effectiveness of a reduced dose of levobupivacaine for TAP block should thus be established. The objectives of our study were to measure plasma concentrations of levobupivacaine after TAP block with 40 ml 0.25 % levobupivacaine (100 mg) and to assess the analgesic effect of TAP block of levobupivacaine dose on postoperative pain after gynecological surgery.

Methods

After approval by the Ethics Committee of Shinshu University School of Medicine (Matsumoto, Japan), written informed consent was obtained from each patient enrolled in the study. This study was registered at the University Hospital Medical Information Network (UMIN000003598). This prospective, randomized, controlled study was conducted in an operating room of a university hospital during a 12-month period. Patients undergoing open gynecological surgery ($n = 40$) were randomly divided by computer-generated randomization into two groups receiving (TAP group) or not receiving (non-TAP group) TAP block. Exclusion criteria were hepatic disorder, renal disorder, allergies to amino-amide local anesthetics, body mass index over 35, and weight under 40 kg (to limit the maximum levobupivacaine dose to 2.5 mg/kg). Patients were excluded if their incisions extended above the umbilicus.

No premedication was given. Standard monitoring (pulse oximetry, electrocardiogram, and noninvasive blood pressure) and bispectral index (BIS) monitoring were performed. General anesthesia was induced with propofol by target-controlled infusion (TCI 3 μg/ml) and remifentanil (0.2 μg/kg/min). After rocuronium (0.8 mg/kg) had been intravenously administered to facilitate tracheal intubation, the trachea was intubated, and the patient was mechanically ventilated. An arterial catheter was then inserted into the left radial artery. In the TAP group, bilateral ultrasound-guided TAP blocks with levobupivacaine were performed under general anesthesia before surgery. Ultrasonographic guidance was with an S-nerve™ transportable ultrasound device (Sonosite, Bethell, WA, USA) and an L38 $\times$ 10^{-5} MHz linear array transducer. In accordance with a method described elsewhere [3], TAP block was performed at the level of the anterior axillary line between the 12th rib and iliac crest. Twenty ml 0.25 % levobupivacaine was slowly injected under direct ultrasonographic guidance. A similar procedure was performed on the contralateral side of the abdomen, with injection of another 20 ml of the same solution. Heparinized arterial blood samples (each 3 ml) were obtained from the arterial catheter before and 5, 10, 15, 30, 60, 120, and 180 min after the block. Each sample was centrifuged at 1500*g* for 10 min, and then the plasma supernatant was pipetted into a glass vial and the vial was stored at −30 °C until analysis. In the non-TAP group, TAP block was not performed.

Anesthesia was maintained with target propofol (3–4 μg/ml) and remifentanil (0.1–0.5 μg/kg/min) concentrations. The initial target concentration of propofol was 3 μg/ml, and the initial rate of infusion of remifentanil was 0.2 μg/kg/min. The doses of propofol and remifentanil were alternately increased if BIS exceeded 60 and reduced if BIS was lower than 40. Both groups received an intravenous bolus of morphine (2 mg) and fentanyl (200 μg) after peritoneum closure. Postoperative pain was treated with intravenous patient-controlled analgesia (IV-PCA) using morphine. For both groups the PCA device (CADD-Legacy PCA, model 6300; Smith Medical Japan, Tokyo, Japan) was programmed to deliver 1 mg morphine with 5-min lockout and with no background infusion. Each patient was assessed 3 and 24 h after the end of surgery by an investigator who was unaware of the study group for morphine consumption and for visual analog scale (VAS) for pain at rest and with movement. In cases of postoperative nausea or vomiting, subjects received 10 mg intravenous metoclopramide.

A method for measurement of plasma concentration of levobupivacaine by liquid chromatography–tandem mass spectrometry (LC–MS–MS) with electrospray ionization (ESI) had already been developed. LC was performed with an Accela™ high-speed LC system (Thermo Fisher Scientific, Waltham, MA, USA), and MS was performed with TSQ Quantum Ultra™ (Thermo Fisher Scientific). Sample preparation was conducted by the deproteination method. Briefly, levobupivacaine and praziquantel (used as internal standard) were extracted from 20 μl human plasma after precipitation by addition of acetonitrile. Chromatographic separation was then performed on an XBridge C_{18} column with 38 % acetonitrile in 5 mM ammonium acetate (pH 5.2) as isocratic mobile phase. The chromatographic analysis time was 10 min per sample. The calibration curve was linear between 0.5 and 2000 ng/ml with $1/x^2$ weighting ($r \geqq 0.99$).

A reduction of 3-h morphine consumption of 40 % was regarded as clinically relevant for sample size calculation. On the basis of initial pilot data, a 3-h requirement of 8 mg of morphine, with a standard deviation of 3 mg, was projected for the non-TAP group. A sample size of 16

Table 1 Patient demographic data

Group	TAP ($n = 20$)	Non-TAP ($n = 20$)	P value
Age (year)	56 ± 14	57 ± 16	0.725
Weight (kg)	53 ± 10	52 ± 8	0.587
Height (cm)	155 ± 8	154 ± 8	0.911
Operative duration (min)	176 ± 50	180 ± 79	0.818
Consumption of remifentanil (mg)	2.3 ± 0.8	2.9 ± 1.2	0.106
Types of operation			
Hysterectomy	6	8	
Hysterectomy + ovariectomy	9	8	
Hysterectomy + ovariectomy + pelvic lymphadenectomy	5	4	

Data are reported as mean ± SD and numbers

Table 2 Postoperative VAS and morphine consumption

Group	TAP	Non-TAP	P value
Morphine consumption (mg)			
3 h	2.8 ± 1.6	6.4 ± 4.8	0.030
3–24 h	10.4 ± 6.7	9.4 ± 6.0	0.521
VAS at rest			
3 h	33 ± 23	38 ± 19	0.228
24 h	19 ± 15	25 ± 16	0.242
VAS with movement			
3 h	52 ± 22	62 ± 19	0.361
24 h	49 ± 17	51 ± 21	0.554

Data are expressed as means ± SD

VAS visual analog scale

per group was obtained with $\alpha = 0.05$ and $\beta = 0.2$. We planned to recruit 20 patients per group to minimize any effect of data loss. Normally distributed continuous data were analyzed by use of Student's t test. Two-way analysis of variance (ANOVA) followed by Fisher's least-significant difference test was used for comparison of VAS scores and amount of morphine consumed in the TAP and non-TAP groups. All statistical analysis were performed with GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). Data are reported as mean ± SD. A P value < 0.05 was regarded as statistically significant.

Results

The two groups were comparable in terms of age and weight (Table 1). Surgical duration, intraoperative fluids, and estimated blood loss were similar in the two groups. Although remifentanil consumption during surgery was lower in the TAP group than in the non-TAP group, the difference was not statistically significant ($P = 0.106$). Total morphine consumption 3 h after surgery was significantly lower in the TAP group than in the non-TAP group (Table 2). Morphine consumption from 3 to 24 h after surgery was not significantly different in the non-TAP and TAP groups. VAS at rest for both groups decreased substantially from 3 to 24 h after surgery. VAS with movement decreased slightly from 3 to 24 h after surgery. VAS at rest or with movement 3 and 24 h after surgery were not significantly different in the non-TAP and TAP groups.

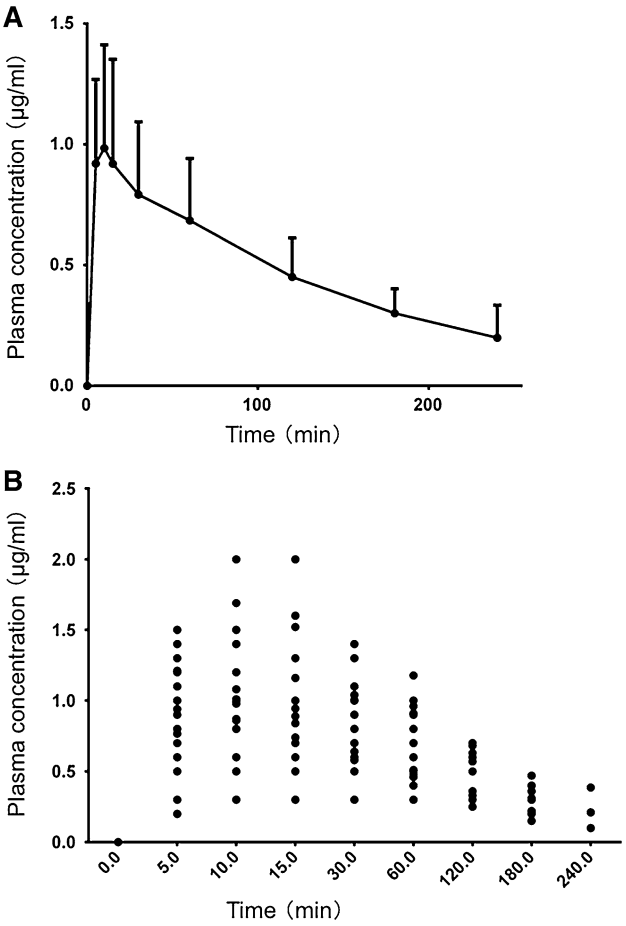

Fig. 1 Plasma concentration of levobupivacaine after transversus abdominis plane block with 40 ml 0.25 % levobupivacaine (20 ml on each side). **a** Plasma concentration of levobupivacaine, mean (SD). **b** Scatter plots of plasma concentration of levobupivacaine

Mean levobupivacaine concentration reached a maximum 10 min after TAP block (0.99 ± 0.43 μg/ml); the highest concentration was 1.99 μg/ml (Fig. 1). Consumption of metoclopramide in the two groups was not significantly different. No seizure, arrhythmia, bradycardia (heart rate <50 beats per minute), or hypotension (mean arterial blood pressure <60 mmHg) was observed for any patient.

Discussion

The maximum mean plasma concentration of levobupivacaine was 0.99 ± 0.43 μg/ml in this study. The highest plasma concentration of levobupivacaine was 1.99 μg/ml, which was observed for two patients. In a previous study with human volunteers [5] the threshold plasma concentration of levobupivacaine for inducing neurological symptoms was 2.62 μg/ml. Thus, the fact that bilateral injections of 0.25 % 20 ml levobupivacaine did not reach a toxic level in any of the patients in this study indicates that TAP block with a total dose of 100 mg of levobupivacaine is a safe technique in terms of systemic toxicity of levobupivacaine. However, the highest plasma concentration of 1.99 μg/ml was also seen in two patients. Thus, if a much higher dose of levobupivacaine, for example bilateral injections of 0.375 % 20 ml levobupivacaine (150 mg), is used for TAP block, the risk of systemic toxicity would be greatly increased.

In this study, the TAP block reduced morphine consumption 3 h after surgery, and results from the VAS at rest were relatively low in the two groups after 3 h. Because the mean duration of surgery in this study was approximately 3 h, TAP block with a total dose of 100 mg of levobupivacaine used in this study might have been effective for postoperative pain at rest at least for approximately 6 h after the block. Morphine consumption from 3 to 24 h was not significantly different between the two groups. However, this may not directly imply that TAP block with 0.25 % levobupivacaine does not have a long-lasting analgesic effect. Results from the VAS test at rest 24 h after surgery were 19 ± 15 mm in the TAP group and 25 ± 16 mm in the non-TAP group, and morphine consumption was 10.4 ± 6.7 mg in the TAP group and 9.4 ± 6.0 mg in the non-TAP group. Thus, the fact that pain intensity and morphine consumption during a period of 3–24 h after surgery were low might be the reason no significant differences in pain intensity were found in this study. Unfortunately, the results of our study did not lead to a firm conclusion that the analgesic effect of TAP block with 0.25 % levobupivacaine is compatible with 0.375 % or more levobupivacaine for patients undergoing open gynecological surgery. To clarify this issue, further study is necessary. However, because TAP block with 0.375 % or more levobupivacaine would be associated with greater risk of systemic toxicity as a result of the local anesthetic, performance of TAP block with 0.375 % or more might not be ethically allowed in further clinical trials.

It has been reported that TAP block with 30 ml 0.25 % levobupivacaine (15 ml on each side) also relieved postoperative pain and its efficacy is comparable with that with 30 ml of 0.5 % levobupivacaine (15 ml on each side) [13]. It has also recently been shown that TAP blocks with 30 ml 0.25 and 0.5 % ropivacaine reduced postoperative pain after gynecological laparoscopic surgery to similar extents and that there were no significant differences between pain score and opioid consumption in the two groups [14]. Thus, it is likely that TAP block with 0.25 % levobupivacaine and ropivacaine maintains an analgesic effect on postoperative pain comparable with that of higher doses (0.5 %) of levobupivacaine and ropivacaine. TAP block is used as part of a multimodal analgesic regimen for lower abdominal surgery. If there is no great difference between the analgesic potency of 0.25 % and much higher concentrations of levobupivacaine for TAP block, TAP block with 0.25 % levobupivacaine, which is less toxic, might be recommended as a postoperative analgesic technique. Indeed, TAP block with 0.25 % levobupivacaine combined with IV-PCA morphine could provide sufficient postoperative analgesia after open gynecological surgery in this study.

In this study, pain intensity with movement was relatively high in the TAP group and not significantly different from that in the non-TAP group 3 and 24 h after surgery. Although these results were slightly disappointing, a recent meta-analysis study has also shown that TAP block with relatively high doses of local anesthetics is effective for postoperative pain at rest but not for postoperative pain with movement after laparoscopic abdominal surgery [15]. Taken together, efficacy of TAP block for postoperative pain at rest has been established; however, it is still uncertain whether TAP block has an analgesic effect on postoperative pain with movement. Further study is necessary to examine the analgesic effect of TAP block on postoperative pain with movement.

In conclusion, TAP block with a total of 100 mg levobupivacaine is a safe and efficacious technique as a multimodal analgesic regimen for postoperative pain after open gynecological surgery.

References

1. McDonnell JG, O'Donnell B, Curley G, Heffernan A, Power C, Laffey JG. The analgesic effect of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. Anesth Analg. 2007;104:193–7.

2. Hebbard P, Fujiwara Y, Shibata Y, Royse C. Ultrasound-guided transversus abdominis plane (TAP) block. Anesth Intensive Care. 2007;35:616–7.
3. El-Dawlatly AA, Turkistani A, Kettner SC, Machata AM, Delvi MB, Thallaj A, Kapral S, Marhofer P. Ultrasound-guided transversus abdominis plane block: description of a new technique and comparison with conventional systemic analgesia during laparoscopic cholecystectomy. Br J Anaesth. 2009;102:763–7.
4. Carney J, McDonnell JG, Ochana A, Bhinder R, Laffey JG. The transversus abdominis plane block provides effective postoperative analgesia in patients undergoing total abdominal hysterectomy. Anesth Analg. 2008;107:2056–60.
5. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998;46:245–9.
6. Stewart J, Kellett N, Castro D. The central nervous system and cardiovascular effects of levobupivacaine and ropivacaine in healthy volunteers. Anesth Analg. 2003;97:412–6.
7. Toju K, Shiraishi K, Hakozaki T, Isosu T, Murakawa M. Plasma ropivacaine concentration following ultrasound-guided subcostal transversus abdominis plane block in adults. J Anesth. 2014;29(1):146–8 (Epub ahead of print).
8. Griffiths JD, Barron FA, Grant S, Bjorksten AR, Hebbard P, Royse CF. Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block. Br J Anaesth. 2010;105:853–6.
9. Griffiths JD, Le NV, Grant S, Bjorksten AR, Hebbard P, Royse CF. Symptomatic local anaesthetic toxixity and plasma ropivacaine concentrations after transversus abdominis plane block for Caesarean section. Br J Anaesth. 2013;110:996–1000.
10. Torup H, Mitchell AU, Breindahl T, Hansen EG, Rosenberg J, Møller AM. Potentially toxic concentrations in blood of total ropivacaine after bilateral transversus abdominis plane blocks; a pharmacokinetic study. Eur J Anaesthesiol. 2012;29:235–8.
11. Corvetto MA, Echevarría GC, De La Fuente N, Mosqueira L, Solari S, Altermatt FR. Comparison of plasma concentrations of levobupivacaine with and without epinephrine for transversus abdominis plane block. Reg Anesth Pain Med. 2012;37:633–7.
12. Weiss E, Jolly C, Dumoulin JL, Meftah RB, Blanié P, Laloë PA, Tabary N, Fischier M, Le Guen M. Convulsions in 2 Patients after bilateral ultrasound-guided transversus abdominis plane blocks for cesarean analgesia. Reg Anesth Pain Med. 2014;39:248–51.
13. Ra YS, Kim CH, Lee GY, Han JI. The analgesic effect of the ultrasound-guided transverse abdominis plane block after laparoscopic cholecystectomy. Korean J Anesthesiol. 2010;58:362–8.
14. De Oliveira GS, Jr Fitzgerald PC, Marcus RJ, Ahmad S, McCarthy RJ. A dose-ranging study of the effect of transversus abdominis block on postoperative quality of recovery and analgesia after outpatient laparoscopy. Anesth Analg. 2011;113:218–25.
15. De Oliveria GS, Jr Castro-Alves LJ, Nader A, Kendall MC, McCarthy RJ. Transversus abdominis plane block to ameliorate postoperative pain outcomes after laparoscopic surgery: a meta-analysis of randomized controlled trials. Anesth Analg. 2014;118:454–63.