Original Article

Ropivacaine pharmacokinetics in the arterial and venous pools after ultrasound-guided continuous thoracic paravertebral nerve block

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Abstract

Background and Aims: Although thoracic paravertebral blockade (TPVB) is employed in thoracic surgery to ensure satisfactory postoperative analgesia, large doses of anesthetics are required and manifestations of local anesthetic systemic toxicity (LAST) may appear. Currently, there are limited data on the pharmacokinetics of ropivacaine after continuous TPVB. The aim of this prospective study was to investigate ropivacaine kinetics, in the arterial and venous pools, after continuous TPVB and assess the risk of LAST.

Material and Methods: Immediately after induction of general anesthesia, an ultrasound-guided continuous TPVB at T5 or T6 or T7 thoracic level was performed in 18 adult patients subjected to open thoracotomy. A 25-ml single bolus injection of ropivacaine 0.5% was administered through thoracic paravertebral catheter, followed by a 14 ml/h continuous infusion of ropivacaine 0.2% starting at the end of surgery. Quantification of total ropivacaine concentrations was performed using a validated high-performance liquid chromatography method. Population pharmacokinetic models were developed separately for arterial and venous ropivacaine data.

Results: The best model was one-compartment disposition with an additional pre-absorption compartment corresponding to thoracic paravertebral space. Gender had a significant effect on clearance, with females displaying lower elimination than males. Some patients had ropivacaine concentrations above the toxic threshold, but none displayed evidence of LAST. Continuous thoracic paravertebral nerve blocks provided adequate postoperative analgesia.

Conclusion: Ropivacaine doses at the upper end of clinical use (800 mg/d) did not inflict the manifestations of LAST and provided adequate postoperative pain control. Pharmacokinetic models were developed, and the effect of gender was identified.

Keywords: Pain management, population pharmacokinetics, ropivacaine, thoracic paravertebral nerve block, ultrasound

Introduction

Thoracic paravertebral blockade (TPVB) is often employed in open thoracic surgery to ensure satisfactory postoperative analgesia, which is now considered equivalent to thoracic epidural analgesia.[1-4] Ultrasound guidance is strongly recommended to facilitate the application of TPVB and to improve its effectiveness and safety.[4] Although TPVB provides satisfactory postoperative analgesia in patients undergoing open thoracotomy, large volumes/doses of local anesthetics are required; thus, the manifestations of local anesthetic systemic toxicity (LAST) are always a concern.[1-4] In fact, LAST has been reported after

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continuous TPVB (CTPVB) with ropivacaine.[5,6] Additionally, bilateral TPVBs have resulted in potentially toxic total plasma concentrations of ropivacaine and postoperative mental state changes in patients subjected to coronary artery bypass surgery.[5] Furthermore, total plasma ropivacaine concentrations of 2.2 μg/ml have been considered the systemic toxicity threshold.[6] Of note, after CTPVB, toxic plasma concentrations of ropivacaine (3.2 μg/ml) have also been reported, which is mainly attributed to the presence of severe hypoalbuminemia (albumin 24 g/l) that led to the sudden cardiac death of an adult patient who underwent lobectomy.[7]

From a pharmacological standpoint, the correlation between the concentrations of local anesthetics in plasma and their pharmacodynamic/toxicologic responses are contingent upon various physiological, anatomical, and pharmacokinetic (PK) factors.[8] The correlation between systemic concentrations of local anesthetics and the clinical manifestation of central nervous system (CNS) and cardiovascular toxicity has been established.[9] Nevertheless, there are only limited data available pertaining to the PK of ropivacaine after CTPVB. Karmakar *et al.*[9] have advocated that the absorption of ropivacaine from tissues displays one rapid and one slow phase, with the maximum concentrations (Cmax) and time to maximum concentrations (Tmax) differing between arterial and venous plasma samples. In contrast, no difference in absorption kinetics was observed by Zhang *et al.*[10]

A useful tool to achieve the desired systemic exposure and clinical outcome without adverse effects is the population PK modeling because it allows to explore significant relationships between covariates and parameters, thus predicting drug exposure as well as drug safety and efficacy. To date, population studies on the PK have shown that variables such as body weight, age, and protein binding may influence the kinetics of ropivacaine.[11-15]

Based on the abovementioned discourse, the primary goal of this study was to explore the PK of ropivacaine and to identify potential factors affecting its PK profile in patients undergoing an ultrasound-guided CTPVB for postoperative analgesia purposes. For this reason, a single bolus injection of ropivacaine via a thoracic paravertebral (PVT) catheter (before the beginning of surgery) and a continuous thoracic PVT infusion (initiated at the end of surgery) were implemented. A secondary purpose of the study was to identify and thoroughly monitor postoperative pain intensity (pharmacodynamic parameter) and clinical signs of LAST.

Material and Methods

The study (ClinicalTrials.gov Identifier: NCT03721406) was a single-center prospective PK clinical study approved by the ethics committee of the University Hospital "Attikon" (protocol number 26/6/2018, sixth meeting) and conducted in line with the ethical standards of the Helsinki Declaration.

Written informed consent was obtained for the study from the patients. The inclusion criteria for participating in the study were the following: male or nonpregnant female subjects, patients of physical status I–III (according to the American Society of Anesthesiologists [ASA] classification), and patients scheduled for elective open thoracotomy under combined general anesthesia and ultrasound-guided CTPVB. The exclusion criteria were patients' refusal to participate in the study, age <18 years, morbid obesity, scoliosis, previous thoracotomy, or infection at the injection site of the TPVB, empyema, known allergy to any of the study drugs, severe cardiac, hepatic, or other systemic disease, urgent surgery, hypoalbuminemia, and need of reoperation during the study period.

All participants underwent the same protocol of general anesthesia, while radial artery catheterization and an intravenous (IV) line were ensured. Immediately after induction of general anesthesia, with the patient in the lateral position, an ultrasound-guided CTPVB was performed at the T5 or T6 or T7 thoracic level. For implementation of the ultrasound-guided CTVB, a transversal technique at the level of the transverse process was applied by using a two-dimensional curved array transducer (2.5–7.5 MHz) (LOGIQe; GE Healthcare, Waukesha, WI, USA). A 17-gauge, 11-cm Tuohy needle was inserted via an in-plane technique (lateral-to-medial needle pathway) and its final position tip was placed in the transition area from intercostal to PVT space, exactly above the pleura line.[16] An injection of 5 ml saline created an extrapleural detachment pocket at the T5 or T6 or T7 level. An echogenic catheter, with a 7-cm soft end portion (60 cm length; Teleflex, Arrow, Morrisville, NC, USA), was then inserted 3–4 cm into the PVT space.

Intraoperative monitoring consisted of electrocardiography (ECG), invasive arterial pressure measurement, oxygen saturation (SpO_2), urine output, and end-tidal CO_2 pressure ($PETCO_2$).

Initially, after catheter placement and before the beginning of surgery, a 25-ml single-bolus dose of ropivacaine 0.5% was administered via the catheter. After surgery, the catheter was connected to an electronic pump and a continuous infusion

of ropivacaine 0.2% was started with a constant infusion rate of 14 ml/h for the first three postoperative days.

Postoperatively, patients were transferred to the intensive care unit (ICU) on the first postoperative day and then to the ward. Postoperative pain control was based on the concept of multimodal analgesia, including CTPVB, and systemic administration of paracetamol (1 g × 4 IV), tramadol (100 mg × 4 IV), and pregabalin (75 mg × 2 per os). Postoperative pain was assessed at rest and during movement and cough using the visual analog scale (VAS; 0–10). Arterial blood pressure, heart rate, SpO_2, VAS scores, and clinical signs of LAST were all recorded during the first three postoperative days (specifically at 12, 24, 36, 48, and 72 postoperative hours).

Blood urea, serum creatinine, albumin, liver enzymes, activated partial thromboplastin clotting time (aPTT), prothrombin time (PT), international normalized ratio (INR), platelet count (PLT), hematocrit (Ht), and hemoglobin (Hb) were measured before and after the surgical procedure.

To collect ropivacaine from both arterial and venous blood, the cubital vein and radial artery contralateral to the proposed surgery were cannulated with 16- and 20-gauge IV cannulas, respectively. Serial blood samples from radial artery catheter and the IV line were collected at predefined time points as follows:

- *After 25 ml bolus dose of ropivacaine 0.5% was administered in the PVT space*:
  Blood samples from the radial artery catheter and the central venous line were collected at 5, 7.5, 10, 15, and 20 min and at 1, 5, 7.5, 10, 15, 20, 40, and 60 min after the bolus dose, respectively. Both arterial and venous blood samples were also obtained at the end of surgery.
- *After induction of continuous infusion of ropivacaine 0.2% (14 ml/h) in the PVT space*:
  During the postoperative period, blood samples were drawn from the radial artery catheter and central venous line at the following time intervals: arterial samples: 2.5, 7.5, 15, 30, and 60 min, as well as 24, 48, and 72 h after the initiation of the continuous infusion; venous samples: 2.5, 10, 15, 30, and 60 min, and 2, 6, 24, 48, and 72 h after the induction of the continuous infusion.

All blood samples (2.5 ml) were placed in ethylenediaminetetraacetic acid (EDTA) vacutainer tubes and immediately centrifuged (3500 rpm, 10 min). Plasma samples were collected and stored at −70°C until assay. High-performance liquid chromatography (HPLC) was used to quantify total ropivacaine plasma levels (sample volume 1 ml) using a validated method.[17] Blood samples were bioassayed in accordance with Good Laboratory Practice. The lower limit of quantitation (LLOQ) of ropivacaine was equal to 0.084 μg/ml, while the detection limit of ropivacaine was 0.025 μg/ml. The intraday accuracy values ranged from 92.7% to 97.2%, depending on the measured concentration. The precision values were 3.87%, 5.15%, and 2.39% at low, medium, and high concentrations, respectively.

Individual ropivacaine concentration – time (C-t) profiles were analyzed using the stochastic approximation for nonlinear mixed effects expectation maximization algorithm, followed by importance sampling methods. Several structural models were evaluated. IV administration (either bolus or infusion) was assumed to occur in a pre-absorption compartment related to the PVT space. In conjunction with the PVT compartment, one and two distribution compartments were studied using first-order transfer and elimination constants. PK parameters were assumed to follow a lognormal distribution, while various residual error models such as constant, proportional, and combined were tested.

After developing the final best structural model, several covariates were tested either untransformed or centered around the median value. Linear and lognormal (allometric) models were also assessed. In this study, the covariates examined were demographic data (sex, age, weight, height, body mass index [BMI]), biochemical tests (urea, creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), gamma-glutamyl transferase (γGT), prothrombin time (PT), international normalized ratio (INR)), hematological data (haematocrit (Ht), haemoglobin (Hb)), cardiological data (heart rate, systolic and diastolic blood pressure), and pain assessment (using the VAS scale) at rest and movement during the postoperative period (on three occasions: postoperative day 1, 2, and 3). For the patients in this study, other comedications (paracetamol, pregabalin, and tramadol, if needed) did not interact with ropivacaine, and there was no reason to include them as possible covariates. Covariate analyses were carried out utilizing stepwise forward selection and backward elimination. Continuous covariates were investigated either untransformed or centered on the covariate's mean or median value. The Wald test was performed to determine whether the covariates could explain the variation in the final model's parameters. All computational work was performed by developing the appropriate code in the Mlxtran language of Monolix™ v. 2020R1 (Lixoft, Simulation Plus).

Diagnostic plots, goodness-of-fit criteria, comparisons of relative standard deviations of estimated parameters, accuracy of estimates, and changes in Akaike and Bayesian information criteria and log-likelihood were used to select the best model. To

visually assess goodness of fit, plots of observed values versus population-predicted values and individual weighted residuals versus time were used. Visual prediction tests (VPCs) were used to evaluate the model's predictive performance, stability, and robustness. VPCs were created by running 1000 Monte Carlo simulations with 90% confidence intervals.

Noncompartmental analysis was also applied to get estimates for the Cmax, Tmax, and area under the concentration–time curve (AUC). The latter was performed in PKanalix® module of Monolix 2020R1. Since ropivacaine measurements took place both in the arterial and venous pools, the entire population PK and noncompartmental analyses were applied separately to the two blood pools; therefore, two population PK models were developed independently.

Statistical analysis was also performed for comparison of the PK metrics (AUC, Cmax, Tmax) between the arterial and venous blood and for the analysis of pharmacodynamic endpoints, namely, the VAS variables for pain management. The dynamic and static VAS scores are on the ordinal scale, and therefore, nonparametric methods were used. Also, nonparametric methods were used for comparison of Tmax estimates, since Tmax is a discrete numerical variable. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normality of AUC and Cmax values. As expected, AUC and Cmax were found to deviate from normality, and therefore, a log-normal (ln-) transformation was applied. The Kolmogorov–Smirnov and Shapiro–Wilk tests were reapplied to confirm that the ln-transformed AUC and Cmax follow normal distribution, and eventually parametric methods were used in order to have higher statistical power compared to the nonparametric methods. In the case of parametric techniques, independent *t*-test was used for comparison of independent groups (e.g. assessing the gender effect). For pairwise comparisons, such as between the estimates from the arterial and venous pools, a paired *t*-test was applied. In terms of nonparametric approaches (for example, Tmax and VAS score analysis), the Mann-Whitney U test was employed for comparisons between two independent groups, such as the influence of pain.The Wilcoxon test was used for pairwise group comparisons, such as comparing VAS between two consecutive dates. The Friedman's method was utilized to investigate whether there was a difference in pain perception throughout the postoperative period. The significance level was set at 5% in all cases in this study, and a result was considered significant if the estimated *P* value (*P*) was less than the significance level (IBM® SPSS®, v. 26).

Results

Twenty-nine patients subjected to open thoracic surgery were screened, of whom 18 met the eligibility criteria and participated in the study (identifier: NCT03721406). The flowchart of subjects enrolled in the study is shown in Figure 1. Table 1 displays the demographic information of the subjects who were recruited in this study. The median age was 67.5 years, 72.2% of the participants were males, and half of the patients had a BMI greater than 27.2 kg/m^2.

For the total data set, the final best PK model was a one-compartment disposition model linked to a pre-absorption compartment (thoracic PVT space) [Figure 2]. Table 2 depicts the PK parameter estimates for the final PK model. The volume of distribution of the central compartment (Vap) was 160,983.32 ml for the arterial pool and 177,453.29 ml for the venous pool. The clearance estimates from the central compartment (Cl) were 190.48 and 183.03 ml/min for the arterial and venous parts, respectively. Similarly, the distribution rate constant (k_b) from thoracic PVT space to blood (artery or venous) was found to be 0.021 and 0.022 min^{-1}, respectively.

Among all potential covariates tested (see "Materials and Methods" section), either linearly or allometrically, only sex was found to have a significant contribution in ropivacaine clearance. The "sex clearance" constant was -0.17 ($P < 0.001$) for the artery-based model and -0.20 ($P = 0.003$) for the venous-based model, indicating that elimination (through the liver) is significantly lower in women compared to men [Figure 3]. In both cases, the proportional error models

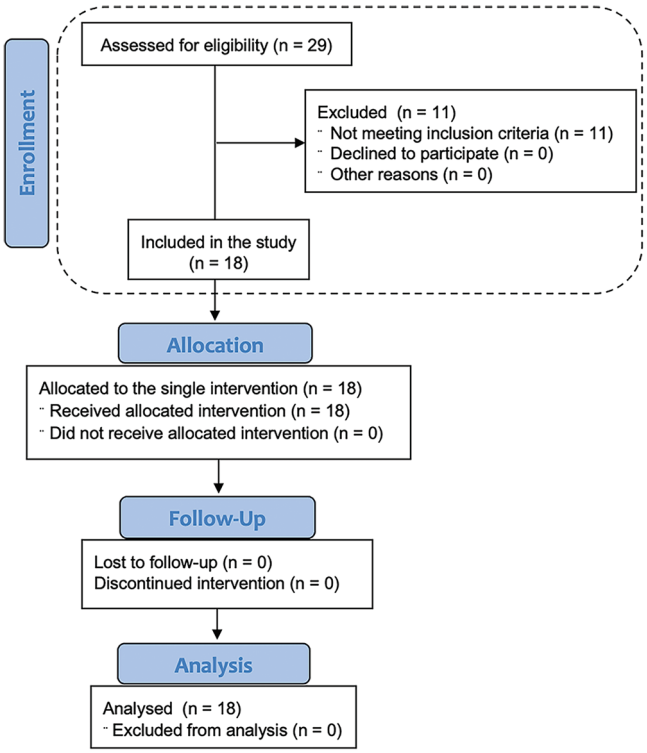

Figure 1: Flowchart of patients enrolled in the study

with b = 0.32 and 0.50 produced the best residual error results. In addition, a positive correlation was found between Cl and Vap (correlation coefficients equal to 0.89 and 0.87 for the arterial and venous parts, respectively).

Graphical evaluation of the final model predictive ability with the visual predictive check plot [Figure 4] revealed that the prediction interval from the developed model included the experimental concentration data (5th, 50th, and 95th percentiles). Further validation plots of the final PK model are shown in Figures 5 and 6, where individual predicted versus observed concentration values are nearly linearly correlated [Figure 4] and individual weighted residuals of C-t [Figure 6a] and concentration [Figure 6b] have a distribution around zero.

The results of the non-compartmental analysis (NCA) analysis are summarized in Table 3, where the basic descriptive statistical criteria are calculated. Paired comparisons revealed no statistically significant differences (*P* values were > 0.05) in the PK estimates (AUC, Cmax, Tmax) between the arterial and venous data.

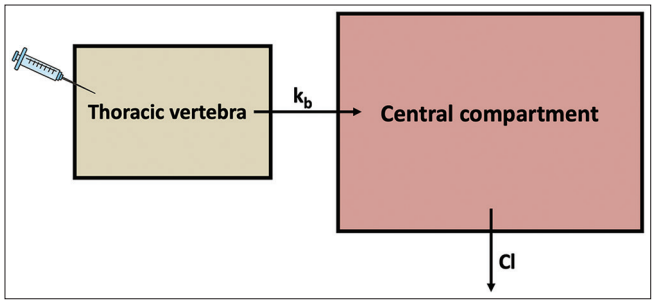

Figure 2: Structural pharmacokinetic model for the description of ropivacaine pharmacokinetics, in the arterial and venous pools, after sequential intravenous bolus and infusion administration

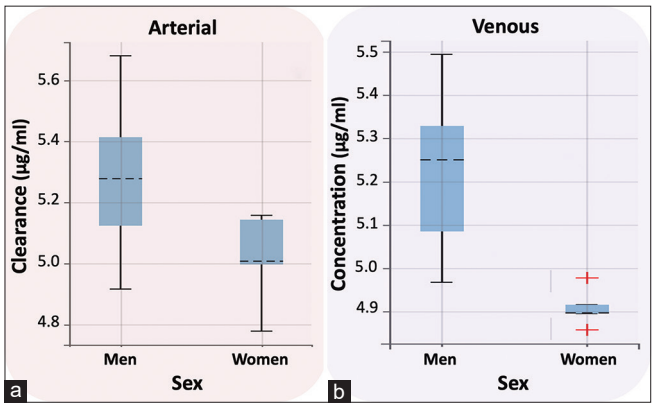

Figure 3: Distribution of clearance values between males and females in the cases of the arterial (a) and venous (b) pools. The boxplot's boundaries correspond to the distribution's quartiles

Table 1: Demographic and biochemical data of the patients included in the study

Patient characteristics	Value
Demographics	
Sample size	18
Age (median, range) (years)	67.5 (32)
Women, *n* (%)	5 (27.8%)
Men, *n* (%)	13 (72.2%)
Body mass index (median, range)	27.2 (16.7)
Biochemical parameters	
Before surgery	
Urea	31.5 (13)
Creatinine	1.0 (0.4)
SGOT	18 (34)
SGPT	14 (33)
γGT	16 (51)
Postsurgery (3rd postoperative day)	
Urea	28.5 (31)
Creatinine	0.7 (0.9)
SGOT	28.5 (31)
SGPT	21 (48)
γGT	21 (48)

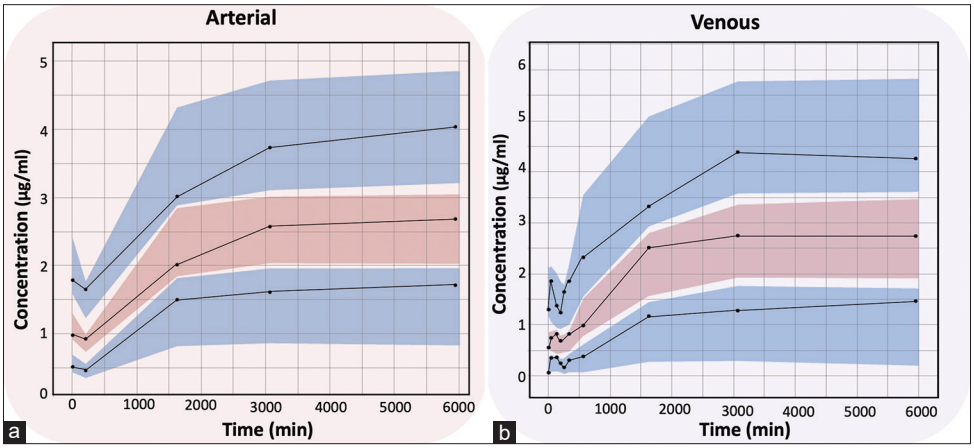

Figure 4: Visual predictive check plot for the final best model of ropivacaine in the arterial (a) and venous (b) pools. The blue lines represent the empirical data's 10th, 50th, and 90th percentiles, while the shaded areas represent the predicted 90% confidence intervals around each range (10th, 50th, and 90th percentiles). A total of 1000 Monte Carlo simulations were used

Table 2: The population parameters of the final ropivacaine pharmacokinetic model

	Average	Standard error	Relative standard error	*P*
Arterial				
Fixed effects				
k_b (min^{-1})	0.021	0.00258	12.3	-
Vap (ml)[a]	160,983.32	13,538	8.4	-
Cl (ml/min)[a]	190.48	9.53	5.0	-
beta_Cl_Sex	−0.17	0.0291	17.1	<0.001
Standard deviation of the random effects				
omega_Vap	0.34	0.062	18.3	-
omega_Cl	0.2	0.039	20	-
Correlations				
corr_Vap_Cl	0.89	0.0489	5.49	-
Error model parameters				
B	0.32	0.017	5.34	-
Venous				
Fixed effects				
k_b (min^{-1})	0.022	0.00315	14.3	-
Vap (ml)[a]	177,453.29	22,122.42	12.5	-
Cl (ml/min)[a]	183.03	7.8	4.26	-
beta_Cl_Sex	−0.20	0.0392	19.6	0.003
Standard deviation of the random effects				
omega_Vap	0.49	0.1	21.0	-
omega_Cl	0.15	0.038	26.1	-
Correlations				
corr_Vap_Cl	0.87	0.0452	5.2	-
Error model parameters				
B	0.5	0.026	5.16	-

Cl=apparent clearance, PVT=paravertebral. Key: k_b, distribution rate constant from thoracic PVT space to blood (artery or venous); Vap, apparent volume of distribution; omega_Vap, between-subject variability values for Vap; omega_Cl; between-subject variability values for Cl; beta_Cl_Sex, constant in the model expressing the decrease of clearance in women; corr_Vap_Cl, correlation coefficient between Vap and Cl; b, proportional component of the error model. [a]Since ropivacaine administration is extravascular, the Vap and Cl estimates actually refer to Vap/F and Cl/F, respectively, where F is the bioavailable fraction

Table 3: Pharmacokinetic estimates from noncompartmental analysis applied independently to concentration-time from single bolus administration in the paravertebral space and to the entire concentration-time data (including both the single-bolus and continuous infusion)

Statistic	Only from the single-bolus part			From the entire profile		
	AUC	Cmax	Tmax	AUC	Cmax	Tmax
Arterial						
Minimum	25.02	0.70	10.0	27.27	0.47	134.5
First quartile	119.42	1.00	15.0	9877.95	0.87	210.0
Median	165.97	1.55	20.0	13073.55	1.17	235.0
Third quartile	229.98	1.85	90.0	14401.95	1.43	270.0
Maximum	428.63	2.25	185.0	17148.74	2.27	365.0
Average	181.44	1.47	52.8	11041.48	1.22	238.4
Coefficient of variation	52.99	32.00	118.0	50.79	40.35	23.8
Venous						
Minimum	26.74	0.43	7.5	158.09	0.41	142.0
First quartile	65.38	0.67	40.0	7334.94	0.87	240.0
Median	90.97	0.94	60.0	11667.97	1.18	253.8
Third quartile	216.34	1.47	108.0	14360.93	1.88	315.0
Maximum	569.69	2.25	185.0	18771.04	8.81	1620.0
Average	144.19	1.09	79.8	10375.93	1.76	354.4
Coefficient of variation	91.96	54.94	64.0	56.21	119.34	104.0

AUC=Area under the concentration-time curve, Cmax=Maximum blood concentration, Tmax=The time at which Cmax occurs

None of the patients developed hypoalbuminemia postoperatively. The remaining biochemical test values were found to lie within the physiological range [Table 1]. As far as the intensity of postoperative pain is concerned, the VAS measurements in

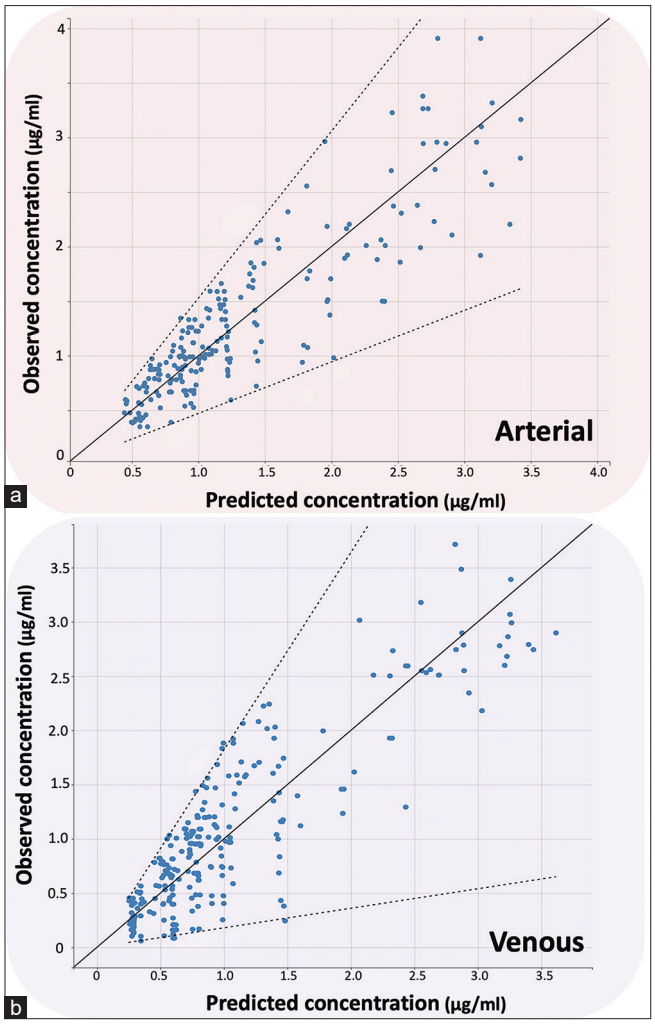

Figure 5: Population observed versus predicted individual concentrations of ropivacaine for the arterial (a) and venous (b) pools. Closed circles represent (predicted, observed) pairs, solid lines represent the ideal situation of unity (i.e. y = x), and dotted lines represent the 90% prediction interval

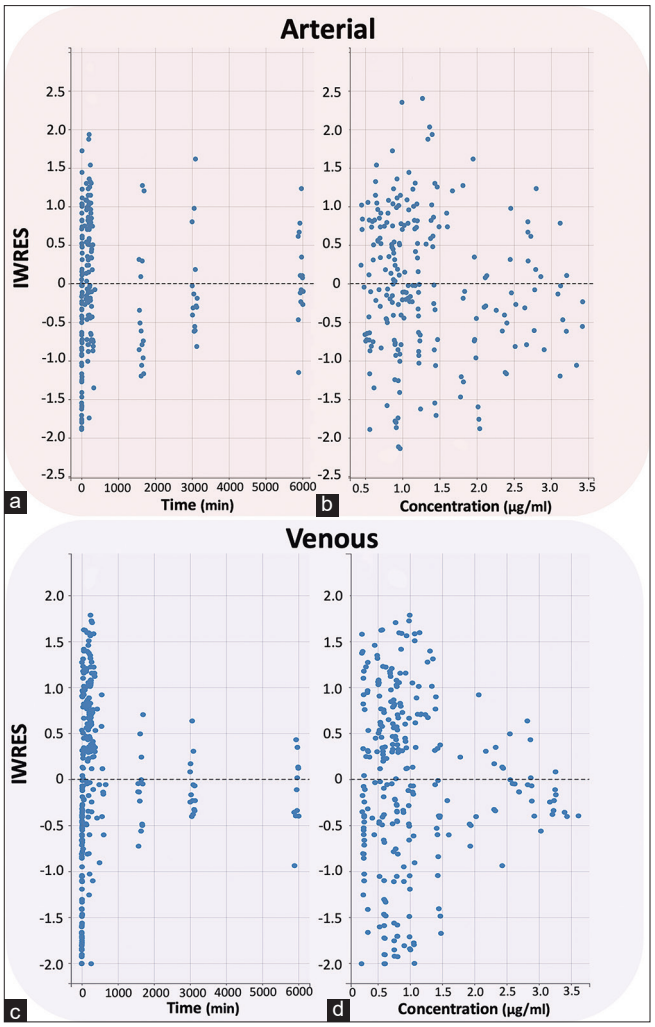

Figure 6: IWRES versus time (a, c) and IWRES versus concentration (b, d). The dotted line depicts the ideal y = 0 situation. IWRES = individual weighted residuals

the 1st, 2nd, and 3rd day post-surgery are shown in Figure 7. It is evident from these bar plots that there was a progressive reduction in pain during the postoperative period, and that the pain experienced at rest was mild for <12% of patients, while only a small percentage experienced mild to severe dynamic pain (during cough). Statistical comparisons with the Friedman's test revealed a statistically significant difference ($P = 0.028$) in the 3rd day compared to the 1st and 2nd days.

Concerning the manifestations of LAST, the patients did not show any sign of CNS toxicity or cardiotoxicity, such as perioral numbness, tinnitus, agitation, dysarthria, confusion, seizures, coma, ventricular arrhythmias, or asystole.

Discussion

The primary goal of this study was to investigate the PK of ropivacaine and to identify possible factors influencing its PK profile in patients undergoing an ultrasound-guided CTPVB for postoperative analgesia. For this, a single bolus injection of ropivacaine administered through a thoracic PVT catheter before surgery and a continuous thoracic PVT infusion initiated at the end of surgery were used. The study's secondary goal was to identify and meticulously monitor postoperative pain intensity and clinical signs of LAST. A ropivacaine population PK model was developed using concentration measurements after TPVB ropivacaine administration both as a single bolus injection and as a continuous infusion in 18 adult patients who underwent open thoracotomy. Ultrasound guidance was employed to make TPVB easier to use and to improve its effectiveness and safety. The final best model for ropivacaine, either for the arterial or venous blood, was a one-compartment disposition model with an additional pre-absorption compartment related to the thoracic PVT space. This one-compartment model was consistent with other published ropivacaine studies in adults, children, and infants.[11-15] It is worth noting that our purpose

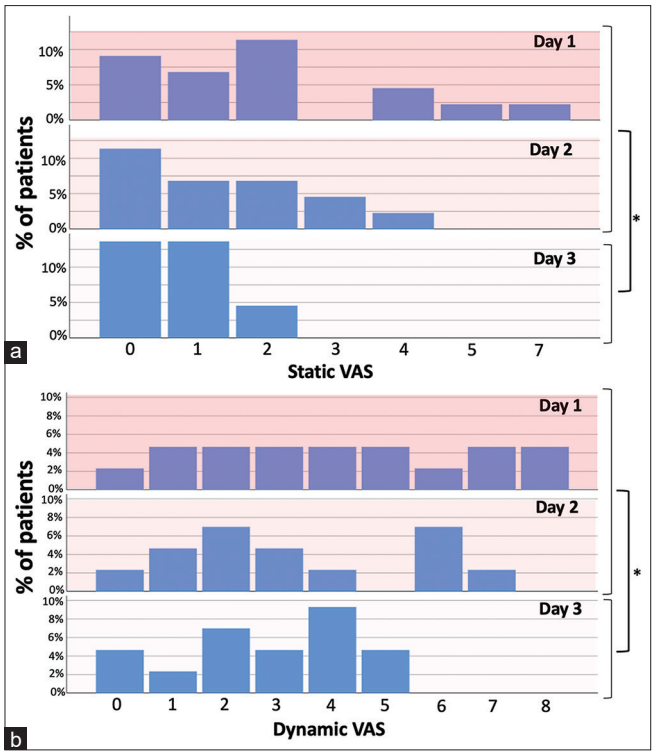

Figure 7: Distribution of static (a) and dynamic (b) VAS scores. The three different panels of bar plots refer to the observations at postoperative days 1, 2, and 3. The asterisk (*) denotes statistically significant difference between the marked days ($P < 0.05$). VAS = visual analog scale

was to investigate separately the PK of ropivacaine in the arterial and venous pools, and not to build a joint model, in order to examine whether there are differences in ropivacaine kinetics between them. Other studies have assumed first-order transfer between arterial and venous blood, aiming to describe venous PK.[9]

Only gender had a significant impact on clearance among the tested covariates, and females were found to exert significantly lower elimination than males [Figure 2]. Significant relationships were not found for other scores describing the liver function (e.g. SGOT, γGT). Because our study involved a small patient group, the inclusion of allometric models was considered necessary, though it could adjust for any sex difference based solely on size. However, the investigation revealed that allometric models were worse compared to the finally chosen model including "sex" as a covariate into clearance. Even though the number of women participants was lower compared to men (5 vs. 13), this imbalance did not affect the validity of the results, since the nonlinear mixed PK modeling is rather robust against imbalances and/or missing data.

All the PK estimates were also found to be similar between the venous and arterial measurements [Table 2], exhibiting comparable results with previous studies.[10] In addition, the clearance and volume of distribution estimates were also in line with other published data.[18] The latter was further validated by the NCA results (AUC, Cmax, Tmax), which showed no statistically significant differences between the arterial and venous blood [Table 3]. This finding is in full accordance with the results of Zhang *et al.*,[10] in their letter to the editor, who also found that there is no difference in the absorption behavior of ropivacaine between the arterial and venous pools.

TPVB dosage regimen of ropivacaine used in the present study to provide both intraoperative and postoperative analgesia is in accordance with the current clinical practice.[4] Our study has contended that CTPVB (as an integral part of multimodal analgesia) provided satisfactory postoperative analgesia, as most patients were pain free at rest, with a low proportion experiencing mild to severe dynamic pain [Figure 6].

Moreover, none of the patients experienced the clinical signs of LAST, even though in some cases [Figure 2], the systemic toxicity threshold was exceeded. From a practicality perspective, we examined the PK profile of the recommended maximum hourly and daily dose of ropivacaine.[8,19] Ropivacaine continuous infusion at 28 mg/h was decided upon, since this dose regimen is considered the maximum hourly dose.[8,19] Nevertheless, considering that in the first 24 h, all patients also received a constant single bolus dose (125 mg), caution was exercised not to exceed a total dose of 800 mg, which is the maximum recommended daily dose.[8,19] Our decision to administer the maximum recommended dose of continuous infusion and the approximate maximum recommended daily dose of ropivacaine relied on the fact that we set out to maximize the potential postoperative analgesic effects of the drug, since open thoracotomy is considered a very painful operation.[1,2] In our study, the continuous infusion was not commenced exactly after the single bolus injection, given that our intention was also to investigate independently the PK of ropivacaine after a single bolus injection during the intraoperative period.

Previously, the toxicity of local anesthetics had been tested in volunteers after continuous IV infusions. Overall, the systemic toxicity of a local anesthetic is analogous to the infusion rate and the total dose, as well as inversely proportional to cardiac output and the infusion time.[6,20] Having examined the systemic toxicity of ropivacaine, researchers attempted to assess the toxic dose thereof in healthy individuals by an IV infusion rate of 10 mg/min. Very interestingly, a high variability of mean maximum tolerated dose has been observed among different studies, ranging from 39 to 124 mg.[6,19,20] In addition, after a continuous infusion rate of 10 mg/min, the toxic levels of ropivacaine (arterial: 4.3 ± 0.6 mg/l and venous: 2.2 ± 0.8 mg/l) revealed large arteriovenous concentration

differences, mainly attributed to rapid IV administration.[6] From a clinical point of view, therefore, the best information about the systemic toxicity of a local anesthetic is obtained by comparing the plasma concentrations that cause symptoms of systemic toxicity with those stemming from every single type of nerve block; that is to say, the PK and clinical examination results should be interpreted in concert.[21] During our study, at certain time points, the plasma concentrations of ropivacaine were higher than those previously quoted.[6,20] Nevertheless, none of our patients experienced symptoms of systemic toxicity. Consequently, in cases of individuals with smaller BMIs, ropivacaine doses at the upper end of clinical use (800 mg/d) infused in the PVT space (through a different PK model than that of IV infusion) resulted in plasma concentrations that were above the threshold of systemic toxicity but not associated with any overt clinical symptoms.

To the best of our knowledge, this is the first study where a population PK model has been developed for describing both the arterial and venous ropivacaine kinetics after ultrasound-guided continuous PVT nerve block. Ropivacaine kinetics are accurately described by the model that was constructed, which also demonstrates that gender has a substantial impact on clearance. It was shown that women excrete a substantially lesser amount of waste than men. Furthermore, it was demonstrated that ropivacaine doses that were at the top end of the clinical use range (800 mg/d) did not inflict any indications of LAST.

Our research does have a few limitations. It was difficult to find any correlations between variables and their influence on PK because of the limited sample size of the recruited population. The utilization of nonlinear mixed effects modeling, on the other hand, makes up for this shortcoming by being able to manage small sample sizes through utilization of sparse sampling and by providing accurate estimates of the model parameters. Despite this, the use of this modeling technique is not without its drawbacks.[22] In addition, in order to get around this methodological flaw, five Markov chains were utilized in the modeling process; all of the obtainable data were reproduced, which resulted in a total of 50 patients, which considerably enhanced the estimations' level of precision. It was reported in the past that after caudal infusion in newborns, the PK of ropivacaine was altered by variables such as age and protein binding.[15] In the research that we conducted, using data from such a limited sample size, we found that the PK of ropivacaine was significantly impacted by one of the covariates (gender). Also, the distribution parameter k_b, which refers to the pre-absorption site, can also be subjected to interindividual variability. However, due to the limited sample size, it was kept fixed. Thusit was not possible to calculate the omega values for k_b. Finally, in order to steer clear of conclusions that could be misconstrued as a whole, our research was conducted specifically on the population (patients undergoing open thoracotomy) that was assigned to this protocol, as well as with the particular type of peripheral nerve block (CTPVB) and the particular dose of ropivacaine.

In conclusion, it is known that TPVB, employed in thoracic surgery, leads to satisfactory postoperative analgesia; however, large doses of anesthetics (e.g. ropivacaine) are required and manifestations of LAST may appear. This study showed that ropivacaine doses, at the upper end of clinical use (800 mg/d), did not inflict the manifestations of LAST, even though in some patients, the ropivacaine concentrations were above the toxic threshold. Also, population PK models were developed for ropivacaine and a significant gender effect was identified for both the arterial and venous models. Gender had a significant effect on clearance, with females displaying lower elimination than males.

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Conflicts of interest

There are no conflicts of interest.

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