タイトル	A comparison of plasma levobupivacaine concentrations following transversus abdominis plane block and rectus sheath block
別タイトル	腹横筋膜面ブロックおよび腹直筋鞘ブロック施行後の血中レボブピバカイン濃度の比較
作成者（著者）	安村, 里絵
公開者	東邦大学
発行日	2017.03
掲載情報	東邦大学大学院医学研究科 博士論文. 61.
資料種別	学位論文
内容記述	主査 : 北村享之 / タイトル : A comparison of plasma levobupivacaine concentrations following transversus abdominis plane block and rectus sheath block / 著者 : Rie Yasumura, Yoshiro Kobayashi, Ryoichi Ochiai / 掲載誌 : Anaesthesia / 巻号・発行年等 : 71(5):544-9, 2016 / 本文ファイル: 査読後原稿 / This is the peer reviewed version of the following article:【Anaesthesia,71,5】, which has been published in final form at DOI: 【10.1111/anae.13414】. This article may be used for non-commercial purposes in accordance With Wiley Terms and Conditions for self-archiving.
著者版フラグ	ETD
報告番号	32661甲第814号
学位授与年月日	2017.03.28
学位授与機関	東邦大学
DOI	info:doi/10.1111/anae.13414
その他資源識別子	http://onlinelibrary.wiley.com/doi/10.1111/anae.13414/abstract
メタデータのＵＲＬ	https://mylibrary.toho-u.ac.jp/webopac/TD18041628

Original article

A Comparison of plasma levobupivacaine concentrations following transversus abdominis plane block and rectus sheath block

R. Yasumura,[1] Y. Kobayashi,[2] R. Ochiai[3]

1 Anaesthesiologist, 2 Chief Anaesthesiologist, Department of Anaesthesia, National Hospital Organization, Tokyo Medical Center, Tokyo, Japan

3 Professor and Chairman of Department of Anaesthesiology, Toho University, School of Medicine, Tokyo, Japan

Correspondence to: R. Yasumura

Email: rie-yasu@estate.ocn.ne.jp

Short running title: Levobupivacaine levels after nerve blocks

Accepted:

Summary

Levobupivacaine is commonly used as the local anaesthetic of choice in peripheral nerve blocks but its pharmacokinetics have not been fully investigated. We compared the changes in plasma concentrations of levobupivacaine following transversus abdominis plane (TAP) block and rectus sheath (RS) block. Fifty females undergoing laparoscopy were randomly allocated to receive either a TAP block (TAP group) or an RS block (RS group). In both groups, 2.5 $mg.kg^{-1}$ levobupivacaine was administered, and blood samples were obtained at 15, 30, 60, and 120 min after injection. The Cmax and Tmax as determined by non-linear regression analysis were 1.05 $\mu g.ml^{-1}$ and 32.4 min in the TAP group and 0.95 $\mu g.ml^{-1}$ and 60.9 min in the RS group, respectively. The plasma concentration of levobupivacaine peaked earlier in the TAP group than in the RS group and the maximum plasma concentration depended on the administered dose but not the procedure.

Introduction

Peri-operative anticoagulant therapy often precludes siting of an epidural block for postoperative pain management. Several reports [1, 2] have shown that a transversus abdominis plane (TAP) block or a rectus sheath (RS) block reduce opioid requirements for postoperative pain, particularly after minimally invasive laparoscopic surgery. However, the adverse effects associated with local anaesthetic systemic toxicity are a particular concern when performing peripheral nerve blocks because of the large volumes of local anaesthetic injected when compared with the amount used in epidural blocks. The development of local anaesthetic systemic toxicity is determined by the dose of the local anaesthetic and the rate of increase in plasma concentration, the latter of which depends on the block procedure and the site of injection [3, 4].

The pharmacokinetics and toxicity of levobupivacaine, a long-acting local anaesthetic, have not been fully investigated. We therefore decided to compare the changes over time in plasma concentrations of levobupivacaine after peripheral nerve block.

Methods

Following local research ethics committee approval written informed consent was obtained from all patients. Inclusion criteria were adult females of ASA physical status I–III, scheduled to undergo laparoscopic surgery for benign gynaecological disease. Exclusion criteria were patients with known allergy to local anaesthetics or a history of renal dysfunction or hepatic dysfunction.

Unpremedicated patients were brought to the operating room, an intravenous cannula was inserted and standard AAGBI monitoring (electrocardiography, non-invasive blood pressure measurement and pulse oximetry) applied. General anaesthesia was induced with 2−3 $mg.kg^{-1}$ propofol, 1−2 $\mu g.kg^{-1}$ fentanyl, and 0.6−1.2 $mg.kg^{-1}$ rocuronium to facilitate tracheal intubation. Anaesthesia was maintained with propofol and remifentanil or fentanyl. Body temperature monitoring and bispectral index (BIS) monitoring (Medtronic, Dublin, Ireland) were continuously performed.

Immediately after the induction of anaesthesia, a peripheral nerve block was performed by an experienced anaesthetist using a US device (S−Nerve®; SonoSite, Bothell, WA, USA) with a 6–15 MHz linear probe and a 21G 100-mm CCR® needle (Hakko, Japan). Patients were randomised to either the transverses abdominis plane (TAP) group or rectus sheath (RS) group. In the TAP group, levobupivacaine (2.5 $mg.kg^{-1}$) was diluted with 0.9% saline to a total of 40 ml injection volume (20 ml per side). According to the method reported previously [5], TAP block was performed bilaterally in the mid-axillary line just inferior to the 12th rib. RS block was performed according to the method reported previously [6]. The same amount of 0.5% levobupivacaine was administered bilaterally to a total of 2.5 $mg.kg^{-1}$.

Venous blood samples were obtained at 15, 30, 60, and 120 min after injection of the study drug. Plasma was separated immediately by centrifugation of blood samples at 4°C. Plasma samples were frozen and stored until measurement of plasma levobupivacaine concentrations by high-performance liquid chromatography (Accela, Thermo Fisher Scientific Co., Ltd., Japan) and liquid chromatography–mass

spectrometry with a triple stage quadruple mass spectrometer (TSQ Quantum ultra, Thermo Fisher Scientific Co., Ltd., Japan). All patients received fentanyl intravenous patient-controlled analgesia (PCA) set at a background rate of 15 μg.hr^{-1} and a demand dose of 15 μg every 20 min as rescue analgesia for postoperative pain management. The plasma concentration of fentanyl at the end of anaesthesia was predicted using the Shafer model. Pain was assessed using a numerical rating scale (NRS) at one hour after surgery and 6 h after the block procedure. In addition to the PCA fentanyl, oral non-steroidal anti-inflammatory drugs (NSAIDs) were administered if required.

G*Power 3 was used to determine the necessary sample size and indicated that 48 patients were needed in order to perform a two-way ANOVA, with an effect size of 0.25 and a statistical power of 0.8. The concentrations of levobupivacaine within and between groups were assessed by two-way ANOVA with the Bonferroni post-hoc test. Patient demographics and surgical characteristics between the groups were compared using the t-test or the Mann-Whitney's U test according to the characteristics of the data distribution and variances. To determine the maximum plasma concentration (Cmax) and time-to-reach Cmax (Tmax) in each group, nonlinear regression analysis was performed using a two-compartment model of measured plasma concentrations. GraphPad Prism software version 6.0 (GraphPad Software, San Diego, CA, USA) software was used for statistical analysis and a p value less than 0.05 was considered statistically significant.

Results

Fifty-four patients were enrolled in the study and randomised to one or other group. After excluding 4 patients because of a change in the surgical procedure or failure to secure a blood sampling route, the data of the remaining 50 patients were analysed. Baseline characteristics of the patients are shown in table 1.

The mean (SD) plasma levobupivacaine concentrations at 15, 30, 60, and 120 min after TAP block were 0.925 (0.427), 0.993 (0.322), 1.017 (0.333), and 0.730 (0.228) μ g.ml^{-1}, and after RS block were 0.550 (0.212), 0.725 (0.250), 0.983 (0.323), and 0.710 (0.178) μ g.ml^{-1}, respectively (Figure 1). The concentrations were significantly different between the groups at 15 and 30 min after peripheral nerve block. However, no significant difference in the maximum plasma concentrations were observed between the TAP group and RS group, (1.156 vs 0.997 μ g.ml^{-1}). Nonlinear regression analysis (Fig. 2) showed that Cmax and Tmax were 1.05 μ g.ml^{-1} and 32.4 min in the TAP group and 0.95 μ g.ml^{-1} and 60.9 min in the RS group, respectively. R^2 was 0.62 and 0.69 in the TAP and RS group, respectively. No significant differences were observed in the NRS scores at 60 min or 6 h after peripheral nerve block, the intra-operative doses of fentanyl, or the predicted plasma fentanyl concentrations at the end of anaesthesia. In addition, the frequency of postoperative analgesia of PCA did not differ significantly between the groups (Table 2). No patient developed clinically serious side effects.

Discussion

In order to prevent the local anaesthetic systemic toxicity, anaesthetists need a good understanding of the pharmacokinetic properties of local anaesthetics, however, little is known regarding the pharmacokinetics of levobupivacaine [7–9], particularly after a peripheral nerve block. There have been no previous studies comparing the pharmacokinetics of levobupivacaine when administered by different techniques, particularly TAP block or RS block.

We found differences in the time course of plasma levobupivacaine concentrations between the TAP and RS groups. In the RS group, a gradual elevation in plasma levobupivacaine concentration was seen, and the time to peak concentration (Tmax) was more than double that in the TAP group. Previous studies on the rise in plasma ropivacaine concentration reported that Tmax was 23.1 and 48.5 min after TAP block [10] and RS block [6], respectively. Similarly, another study [11] reported that Tmax of ropivacaine was 35 and 53 min after TAP and RS block, respectively. These reports showed that the Tmax after RS block was approximately twice as long as the Tmax after TAP block, which is similar to the results we observed with levobupivacaine. Despite some differences in patient background and drug doses, ropivacaine and levobupivacaine are expected to have similar systemic pharmacokinetic profiles because of their virtually identical physical properties. Hence, the findings of our study using levobupivacaine are supported by previous studies.

Kitayama et al [10, 12] proposed two possible explanations for the different changes in plasma concentrations of local anaesthetics after TAP and RS blocks. One of the explanations is that in a TAP block, local anaesthetics are readily absorbed into the blood stream because they are injected into the neurovascular plane between the internal oblique and transversus abdominis muscles. Another explanation is that local anaesthetics are absorbed into the blood stream more gradually following a RS block because they are injected into the fascial plane posterior to the rectus abdominis muscle, where relatively few blood vessels are present. In addition, because the

volume of injectate in our study was greater in the TAP group, the space created by the injection of the local anaesthetic was presumed to be larger in the TAP group than in the RS group. As a result, the contact area between the local anaesthetic injectate and the vascular bed within the injected plane was larger in the TAP group than in the RS group; the larger area probably facilitated absorption of local anaesthetic.

Despite the significantly different rate of increase in plasma levobupivacaine concentration following TAP and RS block procedures, there were no significant differences in the maximum plasma concentration and Cmax according to non-linear regression analysis. After a single administration, the maximum plasma concentration of the drug is determined by the rate of drug absorption, distribution, metabolism and excretion. The elimination half-life of ropivacaine after peripheral nerve block has been reported to be 6.1 h [13], and the elimination half-life of levobupivacaine is expected to be the same because of their similar physical properties. The longer the elimination half-life, the more unlikely it is that the drug would be eliminated during the study period, even if the time to maximum plasma concentrations differ by an hour because of a difference in the site or type of block procedure. Therefore, provided the doses of anaesthetics are the same, differences in the site or type of nerve block are unlikely to generate a significant difference in the maximum plasma concentration. The findings of our study, demonstrating that the plasma concentrations in the TAP group changed little between 15 and 60 min despite the rapid elevation of plasma levobupivacaine, strongly supports the possibility that the rate of levobupivacaine elimination from the circulation was slow after TAP block.

Compared with bupivacaine, levobupivacaine is thought to be less toxic to the central nervous and cardiovascular systems [14], but no study has investigated the plasma concentrations of levobupivacaine following peripheral nerve block to establish the safe concentration range. It has previously been reported that at an arterial concentration of 2.51 $\mu g.ml^{-1}$, no levobupivacaine toxicity was observed in the central nervous or cardiovascular system during general anaesthesia [9]. By contrast, another

study reported that after the intravenous administration of levobupivacaine, there was obvious toxicity to the central nervous system in conscious healthy volunteers with the mean plasma concentration of 2.62 $\mu g.ml^{-1}$ [15]. The highest levobupivacaine concentration observed in our study was 2.29 $\mu g.ml^{-1}$, which is lower than the levels that have been previously been reported in order to avoid systemic toxicity and no patients suffered convulsions or severe cardiovascular collapse. However, in the previous study as well as our study, blood sampling and measurements of plasma concentrations were performed at only a limited number of time points and the concentration within the cerebrospinal fluid was not measured. Therefore, further work is needed to elucidate the safe levobupivacaine concentration range for use in various peripheral nerve blocks. When performing a peripheral nerve block after completing surgery, it is important to remember the time frame of changes in plasma drug concentrations and to continuously monitor for any symptoms of systemic toxicity. The findings of our study suggest that, when using levobupivacaine, it may be necessary to extend the duration of monitoring depending on the type of peripheral nerve block performed.

Similar to previous work a limitation of our study was that the measurement of plasma concentrations was performed only at 15, 30, 60, and 120 min following peripheral nerve block and therefore we might not have fully characterised the changes in plasma concentration of levobupivacaine over time. In addition, it is possible that the plasma concentration of levobupivacaine peaked after 60 min in the RS group. It is also possible that the assessment of pain was biased because variations in the surgical procedures may have affected the postoperative NRS rating and the amount of postoperative analgesic consumption.

In conclusion, this study is the first to report plasma concentrations of levobupivacaine following TAP and RS blocks. Our results demonstrated that the plasma concentration of levobupivacaine peaked earlier in the TAP group than in the RS group. However, the maximum plasma concentration depended on the

administered dose per body weight and not the block procedure itself. We found that, following TAP block the plasma concentration of local anaesthetic did not increase markedly after 15 min, whereas the plasma concentration of local anaesthetic increased beyond 60 min after RS block, suggesting that a longer observation period is needed in order to detect systemic toxicity.

Competing interests

Dr Yasumura was funded by the Health Labour Sciences Research Grant of the Ministry of Health, Labour and Welfare (26090401), Tokyo, Japan. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No other external funding or competing interests declared.

References

1. Azemati S, Khosravi MB. An assessment of the value of rectus sheath block for postlaparoscopic pain in gynecologic surgery. *Journal of Minimally Invasive Gynecology* 2005; **12**: 12-5.

2. McDonnell JG, O'Donnell B, Curley G, Heffernan A, Power C, Laffey JG. The analgesic efficacy of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. *Anesthesia and Analgesia* 2007; **104**: 193-7.

3. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. *Regional Anesthesia and Pain Medicine* 2013; **38**: 289-97.

4. Cox B, Durieux ME, Marcus MA. Toxicity of local anaesthetics. *Best Practice & Research: Clinical Anaesthesiology* 2003; **17**: 111-36.

5. Carney J, Finnerty O, Rauf J, Bergin D, Laffey JG, Mc Donnell JG. Studies on the spread of local anaesthetic solution in transversus abdominis plane blocks. *Anaesthesia* 2011; **66**: 1023-30.

6. Wada M, Kitayama M, Hashimoto H, Kudo T, Kudo M, Takada N, *et al.* Brief reports: plasma ropivacaine concentrations after ultrasound-guided rectus sheath block in patients undergoing lower abdominal surgery. *Anesthesia and Analgesia* 2012; **114**: 230-2.

7. Corvetto MA, Echevarria 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. *Regional Anesthesia and Pain*

Medicine 2012; **37**: 633-7.

8. Ala-Kokko TI, Raiha E, Karinen J, Kiviluoma K, Alahuhta S. Pharmacokinetics of 0.5% levobupivacaine following ilioinguinal-iliohypogastric nerve blockade in children. *Acta Anaesthesiologica Scandinavica* 2005; **49**: 397-400.

9. Costello TG, Cormack JR, Mather LE, LaFerlita B, Murphy MA, Harris K. Plasma levobupivacaine concentrations following scalp block in patients undergoing awake craniotomy. *British Journal of Anaesthesia* 2005; **94**: 848-51.

10. Kitayama M, Wada M, Hashimoto H, Kudo T, Yakoshi C, Hirota K. Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block for open retropubic prostatectomy. *Journal of Anesthesia* 2014; **28**: 576-9.

11. Murouchi T, Iwasaki S, Yamakage M. Chronological Changes in Ropivacaine Concentration and Analgesic Effects Between Transversus Abdominis Plane Block and Rectus Sheath Block. *Regional Anesthesia and Pain Medicine* 2015; **40**: 568-71.

12. Kitayama M, Wada M, Hashimoto H, Kudo T, Takada N, Hirota K. Effects of adding epinephrine on the early systemic absorption kinetics of local anesthetics in abdominal truncal blocks. *Journal of Anesthesia* 2014; **28**: 631-4.

13. Wank W, Büttner J, Maier KR, Emanuelson BM, Selander D. Pharmacokinetics and efficacy of 40 ml ropivacaine 7.5 mg/ml (300 mg), for axillary brachial plexus block – an open pilot study. *European Journal of Drug Metabolism and Pharmacokinetics* 2002; **27**: 53-9.

14. Burlacu CL, Buggy DJ. Update on local anesthetics: focus on levobupivacaine.

Therapeutics and Clinical Risk Management 2008; **4**: 381-92.

15. 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. *British Journal of Clinical Pharmacology* 1998; **46**: 245-9.

Table 1. Baseline characteristics of patients receiving either TAP or RS block. Values are mean (SD) or number.

	TAP group	**RS group**
	n=25	**n=25**
Age; years	39.9 (10.4)	39.1 (7.0)
Weight; kg	52.6 (7.7)	54.8 (7.1)
Body Mass Index; kg.m-2	20.95 (2.96)	21.38 (2.54)
ASA physical status; I,II,III	I=24, II=1	I=24, II=1
Duration of anaesthesia; mins	172.4 (78.5)	184.5 (49.7)
Duration of surgery; mins	125.8 (80.3)	136.1 (49.2)
Levobupivacaine dose; mg	131.2 (19.0)	136.4 (17.9)

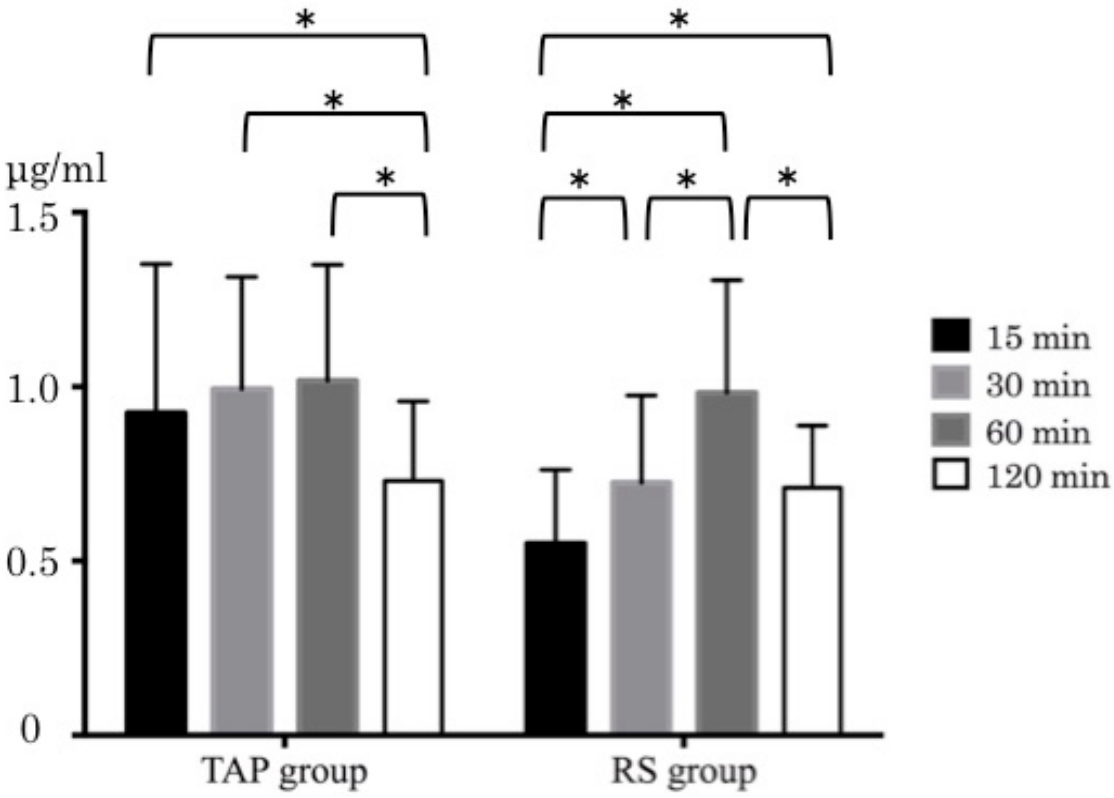
Table 2. Parameters for evaluation of analgesia after the TAP or RS block. Values are mean (SD) or median (IQR).

	TAP group	RS group	P*
NRS at 60 minutes after surgery	3 (1.0-5.0)	3 (1.5-5.0)	0.60
NRS at 6 hours after block	2 (1.0-3.0)	2 (1.0-3.5)	0.85
Fentanyl consumption during anaesthesia (μg)	252.0 (62.05)	277.6 (58.83)	0.14
Predicted fentanyl plasma concentration at the end of anaesthesia (n g /ml)	0.99 (0.87-1.25)	1.04 (0.95-1.15)	0.59
Number of postoperative uses of PCA until 6 hours after block	1 (0-2.0)	2 (0-4.5)	0.23
Number of postoperative uses of NSAIDs until 6 hours after block	0 (0-0)	0 (0-0)	0.42
Time interval of first analgesic drug after block (minutes)	170.5(125.5-240.0)	195.0 (153.5-255.0)	0.30

PCA, Patient control analgesia; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; *, for comparison between groups

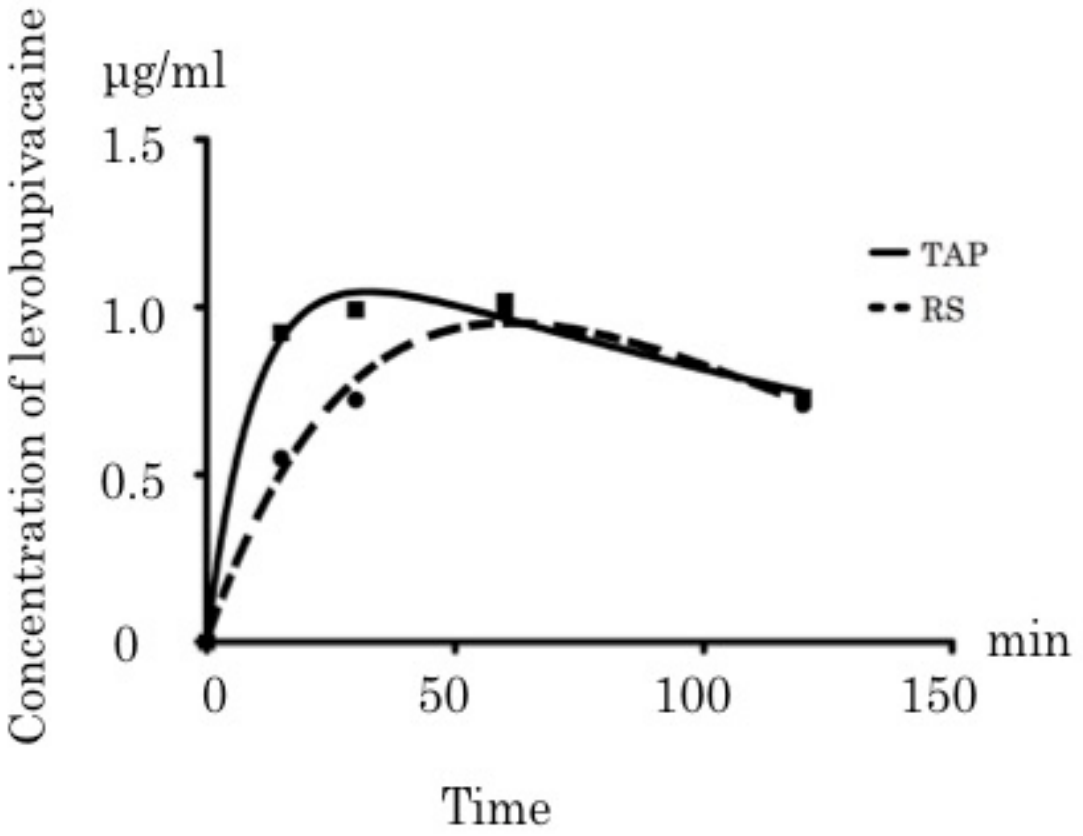
Figure Captions

Fig. 1 Concentration of levobupivacaine within groups. Horizontal line is mean and whisker is standard deviation.



＊p < 0.05, comparisons within groups

Fig. 2 Non-linear regression analysis showing the difference in time to peak mean plasma concentration of local anaesthetic in ― TAP group and -- RS group.



Non-linear regression curve superimposed on means of measured plasma concentrations after the TAP (■) or RS (•) block.