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# Combining ropivacaine transversus abdominis plane block with intravenous lidocaine infusion in adults undergoing colorectal cancer surgery: an open-label, dose-escalation exploratory trial

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## Abstract

**Background** The concurrent use of a ropivacaine transversus abdominis plane (TAP) block with intravenous lidocaine infusion, though effective for pain relief, raises safety concerns regarding local anesthetic systemic toxicity (LAST). This study aimed to assess the dose-risk relationship of LAST in this combination by escalating the ropivacaine dose while fixing the lidocaine dose.

**Methods** In this dose-escalation study, adult patients undergoing colorectal cancer surgery received a 0.2% ropivacaine TAP block (1.5, 2.0 or 2.5 mg $kg^{-1}$) and intravenous lidocaine infusion (2 mg $kg^{-1}$ bolus, followed by 2 mg $kg^{-1}$ $h^{-1}$), both dosed according to ideal body weight (IBW). The primary outcome was the occurrence of LAST, identified by clinical symptoms, new-onset ECG irregularities, etc. Secondary outcomes included plasma concentrations of ropivacaine and lidocaine.

**Results** Nine patients were included in the per-protocol analysis, and 26 were included in the intention-to-treat analysis. No signs of LAST were observed. Plasma ropivacaine concentrations remained consistently below 2.2 μg $mL^{-1}$, however, eight patients in the intention-to-treat population and three patients in the per-protocol population had plasma lidocaine concentrations exceeding 5.0 μg $mL^{-1}$ at 10 min post-bolus. In the per-protocol population, peak plasma ropivacaine concentrations occurred at 30 min (range, 20–60) post-TAP block, with median values of 1.14 (range, 0.85–1.18), 1.42 (range, 1.29–1.80), and 1.96 (range, 1.47–2.06) μg $mL^{-1}$ across dose groups. The peak plasma

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lidocaine concentrations in patients occurred at 10 min post-bolus infusion, with median values of 4.59 μg $mL^{-1}$ (range, 3.24–6.67) and gradually decreased after 2 h. The intention-to-treat analysis found similar results.

**Conclusion** Although no signs of LAST were observed with the combination of a 1.5 to 2.5 mg $kg^{-1}$ ropivacaine TAP block and intravenous lidocaine infusion under general anaesthesia, extreme caution is still warranted regarding the potential risk of LAST.

**Trial registration** This trial was registered at ClinicalTrials.gov (NCT06006026) on 23 August 2023.

**Keywords** Transversus abdominis plane, Ropivacaine, Intravenous lidocaine, Local anesthetic systemic toxicity, Dose-escalation

## Introduction

Postoperative pain severely impairs early mobility and increases the risk of postoperative complications, causing prolonged hospital stays and delayed recovery [1]. Despite advancements in pain management, achieving optimal postoperative analgesia remains a challenge [2]. In colorectal cancer surgery, postoperative pain, especially movement-evoked pain, affects over 50% of patients, highlighting the urgent need for effective pain management strategies [3].

Multimodal analgesia protocols have become increasingly prevalent in clinical practice to address these challenges [4]. Among these approaches, the transversus abdominis plane (TAP) block, which provides extensive pain relief by targeting a broad range of sensory nerves [5–7], and intravenous lidocaine, commonly used perioperatively for its anti-hyperalgesic and anti-inflammatory properties, have both demonstrated significant efficacy in pain relief and opioids reduction [8], particularly in colorectal surgery [9]. Our previous study indicated that combining intravenous lidocaine with local wound infiltration using ropivacaine provided superior pain relief compared to ropivacaine infiltration alone [8]. However, this combination also raises significant safety concerns, particularly regarding the risk of local anesthetic systemic toxicity (LAST) [10].

Despite these safety concerns, a survey of anesthetists in Australian and New Zealand revealed that over 25% of respondents utilized both analgesia protocols in surgical patients [11]. Although international consensus guideline recommends a 4-hour interval between the administration of these local anesthetics to minimize this risk [10], adherence to these guidelines in clinical practice remains suboptimal. Reports indicated that only 37% of anaesthesiologists discontinued lidocaine infusion before performing a local block, while 44% merely reduced the local anesthetic dose instead [11]. This discrepancy between recommended guidelines and actual clinical practice highlights a significant gap, underscoring the need for further investigation into the potential LAST risk when the two local anesthetics are combined and administered across multiple routes.

Given that the effective dosage range for ropivacaine in TAP blocks is reported to be 1.5 mg $kg^{-1}$ to 2.5 mg $kg^{-1}$ [12, 13], and intravenous lidocaine is typically administered as a bolus dose of 1.5-2 mg $kg^{-1}$ followed by a continuous infusion at 1.5-2 mg $kg^{-1}h^{-1}$ [8, 9, 14], our study will fix the lidocaine infusion dose and initiate ropivacaine at lower doses for TAP blocks using a dose-escalation strategy to assess the dose-risk relationship.

## Methods

### Ethics statements

This trial was registered prospectively with ClinicalTrials.gov (NCT06006026, principal investigator: Chunling Jiang, date of registration: August 23, 2023). Ethical approval was obtained from the Ethics Committee of West China Hospital, Sichuan University (approval number HX20201180-1). All patients provided informed consent and were enrolled after registration.

### Study design

This open-label, dose-escalation trial followed a 3 + 3 model to assess whether escalating doses of ropivacaine, as observed in previous studies [12, 13], when combined with a fixed intravenous dose of lidocaine [15], increased the risk of LAST. The trial was conducted at the West China Hospital of Sichuan University from August 28, 2023, to May 15, 2024.

The 3 + 3 dose-escalation model, commonly employed in Phase I trials, was selected in this study due to the uncertainty surrounding the toxicity of combining the two local anesthetics. This approach minimized risk by limiting exposure. The sample size was determined by the number of dose levels tested, with additional patients being included only if necessary to replace incomplete data sets or to further assess potential adverse events.

### Patient recruitment

We included patients aged 18–65 years with an American Society of Anaesthesiologists (ASA) physical status of I–II, who were scheduled for elective colorectal surgery. The exclusion criteria were body weight < 40 kg or > 100 kg, cardiac rhythm disorders or systolic heart failure (including second- and third-degree heart block and

ejection fraction < 50%), severe liver dysfunction (alanine aminotransferase, aspartate aminotransferase, or bilirubin levels 2.5 times higher than normal), severe renal dysfunction (creatinine clearance rate < 60 mL/min), contraindications to lidocaine or ropivacaine, and communication difficulties.

### Anaesthesia management

Upon arrival at the operating room, patients were monitored with electrocardiography (ECG), blood oxygen saturation, blood pressure monitoring, and electroencephalography (EEG). General anaesthesia was induced with midazolam (2 mg), propofol (1.5–2.5 mg $kg^{-1}$), sufentanil (0.2–0.3 μg $kg^{-1}$), and cisatracurium (0.2 mg $kg^{-1}$). After tracheal intubation, anaesthesia was maintained with remifentanil (0.1–0.2 μg $kg^{-1}$ $min^{-1}$) and desflurane or sevoflurane in a mixture of 40% air and 60% oxygen to maintain the Patient State Index (PSI) within a range of 25–50, as monitored by the Masimo Root monitor [16]. After surgery, all patients were extubated in the operating room and transferred to the post-anaesthesia care unit (PACU), where they were monitored according to the institutional PACU protocol [8].

### Study intervention

After anaesthesia induction, an experienced anaesthesiologist performed bilateral TAP blocks using high-frequency linear array ultrasound probes (AnaesusME7 Mindray Bio; Medical Electronics, Shenzhen, China). Success of the TAP block was confirmed using the technique described by Griffiths and colleagues [13] (Supplementary Figure S1). TAP blocks were administered using a dose-escalation approach based on ideal body weight (IBW, IBW = 45.4 + 0.89x(height−152.4) (+4.5 if male) [17], initiating with the lowest dose for three initial patients. Concurrently, patients received an intravenous infusion of lidocaine at a dose of 2.0 mg $kg^{-1}$ over a duration of 10 min, followed by a continuous infusion at 2.0 mg $kg^{-1}$ $h^{-1}$ until the end of surgery. Doses were also calculated based on IBW. If no signs of LAST were observed, an additional three patients were recruited at the next higher dose. Notably, if blood samples could not be obtained for measurement of the plasma concentrations, new patients were enrolled until at least three patients per dosage group had complete blood sample data. In the event of an adverse event related to LAST, three additional patients were enrolled at the same dose level (Fig. 1). The initial dose selection was based on previous studies confirming its safety and efficacy [12]. The dose at which no more than one of the three patients experienced an adverse event related to LAST was designated as the recommended phase 2 dose. Three dose levels were evaluated: 1.5 mg $kg^{-1}$, 2.0 mg $kg^{-1}$, and 2.5 mg $kg^{-1}$ of 0.2% ropivacaine. Further dose escalation beyond 2.5 mg $kg^{-1}$ was not pursued due to potential neurotoxicity reported with 3.0 mg $kg^{-1}$ [18].

### Adverse event management

In the event that patients experienced severe signs of LAST, characterised by generalised seizures, life-threatening arrhythmia or unexplained loss of consciousness, local anaesthetics were discontinued immediately and a 20% lipid emulsion was administered [19]. Adverse events and their treatments were meticulously documented.

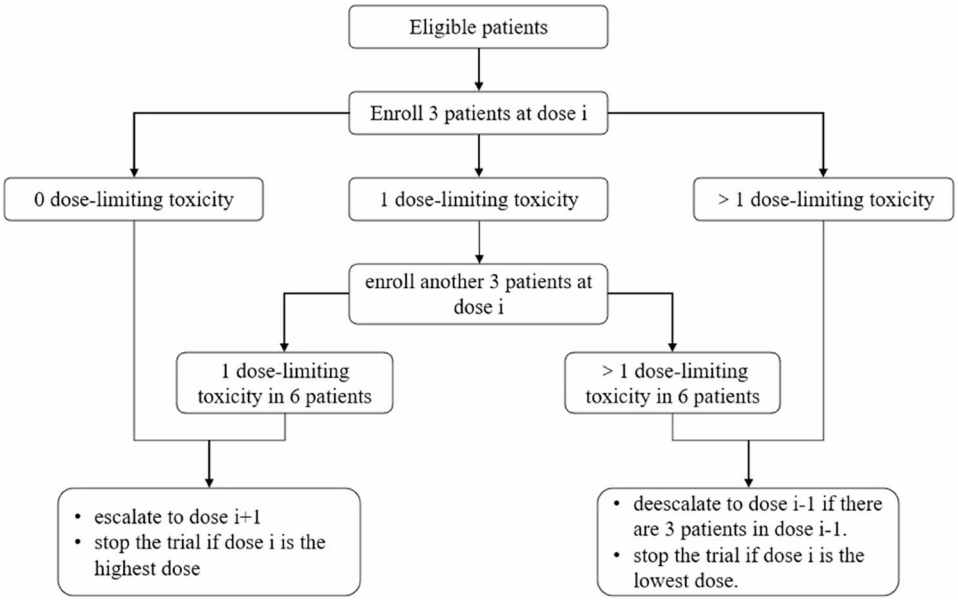


**Fig. 1** Schema of the 3 + 3 design. DLT: dose-limiting toxicity

### Study outcomes

The primary outcome was the occurrence of LAST, identified by clinical symptoms such as dizziness, lightheadedness, metallic taste, perioral numbness, tinnitus, seizures, unexplained loss of consciousness, or new-onset ECG irregularities [19], occurring from the administration of local anesthetics up to 24 h postoperatively. Intraoperative EEG abnormalities, such as continuous or recurrent focal or generalized spikes, sharp waves, or rhythmic theta or delta activity, were also considered as indicators of LAST [20–22].

Secondary outcomes included plasma concentrations of ropivacaine and lidocaine at various time points (10, 20, 30, 45, 60, and 90 min and 2, 4, 6, 12, and 24 h) following the completion of bilateral TAP blocks and the initiation of intravenous lidocaine infusion.

### Data collection

Blood samples were obtained from the contralateral side of the lidocaine infusion site. Samples were processed for serum storage and batch analysis using high-performance liquid chromatography with carbamazepine as the internal standard [23].

Intraoperative adverse events, including new-onset ECG irregularities or EEG abnormalities, such as continuous or recurrent focal or generalized spikes, sharp waves, or rhythmic theta or delta activity [20–22], were assessed by an experienced anaesthesiologist trained in ECG and EEG. After extubation, adverse events, including signs, or ECG changes related to LAST [19, 24], were assessed and monitored by trained assessors at the bedside for up to 24 h postoperatively. All EEG recordings were ultimately evaluated by a neurologist to confirm again. Additionally, postoperative analgesic consumption during 24 h was recorded and converted into intravenous morphine equivalents (mg) using the Practical Pain Management calculator (https://opioidcalculator.practicalpainmanagement.com/), with the NRS score also documented at 24 h postoperatively.

### Statistical analysis

#### *Sample size estimation*

This study followed a 3 + 3 design, with the final sample size depending on real-time response of the patients at each dose level. The maximum sample size was typically six times the number of dose levels, with complete blood samples at each time point [25].

#### *General statistical analysis*

Results of descriptive analysis of normally distributed variables were presented as mean and standard deviation (SD), whereas non-normally distributed data were presented as median (interquartile range, IQR) or median (range). Categorical variables were presented as the number of cases (percentage). Primary analyses were based on the per-protocol (PP) population, and secondary sensitivity analyses were done on the intention-to-treat (ITT) population for the primary and secondary outcomes. The normality of data distribution was assessed by evaluating histograms and using the Shapiro–Wilk test to determine the appropriate comparison tests (parametric versus nonparametric). Statistical analysis was performed using SPSS software (version 22.0; IBM Corp.).

## Results

During the study, 45 patients were screened for eligibility. Of these, 26 were involved and treated with a combination of a ropivacaine TAP block and lidocaine intravenous infusion according to their assigned dose (Supplementary Figure S2). Blood samples were missed at certain time points for 17 patients. Consequently, the PP analysis included 9 patients. The patient enrollment process is illustrated in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram shown in Fig. 2.

The characteristics of the enrolled patients are summarized in Table 1. The median age of the patients was 57 years (IQR: 48–61), with 13 (50%) being male and body mass index (BMI) 23.6 kg $m^{-2}$ (IQR: 22.5–25.8). The duration of anaesthesia was 3.9 h (IQR: 3.3–4.3). The median doses of lidocaine and ropivacaine administered during anaesthesia were 456 mg (IQR: 403–528) and 100 mg (IQR: 85–136), respectively. Intraoperative hemodynamic changes over times were presented in Supplementary Table 1. Postoperative morphine equivalent consumption during 24 h and the NRS score at 24 h were also provided in Table 1.

### Primary outcome

No signs of LAST were observed from the administration of local anaesthetics to 24 h postoperatively in all patients (Table 2). Additionally, no abnormal EEG waves were observed during general anaesthesia. A representative EEG image during anaesthesia, characterized by alpha, theta, and delta waves, was presented in Supplementary Figure S3.

### Secondary outcome

#### *Plasma concentrations of ropivacaine at all time points*

The time course of ropivacaine plasma concentrations was shown in Fig. 3A and B. Throughout the study, ropivacaine plasma concentrations were consistently below the established toxicity threshold of 2.2 μg $mL^{-1}$ in all patients. Peak plasma concentrations of ropivacaine occurred at 30 min (range, 20–60) after TAP block with a medium of 1.14 (range, 0.85–1.18), 1.42 (range, 1.29–1.80), and 1.96 (range, 1.47–2.06) μg $mL^{-1}$ for each dose

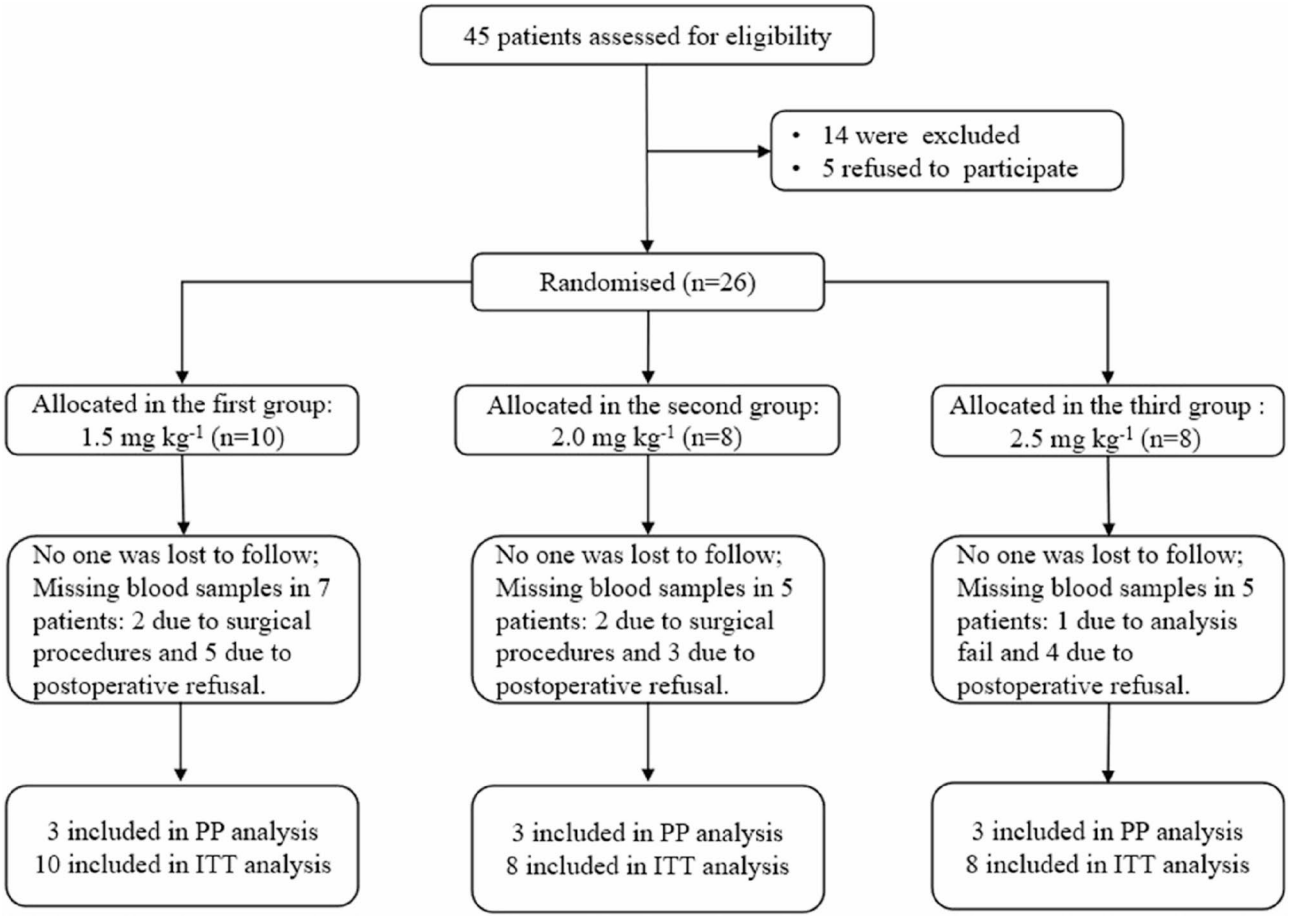


**Fig. 2** Consolidated Standards of Reporting Trials (CONSORT) flow diagram. PP, per-protocol; ITT, intention-to-treat

group in the PP population, respectively (Fig. 3 and Supplementary Figure S4). The median plasma concentration of ropivacaine across all time points was 0.64 μg $mL^{-1}$ in 1.5 mg $kg^{-1}$ group, 0.99 μg $mL^{-1}$ in 2.0 mg $kg^{-1}$ group and 1.38 μg $mL^{-1}$ in 2.5 mg $kg^{-1}$ group in the PP analysis (Supplementary Figure S5). The ITT analysis found similar results: peak plasma concentrations of ropivacaine occurred at 37.5 min (range, 20–60) after TAP block with a medium of 1.05 (range,0.50–1.42), 1.36 (range, 0.72–1.89), and 1.45 (range, 1.19–2.06) μg $mL^{-1}$ for each dose group (Fig. 3 and Supplementary Figure S4).

#### *Plasma concentrations of Lidocaine at all time points*

The plasma lidocaine concentrations in the PP and ITT population were shown in Fig. 3C and D. Consistent concentration timings were found in both the PP and ITT patient populations. Most patients exhibited a peak plasma concentration at 10 min after the initial bolus intravenous infusion, with median peak concentrations of 4.59 (range, 3.24–6.67) and 4.56 (range, 2.79–7.16) μg $mL^{-1}$ in the PP and ITT populations. The concentration dramatically dropped after 10 min post-bolus infusion and fluctuated between 1.68 and 4.22 μg $mL^{-1}$ for up to 2 h, then gradually decreased in the PP populations (Supplementary Figure S6). Among these patients, three in the PP population and eight in the ITT population had plasma concentrations exceeding the established toxicity threshold of 5.0 μg $mL^{-1}$ at the 10 min timepoint (Fig. 3 and Supplementary Figure S7).

## Discussion

This study explored the dose-risk relationship of LAST associated with the combined use of a 0.2% ropivacaine TAP block, administered at escalating doses of 1.5, 2.0, and 2.5 mg $kg^{-1}$, alongside a 2% intravenous lidocaine infusion (2 mg $kg^{-1}$ bolus, followed by continuous infusion at 2 mg $kg^{-1}$ $h^{-1}$) in adult patients undergoing colorectal cancer surgery. Although no clinical symptoms of LAST were observed and ropivacaine plasma concentrations remained well below the established toxicity threshold, 8 out of 26 patients had plasma lidocaine concentrations exceeding 5.0 μg $mL^{-1}$. These findings suggest that while the combination of 1.5–2.5 mg $kg^{-1}$ ropivacaine TAP block and intravenous lidocaine infusion may not result in overt clinical manifestations of LAST, potential risks may still need to be considered.

**Table 1** Baseline characteristic and perioperative data of all patients

| | 1.5 mg $kg^{-1}$ group *n* = 10 | 2.0 mg $kg^{-1}$ group *n* = 8 | 2.5 mg $kg^{-1}$ group *n* = 8 | All *n* = 26 |
|---|---|---|---|---|
| Baseline characteristic | | | | |
| Age (y) | 58(52–64) | 58(47–64) | 50(47–58) | 57(48–61) |
| Sex (male, n [%]) | 5(50.0%) | 3(37.5%) | 5(62.5%) | 13(50.0%) |
| Height (cm) | 161(152–168) | 159(155–167) | 167(160–170) | 162(157–168) |
| Weight (kg) | 58(53–67) | 60(54–73) | 69(62–73) | 61(55–71) |
| BMI (kg $m^{-2}$) | 22.8(22.3–24.4) | 24.2(22.1–25.8) | 24.5(22.9–27.0) | 23.6(22.5–25.8) |
| Baseline BP (mmHg) | | | | |
| SBP | 123(119–142) | 121(112–138) | 122(114–140) | 122(118–140) |
| DBP | 76(67–88) | 73(66–81) | 76(66–83) | 75(67–84) |
| HR (beats/min) | 73(61–79) | 66(56–87) | 70(63–75) | 71(62–77) |
| ASA physical status | | | | |
| 2 (n, [%]) | 9(90.0%) | 7(87.5%) | 8(100.0%) | 24(92.3%) |
| 3 (n, [%]) | 1(10.0%) | 1(12.5%) | 0(0.0%) | 2(7.7%) |
| Preoperative chemotherapy (n, [%]) | 4(40.0%) | 1(12.5%) | 1(12.5%) | 6(23.1%) |
| Preoperative test | | | | |
| Hb (g $L^{-1}$) | 128(117–132) | 117(102–132) | 110(102–119) | 118(105–131) |
| ALT (IU $L^{-1}$) | 19(11–34) | 16(9–23) | 12(8–31) | 16(10–29) |
| AST (IU $L^{-1}$) | 23(14–34) | 20(15–21) | 17(15–29) | 19(14–31) |
| Alb (g $L^{-1}$) | 40(37–42) | 40(38–42) | 42(42–43) | 41(38–42) |
| Cre (mmol $L^{-1}$) | 70(57–75) | 62(56–69) | 84(62–90) | 68(58–84) |
| Intraoperative data | | | | |
| Ropivacaine dose (mg) | 83(67–93) | 102(95–126) | 157(131–164) | 100(85–136) |
| Lidocaine bolus dose (mg) | 111(89–124) | 102(95–126) | 126(105–131) | 111(98–128) |
| Lidocaine total dose (mg) | 446(367–483) | 487(426–623) | 477(378–551) | 456(403–528) |
| Remifentanil dose (mg) | 1.5(1.1–1.6) | 1.6(1.0-1.9) | 1.2(0.9–1.7) | 1.4(1.0-1.7) |
| Sufentanil dose (μg) | 27.5(20-32.5) | 27.5(25–30) | 27.5(23.1–34.4) | 27.5(24.4–32.5) |
| Anaesthesia duration (h) | 3.9(3.1–4.2) | 4.4(4.0-4.8) | 3.3(3.2–3.8) | 3.9(3.3–4.3) |
| Surgery duration (h) | 2.6(2.0–3.0) | 2.8(2.5–3.4) | 2.3(2.1–2.8) | 2.6(2.2-3.0) |
| Fluid infusion (ml) | 1450(1200–1625) | 1850(1450–2300) | 1300(1225–1888) | 1525(1300–1700) |
| Blood loss (ml) | 20(20–30) | 20(20–28) | 25(20–48) | 20(20–30) |
| Urine output (ml) | 200(138–325) | 375(263–675) | 175(113–300) | 275(150–400) |
| Postoperative 24 h | | | | |
| Morphine equivalent (mg) | 36.8 ± 12.0 | 37.8 ± 11.3 | 35.5 ± 11.5 | 36.7 ± 11.6 |
| NRS score at rest | 1.4 (0.8) | 1.5 (0.5) | 1.4 (0.4) | 1.4(0.6) |
| NRS score during movement | 3.6 (0.5) | 3.6 (0.8) | 3.2 (0.6) | 3.5(0.6) |

Data are presented as absolute number (%), median (interquartile range)

*M* Male, *F* Female, *BMI* Body mass index, *BP* Blood pressure, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *HR* Heart rate, *Hb* Haemoglobin, *AST* Aspartate aminotransferase, *ALT* Alanine transaminase, *Cre* Creatinine.

Colorectal cancer surgery is one of the most frequently performed surgical procedures worldwide, with approximately 1.2 million patients undergoing this surgery annually. Inadequate postoperative pain management not only impedes recovery but also increases the risk of chronic pain development, which significantly impacts the patient's long-term quality of life [26]. Ropivacaine is commonly used in TAP blocks for abdominal surgeries, due to its favorable pharmacological profile, including reduced motor blockade, lower cardiotoxicity, and extended analgesia duration [27]. Unlike previous reports of neurotoxic symptoms such as tongue paresthesia, metallic taste, and slurred speech in patients receiving 2.5 mg $kg^{-1}$ ropivacaine TAP blocks during cesarean section [13], our study did not observe any signs of LAST. The discrepancy may be partly due to the ideal body weight other than actual body weight for dose calculations in our study, which helps mitigate the risk of overdose [10, 13]. Additionally, we observed a dose-dependent increase in ropivacaine plasma concentration, with the 2.5 mg $kg^{-1}$ group exhibiting higher median levels compared to the two lower dose groups. A consistent time-concentration relationship was also noted, with peak plasma concentrations occurring between 20 and 60 min post-TAP block, regardless of the total dose. This is consistent with the findings of Toju et al., who

**Table 2** Signs of LAST from the administration of local anaesthetics to postoperative 24 h

| Symptoms of LAST | Intraoperative *n* = 26 | Postoperative *n* = 26 |
|---|---|---|
| Abnormalities of EEG | 0 | - |
| New-onset ECG irregularities | 0 | 0 |
| Dizziness | - | 0 |
| Light-headedness | - | 0 |
| Metallic taste | - | 0 |
| Peri-oral numbness | - | 0 |
| Tinnitus | - | 0 |
| Seizure activity | - | 0 |
| Loss of consciousness | - | 0 |
| Death | 0 | 0 |

*LAST* Local anaesthetic systemic toxicity, *EEG* Electroencephalography, *ECG* Electrocardiography

reported similar timing of peak concentrations following a 3 mg $kg^{-1}$ ropivacaine TAP block [28]. Given the stable pharmacokinetic profile of ropivacaine TAP blocks across dosages ranging from 1.5 to 3.0 mg $kg^{-1}$, it appears that the peak plasma concentration period may require enhanced monitoring and management, particularly at higher doses, to minimize the potential for toxic effects.

In this study, although some patients exhibited plasma lidocaine concentrations exceeding the commonly cited neurologic toxicity threshold of 5.0 μg $mL^{-1}$ [29], no LAST events were reported. This observation is consistent with findings by Suena et al., who reported no correlation between plasma lidocaine levels above 5.0 μg $mL^{-1}$ and LAST occurrence [30]. The variability in lidocaine toxicity thresholds, ranging from 5.0 to 15 μg $mL^{-1}$ [31], indicates a broader spectrum of safe plasma levels [14, 29, 32], possibly influenced by patient-specific factors such as

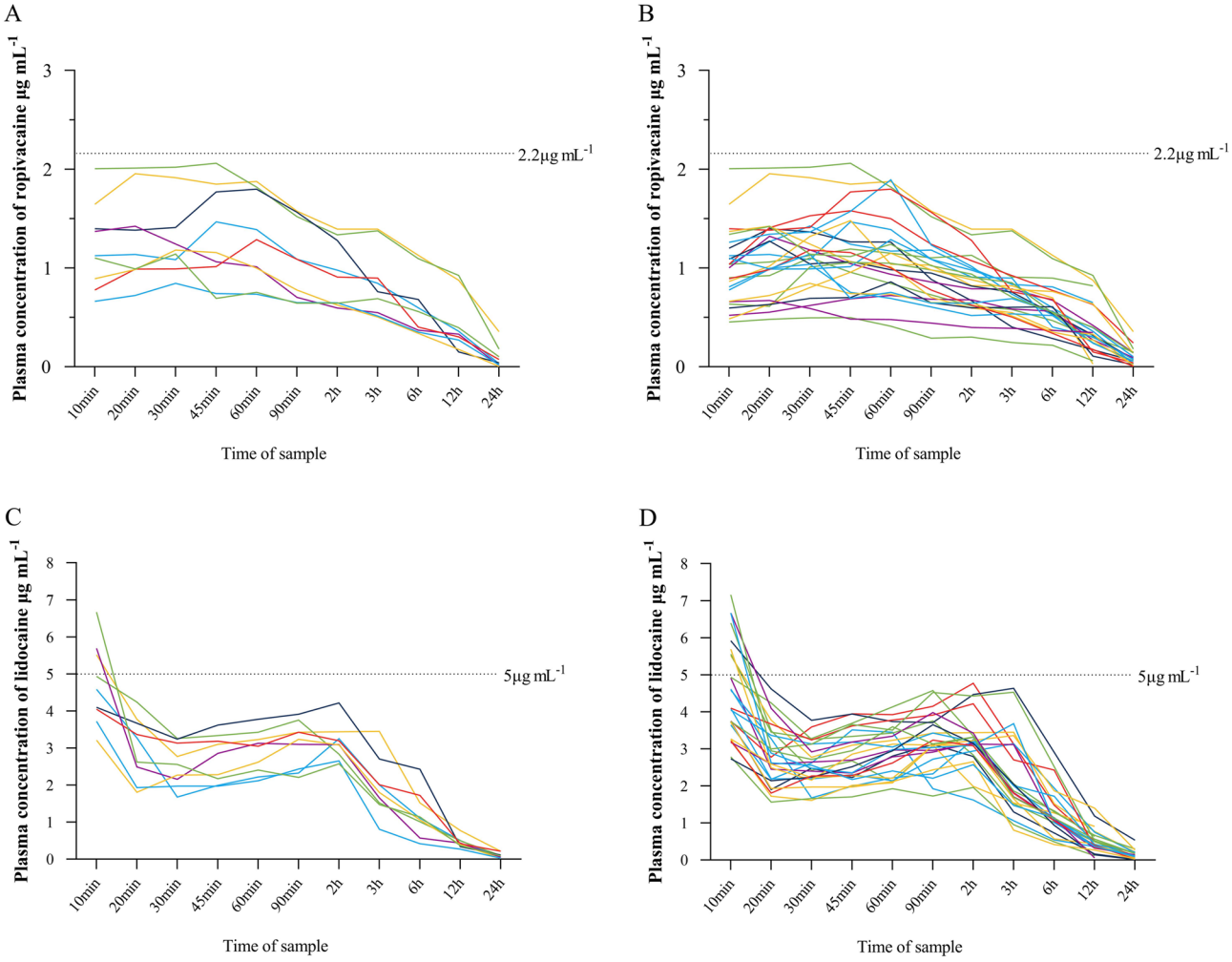


**Fig. 3** Plasma concentrations of ropivacaine and lidocaine at each time point in the PP analysis and ITT analysis. **A**, plasma concentrations of ropivacaine at each time point in the PP analysis (*n* = 9); **B**, plasma concentrations of ropivacaine at each time point in the ITT analysis (*n* = 26); **C**, plasma concentrations of lidocaine at each time point in the PP analysis (*n* = 9); **D**, plasma concentrations of lidocaine at each time point in the ITT analysis (*n* = 26). PP, per-protocol; ITT, intention-to-treat

gender, comorbidities, and physiological characteristics [33, 34]. Notably, the toxicity thresholds established for single-drug use may not be appropriate when these drugs are combined. Although ropivacaine is primarily bound to albumin and lidocaine binds to α−1 acid glycoprotein (AGP), the two drugs may exhibit overlapping binding at the F1*S site of AGP [35]. This overlap could potentially elevate the free fraction of both drugs, thereby increasing the risk of LAST. Furthermore, the concurrent use of general anesthetics might alter the threshold for LAST threshold [36], adding further complexity to this clinical scenario.

Nonetheless, our study represents a pioneering effort in evaluating the risk of concurrent administration of escalating doses of ropivacaine for TAP block and intravenous lidocaine infusion in patients undergoing colorectal surgery. This investigation highlights that careful attention to the potential risk of LAST is still warranted when using the two local anesthetics in combination. A key strength of our study was the implementation of EEG monitoring during general anaesthesia, which may help to detect potential neurotoxicity of local anaesthetics. Previous research has demonstrated that the plasma concentration threshold for lidocaine's neurotoxicity (15 μg $mL^{-1}$) is lower than that for cardiovascular toxicity (21 μg $mL^{-1}$) [31, 37]. Therefore, relying solely on ECG monitoring during general anaesthesia may underestimate its toxicity. Combining the EEG and ECG may offer a more comprehensive approach to detecting LAST under general anaesthesia. Moreover, the precise in local anaesthetic administration achieved through ultrasound guidance by experienced anaesthesiologists further minimized the risk of inadvertent leakage into the surrounding musculature, which can affect drug absorption and increase the risk of toxicity [38]. Rosenberg et al. have recommended tailoring local anaesthetic dosage based on technique specificity rather than a maximum safe dose [39].

Our study also acknowledged several limitations. Firstly, the small sample size, while a limitation, was a necessary consequence of adhering to the 3 + 3 dose-escalation trial design. Given the undefined toxicity risks associated with the combined use of the two local anesthetics, a minimal-risk exposure strategy was adopted to prioritize patient safety. As a result, the sample size was limited, preventing the ability to draw definitive conclusions about safety. Secondly, we cannot assess the analgesic efficacy due to the small sample size. While the dose levels for ropivacaine and lidocaine were selected based on existing studies reporting their effectiveness for postoperative pain relief in various surgical settings, either alone or in combination [8, 12, 13], it remains uncertain whether higher doses of ropivacaine would offer superior analgesia. Thirdly, we did not measure the unbound (free) concentration of ropivacaine or lidocaine. The toxicity of local anesthetics, however, is primarily determined by the free fraction of the drug, which represents the pharmacologically active component, rather than the total plasma concentration, this limits our ability to assess toxicity accurately. Finally, the toxicity levels referenced for intravenous lidocaine and ropivacaine TAP block were based on the established safety thresholds for each drug when used individually; however, these thresholds may not be suitable when the drugs are combined. The lack of a universally accepted toxicity threshold for their combined use presents a significant challenge in evaluating their safety. Future studies are needed to define safe thresholds and establish more precise guidelines for their combined use.

## Conclusions

Although no signs of LAST were observed with the combination of a 1.5 to 2.5 mg $kg^{-1}$ ropivacaine TAP block and a fixed-rate intravenous lidocaine infusion, caution is strongly advised regarding the risk of LAST when using this combination. Safe thresholds for the combined use of these local anesthetics have not yet been established, underscoring the need for further studies to define these limits more accurately.

### Abbreviations

| | |
|---|---|
| TAP | Transversus abdominis plane |
| LAST | Local anesthetic systemic toxicity |
| MTD | Maximum tolerated dose |
| ASA | American society of anaesthesiologists |
| ECG | Electrocardiography |
| EEG | Electroencephalography |
| PSI | Patient state index |
| PACU | Post-anaesthesia care unit |
| IBW | Ideal body weight |
| SD | Standard deviation |
| IQR | Interquartile range |
| PP | Per-protocol |
| ITT | Intention-to-treat |
| CONSORT | Consolidated standards of reporting trials |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03225-5.

Additional file 1: Supplementary Figure S1: Image of the transversus abdominis plane block. EO, external oblique; IO, internal oblique; TA, transversus abdominis; Grey curve: local anesthetic distribution. Supplementary Figure S2: Patients enrolment timeline. Supplementary Figure S3: A representative image of electroencephalography during general anaesthesia. Supplementary Figure S4: Median plasma concentration of ropivacaine at each time point in the PP analysis (A) and ITT analysis (B). PP, per-protocol; ITT, intention-to-treat. Supplementary Figure S5: Median plasma concentration of ropivacaine within each group in the PP analysis (A) and ITT analysis (B). PP, per-protocol; ITT, intention-to-treat. Supplementary Figure S6: Median plasma concentration of lidocaine at each time point in the PP analysis (A) and ITT analysis (B). PP, per-protocol; ITT, intention-to-treat. Supplementary Figure S7: Median plasma concentration of lidocaine in the PP analysis and ITT analysis. PP, per-protocol; ITT, intention-to-treat.

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**Authors' contributions**
Li Zhou, Lulong Bo and Chunling Jiang: these authors helped to design the study and revise the manuscript; Mengmeng Zhou, Yan Xu: these authors helped to analyse and intepretate data; Xiaoting Hao: this author helped to analyse electroencephalogram. Feng Yu, Jingwen Wu, Lajing Luowu, Qianqian Tang, Kun Shao, Mao Ye: these authors helped to collect date; All authors helped to draft the manuscript. All authors read and approved the final manuscript.

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**Data availability**
The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of West China Hospital, Sichuan University (approval number HX20201180-1). All patients provided informed consent and was enrolled after registration.

**Consent for publication**
All participants provided written informed consent for publication of anonymized data.

**Competing interests**
The authors declare no competing interests.

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