

# Lung-Protective Effects of Lidocaine Infusion on Patients with Intermediate/ High Risk of Postoperative Pulmonary Complications: A Double-Blind Randomized Controlled Trial

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**Purpose:** The non-local anesthetic effects of lidocaine have been widely reported, but there are still few studies on lung protection. We aimed to test the hypothesis that intravenous infusion of lidocaine exerts lung-protective effects in patients at intermediate/high risk of postoperative pulmonary complications (PPCs) on major abdominal surgery.

**Patients and Methods:** Patients  $\geq 18$  years, ASA II or III, with intermediate/high risk for PPCs, were included. Patients were randomly assigned into group lidocaine (received a bolus of lidocaine 1.5 mg kg<sup>-1</sup> before the induction of anesthesia, then followed by a continuous infusion of 2.0 mg kg<sup>-1</sup> h<sup>-1</sup> intraoperatively until the end of surgery) or group control (received 0.9% saline in place of lidocaine at the same time points). The incidence of PPCs within 7 postoperative days was measured, defined as a collapsed composite outcome of atelectasis, respiratory infection, pleural effusion, pneumonia, respiratory failure or acute respiratory distress syndrome (ARDS) developed within 7 postoperative days, or hospital discharge, whichever came sooner.

**Results:** Of 200 subjects screened, 195 patients were finally analyzed. Overall, 35.9% (70/195) patients sustained PPCs, which occurred fewer in group lidocaine 25.8% (25/97), compared with group control 45.9% (45/98) (relative risk: 0.56, 95% CI: 0.38 to 0.84; absolute risk reduction: -20.1%;  $P = 0.003$ ). Considering single PPCs episode, the most common PPC in both groups was atelectasis. The atelectasis incidence was 11.3% (11/97) in group lidocaine, much lower than that in group control 29.6% (29/98) (relative risk: 0.38, 95% CI: 0.20 to 0.72; absolute risk reduction: -18.3%,  $P = 0.002$ ). However, the incidences of any other PPCs episodes were similar between the two groups.

**Conclusion:** Intraoperative intravenous infusion lidocaine could decrease the incidence of PPCs in patients at intermediate/high risk of postoperative pulmonary complications undergoing major abdominal surgery.

**Keywords:** postoperative pulmonary complications, lidocaine, lung injury, pulmonary protection

## Introduction

Postoperative pulmonary complications (PPCs) are one of the main causes of morbidity and mortality in patients undergoing surgery requiring anesthesia,<sup>1</sup> especially within the first postoperative week.<sup>2</sup> The incidence of PPCs in major surgery ranges from 11%-59%, which differ depending on the PPCs definitions and types of surgery.<sup>3</sup> The reasons for PPCs are complex and the underlying mechanisms are unclear, which may include the prior health status of the patient and the effects of anesthesia and surgical trauma.<sup>4</sup> The patient's overall health has a strong influence on the development of complications. Surgery and anesthesia can induce inflammatory responses. A previous study found that

inflammation plays a key role in the development of PPCs.<sup>5</sup> In addition, respiratory depression caused by opioids, and postoperative pain-induced voluntary limitation of respiratory motion can also increase the risk of PPCs.<sup>6,7</sup>

Lidocaine, an amide-based local anesthetic and membrane stabilizer, is widely used in local nerve block and anti-arrhythmia. Recently, numerous studies have found that lidocaine also has anti-inflammatory effects.<sup>8–10</sup> Intravenous administration lidocaine could attenuate lung injury induced by endotoxin, hyperoxia, and ischemia/reperfusion injury by inhibiting inflammatory cascade reaction.<sup>11–13</sup> Several clinical studies showed that perioperative administration of lidocaine was significantly associated with attenuation of the surgery-induced release of pro-inflammatory cytokines, and decreased C-reactive protein levels.<sup>10,14</sup> Besides, intravenous infusion of lidocaine can also exert analgesia and relieve postoperative pain, which can further reduce opioid consumption.<sup>15</sup>

Therefore, considering these non-local anesthetic effects of lidocaine are associated with PPCs risk factors, we hypothesized that intravenous infusion of lidocaine may alleviate lung injury, protect pulmonary function, reduce the incidence of PPCs and improve the prognosis in surgical patients.

## Patients and Methods

Ethical approval for this study was provided by the Ethical Committee of the Affiliated Hospital of Xuzhou Medical University, Jiangsu, China (Chairperson Prof Tie Xu) on 1 January 2019 with protocol number XYFY2019-KL105-01. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR1900021677). This report adheres to the CONSORT guidelines. The study was conducted according to the guidelines of the Declaration of Helsinki with Good Clinical Practice. All participants provided written informed consent before enrolment.

## Participants

Patients aged  $\geq 18$  years, ASA classification II to III, with an intermediate-to-high risk for PPCs (defined by Assess Respiratory Risk in Surgical Patients in Catalonia score (ARISCAT) $\geq 26$ ; Low Risk $<26$ , Intermediate Risk 26–44, High Risk $\geq 45$ ),<sup>16</sup> and undergoing selective abdominal surgery under general anesthesia were eligible for inclusion. Exclusion criteria were: body mass index (BMI) $>30$  kg m<sup>-2</sup>, emergency surgery, preoperative ventilator use, Adams syndrome, severe heart block (II or III atrioventricular block, double-bundle branch block), severe sinoatrial node dysfunction, congestive heart failure, liver parenchyma damage (ALT or AST $>2\times$  normal value), Child-Pugh grade C cirrhosis, renal failure (SCr $>177$   $\mu\text{mol l}^{-1}$ ), respiratory failure, epilepsy history, lidocaine allergy, steroid anti-inflammatory drug use 24 h before surgery, pregnancy, and refusal to provide written informed consent or to participate in testing. Rejection criteria included operation cancellation, voluntary patient dropout, short surgery duration ( $<2$  hours), and/or serious perioperative adverse events.

## Randomization and Masking

Patients were allocated randomly to group lidocaine or group control in a 1:1 ratio. Randomization was done with a web-based computer-generated block randomization procedure after stratified according to the type of surgery (laparoscopy or open) and surgery site (upper or lower abdomen). The allocation sequence was generated by one of the independent investigators, who provided the randomization assignments to the operating room pharmacy that assigned patients to the study groups and prepared all of the study medications. Intervention staff, patients, outcome assessors, and investigators involved in trial and data management were masked to group assignment.

## Intervention

Patients in group lidocaine received a bolus of lidocaine 1.5 mg kg<sup>-1</sup> (10 mg mL<sup>-1</sup> in a 20-mL syringe) before the induction of anesthesia, then followed by a continuous infusion of 2.0 mg kg<sup>-1</sup> h<sup>-1</sup> (10 mg mL<sup>-1</sup> in a 50-mL syringe) intraoperatively until the end of surgery. Patients in group control received 0.9% saline in place of lidocaine at the same time points.

## Perioperative Management

Patients were given 2 mg of midazolam (i.v.) after entering the operating room. Standard intraoperative monitoring was applied, which included electrocardiography, capnography, pulse oximetry, and bispectral index (BIS) monitoring. In addition, a radial artery cannula was placed for monitoring arterial pressure and blood gas. Anesthesia was induced with

lidocaine ( $1.5 \text{ mg kg}^{-1}$ ) (or the same volume of 0.9% saline), propofol  $1\text{--}2 \text{ mg kg}^{-1}$ , sufentanil  $0.5 \text{ }\mu\text{g kg}^{-1}$ , and cisatracurium  $0.2 \text{ mg kg}^{-1}$ . The lidocaine or 0.9% saline infusion was initiated after induction and dosed as described above. Anesthesia was maintained by remifentanyl ( $0.1\text{--}0.3 \text{ }\mu\text{g kg}^{-1} \text{ min}^{-1}$ ) and propofol, combined with sevoflurane 1%. Maintain the BIS values between 40 and 60 by adjusting the dose of propofol. All patients accepted ultrasound-guided bilateral transverse abdominis plane block (0.25% ropivacaine 40 mL) after anesthesia induction. Mean arterial pressure was maintained within  $\pm 20\%$  of the baseline. Hypotension was treated with phenylephrine  $40 \text{ }\mu\text{g}$ , ephedrine  $5 \text{ mg}$ , or a fluid bolus; episodes of hypertension were managed by increasing the propofol or remifentanyl infusion rate. Lung protective ventilation was used during surgery (the combination of tidal volume  $8 \text{ mL kg}^{-1}$  predicted body weight or lower and PEEP  $5 \text{ cm H}_2\text{O}$  or higher, with a recruitment manoeuvre, fraction of inspired oxygen 60%). Cisatracurium was injected intermittently according to requirements. Patients in both groups received i.v. acetaminophen  $1 \text{ g}$  at the beginning of the stitching. At the end of the surgical procedure, neuromuscular block was reversed and extubation was attempted in the operating theatre. Patients who did not meet extubation criteria were transferred to the post-anesthesia care unit (PACU).

Postoperative patient-controlled intravenous analgesia (PCA) was performed with drug formulations (sufentanil  $2 \text{ }\mu\text{g kg}^{-1}$ , tropisetron  $10 \text{ mg}$ , 0.9% saline diluted to  $100 \text{ mL}$ ) using a set lock time of  $15 \text{ min}$ , a background infusion dose to  $2 \text{ mL h}^{-1}$ , and the PCA was set at  $0.5 \text{ mL times}^{-1}$ . Patients were assessed for pain at PACU by nurses and every 15 min thereafter (0 to 10 cm, Visual Analogue Scale (VAS) score, 0 indicates “no pain” and 10 indicates “most severe pain”; 1–3, mild pain; 4–6, moderate pain; 7–10, severe pain). Moderate pain was treated with hydromorphone  $0.25 \text{ mg}$ , and severe pain with hydromorphone  $0.5 \text{ mg}$ , to reduce pain scores to less than or equal to 3. Discharge to the surgical wards when Aldrete scores of greater than or equal to 8 out of 10 were achieved. Pain was managed on the first 2 postoperative days using the PCA device, which was discontinued at the discretion of the managing surgical service. Patients were transitioned to tramadol  $50 \text{ mg}$  tablets when able to resume oral intake. Pain was assessed and treated by surgical ward nurses per standard protocols, to maintain pain scores less than or equal to 3.

## Endpoints

We initially used the CC-16 protein as the main outcome of this study, but considered that the relationship between CC-16 protein concentration and lung damage remains controversial.<sup>5,17</sup> As a composite clinical indicator, PPCs can directly and comprehensively reflect the postoperative lung function of patients, which may better reflect the lung protection effect of intraoperative intravenous infusion lidocaine. Therefore, we changed CC-16 to a secondary outcome, and changed the primary outcome to the incidence of PPCs, defined as a collapsed composite outcome of atelectasis, respiratory infection, pleural effusion, pneumonia, respiratory failure or acute respiratory distress syndrome (ARDS) developed within 7 postoperative days (PODs), or hospital discharge, whichever came sooner. This was approved by the Ethics Committee and written informed consent was obtained from all patients. Assessors masked to group allocation assessed participants prospectively and daily until the seventh postoperative day. Participants were screened using standardized validated diagnostic criteria (Box 1).<sup>18,19</sup> A PPC was diagnosed when one or more of these criteria were present at any time. Patients discharged before the end of follow-up without any PPCs were considered as without PPCs at 7 PODs.

The secondary outcomes included: (1) plasma concentration of CC-16, IL-6, and IL-10; (2) parameters reflecting pulmonary function and mechanics: oxygenation index ( $\text{OI}=\text{PaO}_2/\text{FiO}_2$ , respiratory index ( $\text{RI}=\text{A-aDO}_2/\text{PaO}_2$ ), dynamic lung compliance ( $\text{C}_{\text{dyn}}=\text{Vt}/(\text{P}_{\text{max}}-\text{PEEP})$ ) and driving pressure ( $\Delta\text{P}$ ); (3) hemodynamics (heart rate and mean arterial pressure); (4) postoperative total opioid consumption (in mg morphine equivalents (MEQ)); (5) postoperative pain level (0 to 10 cm, Visual Analogue Scale (VAS) score, 0 indicates “no pain” and 10 indicates “most severe pain”); (6) gastrointestinal recovery; (7) The quality of recovery-40 score (QoR-40 score) at 24 h postoperatively; (8) length of hospital stay (defined as the time from the end of the surgery to discharge); (9) adverse events (death, arrhythmia, light-headedness, perioral numbness, and dizziness).

## Data Collection

The day before the operation, the patient’s baseline characteristics were recorded. On the operation day, the patient’s heart rate and mean arterial blood pressures (MAP) were recorded at four timepoints: pre-induction ( $T_0$ ), 1 hour after

**Box I** Postoperative Pulmonary Complications Diagnostic Criteria

<b>Atelectasis</b>	CXR with lung opacification with mediastinal shift, hilum or hemidiaphragm shift towards the affected area, with compensatory hyperinflation in adjacent non-atelectatic lung
<b>Respiratory infection</b>	Antibiotics for suspected infection with one or more of the following: new or changed sputum, new or changed lung opacities, fever, white blood cell count $>12 \times 10^9 \text{ L}^{-1}$
<b>Pleural effusion</b>	CXR with blunting of costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in an upright position, displacement of adjacent anatomical structures, or (in supine position) hazy opacity in one hemithorax with preserved vascular shadows
<b>Pneumonia</b>	CXR with at least one of the following: infiltrate, consolidation, cavitation; plus at least one of the following: fever $>38^\circ\text{C}$ with no other cause, white cell count $<4$ or $>12 \times 10^9 \text{ L}^{-1}$ , $>70$ years of age with altered mental status with no other cause; plus at least two of the following: new purulent/ changed sputum, increased secretions/ suctioning, new/worse cough/dyspnoea/tachypnoea, rales/bronchial breath sounds, worsening gas exchange
<b>Respiratory failure</b>	Postoperative $\text{PaO}_2 < 8 \text{ kPa}$ (60 mm Hg) on room air, a $\text{PaO}_2: \text{FIO}_2$ ratio $<40 \text{ kPa}$ (300 mm Hg), or arterial oxyhaemoglobin saturation measured with pulse oximetry $<90\%$ and requiring oxygen therapy
<b>ARDS</b>	Rapid onset of hypoxia with a $\text{PaO}_2/ \text{FIO}_2$ ratio $\leq 300$ and bilateral pulmonary infiltrates in the absence of left atrial hypertension

**Note:** Data from these studies.<sup>18,19</sup>

**Abbreviations:** CXR, chest x-ray; ARDS, acute respiratory distress syndrome.

ventilation ( $T_1$ ), 2 hours after ventilation ( $T_2$ ), and at the end of surgery ( $T_3$ ). Radial arterial blood samples were also collected at the four-time points and were analyzed using Roche Cobas B123 POC blood gas analyzer (Roche Group, Basel, Switzerland). Venous blood samples were collected from the peripheral venous line at  $T_0$ - $T_3$  time points and 24 hours after surgery ( $T_4$ ). These samples were centrifuged at 3000 rpm for 10 min at  $4^\circ\text{C}$ , and the supernatant was stored at  $-80^\circ\text{C}$  for further test. The concentrations of IL-6, IL-10, and CC-16 in plasma were measured using sandwich enzyme-linked immunosorbent assay (ELISA) with commercially available kits (Wuhan Cloud-Clone Co., Ltd, Wuhan, China) according to the manufacturer's instruction. Respiratory parameters ( $T_1$ - $T_3$ ), intraoperative medication, i.v. fluid, transfusion, urine output, and surgery time were also recorded. PACU nurses documented the level of pain (using VAS score), the total doses of analgesic drugs. The QoR-40 score at 24 hours postoperatively was assessed by follow-up staff. The staff also recorded postoperative pain level, opioid consumption, gastrointestinal recovery (include first defecation or bowel movements, time to first flatus, ileus (postoperative ileus were identified by the presence of two or more clinical indicators of gastrointestinal dysfunction, at least one for each of the two following criteria: (1) presence of vomiting or abdominal distension and (2) absence of flatus/stool or not tolerating oral diet.)), length of hospital stay. Possible lidocaine-related adverse events were noted. PPCs in the postoperative period were collected until day 7 or hospital discharge, whichever came first.

## Sample Size

We originally planned to use CC-16 as the primary outcome measure. According to previous studies, postoperative plasma levels of CC-16 in patients undergoing abdominal surgery was  $17.8 \text{ ng mL}^{-1}$ , the standard deviation was 9.4.<sup>5,20</sup> Assuming that intravenous infusion of lidocaine can reduce CC-16 by 30%, 53 patients in each group can provide 80% power with a significance level of 0.05. We planned to recruit 62 patients in each group to compensate for 15% dropouts. Since we changed the primary outcome measure, we recalculated the sample size based on the new primary outcome measure. A new sample size calculation was based on a previous study that the incidence of PPCs for patients with intermediate to high risk of PPCs is about 48%.<sup>21</sup> Therefore, assuming an expected clinical intergroup difference of 20% as the significance threshold and anticipating a 10% dropout rate, the estimated sample size of 200 patients provided 80% power with a significance level of 5% to detect a 20% reduction in PPCs incidence between groups. PASS 11.0 (NCSS, LLC, Kaysville, USA) was used for sample size calculation. All of the final statistical analysis was based on the new sample size.

## Statistical Analysis

The measurement data used the Shapiro–Wilk test to determine the normality of the data distribution, and the Levene method was used to test the homogeneity of variance. Normally distributed continuous variables were presented as the

mean  $\pm$  standard deviation (mean  $\pm$  SD) and were compared using Student's *t*-test. Nonnormally distributed continuous data were reported as median (interquartile range, IQR) and compared using the Mann–Whitney *U*-test. Median differences and their 95% CIs were estimated using the Hodges–Lehmann estimator. Categorical data were reported as frequency (%) and were analyzed using the chi-squared test or Fisher's exact test. We used Kaplan–Meier curves and hazard ratios (HRs) for time to first diagnosis of PPC. Serial parameters reflecting lung function, hemodynamic data, VAS score were analyzed using two-way repeated-measures ANOVA. The group-by-time interaction term was tested first. If significant, between-group differences at each time point were tested at  $\alpha=0.05$ . If not significant, the treatment main effect was tested next. Otherwise, Bonferroni correction was applied at each time point. The criterion for rejection of the null hypothesis was a two-tailed  $P<0.05$ . All statistical analyses were performed using SPSS software (version 24.0; SPSS Inc., IBM, Chicago, IL, USA).

## Results

### Subject Characteristics

Figure 1 shows the flowchart of this study. In total, 200 subjects were enrolled and 100 were randomized to each study group from April 2019 to January 2020. Three subjects in group lidocaine and two subjects in group control were excluded because of the operation time  $<2$  hours and voluntary withdrawal. As a result, 97 subjects in group lidocaine and 98 subjects in group control were analyzed. There were no study protocol violations. Complete data were available for the primary and secondary endpoints. The groups were comparable concerning age, gender, height, weight, BMI, ASA physical status, current smoking, ARISCAT score, the form of surgery, site of surgery, i.v. fluid, transfusion, urine output, surgery time, anesthesia time, and nasogastric tubes (Table 1).

### Primary Outcome: Postoperative Pulmonary Complications

As presented in Table 2, there were 35.9% (70/195) patients who sustained PPCs. Twenty-five subjects in the group lidocaine (25/97; 25.8%) and forty-five subjects in the group control (45/98; 45.9%) were evaluated as developing PPCs within the first

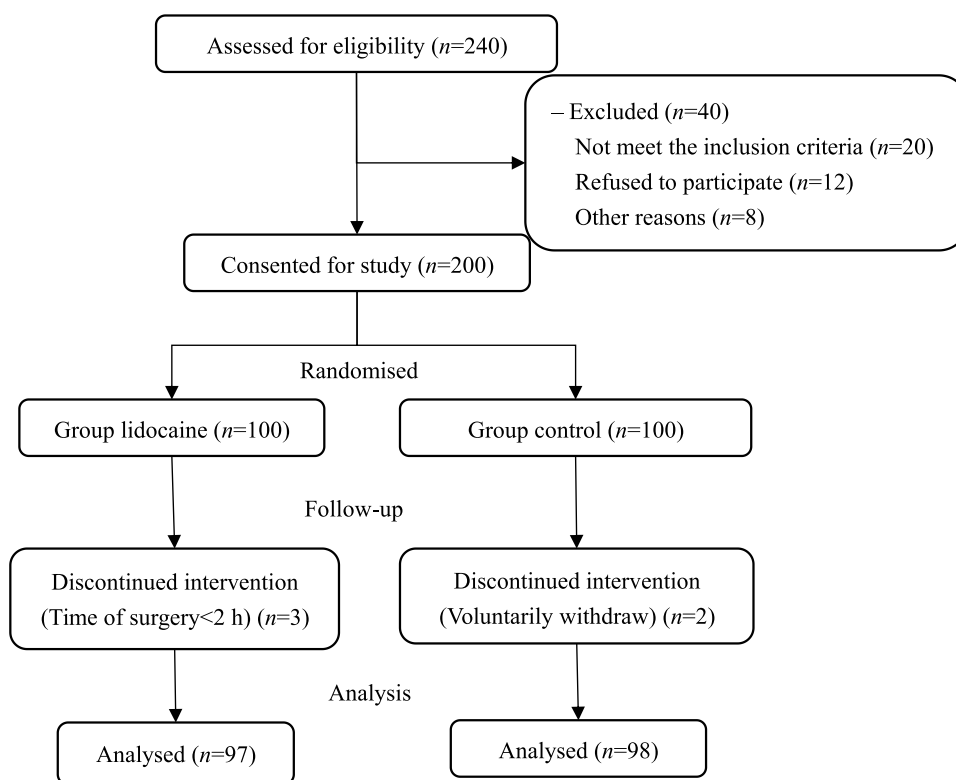


Figure 1 CONSORT flowchart diagram.

**Table I** Patients' Characteristics, Type of Surgery and Intraoperative Variables

Variables	Control (n=98)	Lidocaine (n=97)	P
<b>Age (years)</b>	66±7	64±8	0.086
<b>Gender (Male/Female)</b>	48/50	47/50	0.941
<b>Height (m)</b>	1.65±0.07	1.66±0.08	0.969
<b>Weight (kg)</b>	64.0±9.7	62.4±9.5	0.365
<b>BMI (kg m<sup>-2</sup>)</b>	23.5±3.2	22.8±2.8	0.245
<b>Current smoking</b>	15(15.3)	13(13.4)	0.705
<b>ASA</b>			0.304
II	75(76.5)	80(82.5)	
III	23(23.5)	17(17.5)	
<b>ARISCAT score</b>			0.521
Intermediate	60(61.2)	55(56.7)	
High	38(38.8)	42(43.3)	
<b>Form of surgery</b>			0.718
Laparoscopy	52(53.1)	52(53.6)	
Open	46(46.9)	45(46.4)	
<b>Site of surgery</b>			0.953
Upper abdomen	59(60.2)	58(59.8)	
Lower abdomen	39(39.8)	39(40.2)	
<b>I.V. fluid (mL)</b>	1074±190	1118±177	0.096
<b>Transfusion requirements</b>			
Blood red cells	3(3.1)	4(4.1)	0.721
Fresh frozen plasma	2(2.0)	3(3.1)	0.683
Platelets	0(0)	0(0)	
<b>Urine output (mL)</b>	786±160	802±143	0.471
<b>Propofol (mg)</b>	431±77	296±48	<0.001
<b>Remifentanil (mg)</b>	1.4±0.3	1.0±0.2	<0.001
<b>Surgery time (min)</b>	186±38	178±34	0.131
<b>Anesthesia time (min)</b>	221±38	212±34	0.076
<b>Nasogastric tubes</b>	48(49.0)	52(53.6)	0.518

**Note:** Data are mean±SD or n (%).

**Abbreviations:** ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; BMI, body mass index; ASA, American Society of Anesthesiologists; I.V., intravenous.

7 postoperative days or until hospital discharge (relative risk:0.56, 95% CI: 0.38 to 0.84; absolute risk reduction: -20.1%,  $P=0.003$ ). Considering single PPCs episode, the most common PPC in both groups was atelectasis. The atelectasis incidence was 11.3% (11/97) in group lidocaine, much lower than that in group control 29.6% (29/98) (relative risk: 0.38, 95% CI: 0.20 to 0.72; absolute risk reduction: -18.3%,  $P=0.002$ ). However, the incidences of any other PPCs episodes were similar between the two groups. Kaplan-Meier cumulative survival rates were 71.2% in group lidocaine versus 51.0% in group control at 7 postoperative days (Hazard ratio: 0.40, 95% CI: 0.30 to 0.77,  $P=0.002$ , [Figure 2](#)).

## Secondary Endpoints

### Plasma Concentration of CC-16, IL-6, and IL-10 at T<sub>0</sub>-T<sub>4</sub>

Surgery and anesthesia can result in inflammatory responses. As shown in [Figure 3](#), after anesthesia induction, the concentrations of IL-6, IL-10, and CC-16 were increased in both groups and reached peak levels at the end of surgery. However, lidocaine administration effectively inhibited the increase of IL-6 concentrations (T<sub>2</sub>, 31.8 (27.0 to 34.4) vs 34.9 (30.3 to 39.5) pg mL<sup>-1</sup>; T<sub>3</sub>, 95.4 (58.2 to 242.1) vs 122.4 (68.8 to 265.3) pg mL<sup>-1</sup> respectively, [Figure 3A](#)). In addition, the concentration of IL-6 decreased more rapidly in group lidocaine compared with group control (T<sub>4</sub>, 78.4 (48.1 to 218.2) vs 118.3 (65.0 to 253.6) pg mL<sup>-1</sup>, [Figure 3A](#)). The concentration of IL-10 in each group shows no

**Table 2** Primary and Secondary Outcomes

	Lidocaine (n=97)	Control (n=98)	P-value
<b>PPCs (%)</b>	25 (25.8)	45 (45.9)	0.003
Atelectasis	11 (11.3)	29 (29.6)	0.002
Respiratory infection	9 (9.3)	16 (16.3)	0.141
Pleural effusion	6 (6.2)	9 (9.2)	0.432
Pneumonia	6 (6.2)	10 (10.2)	0.307
Respiratory failure	2 (2.1)	4 (4.1)	0.683
ARDS	0 (0)	2 (2.0)	0.497
<b>Postoperative opioids consumption (MEQ) (mg)</b>	102.7 ±21.3	141.4 ±22.9	<0.001
<b>Postoperative pain</b>			
In the PACU	2.6 ±1.0	2.9 ±1.0	0.109
4 hours after surgery	2.9 ±1.0	4.0 ±1.4	<0.001
8 hours after surgery	4.1 ±0.9	4.3 ±1.2	0.396
12 hours after surgery	4.6 ±0.8	4.5 ±0.6	0.103
24 hours after surgery	3.2 ±0.9	3.2 ±1.1	0.560
<b>Gastrointestinal recovery</b>			
First defecation or bowel movements (hours)	41.8 ±8.0	48.1 ±8.8	<0.001
Time to first flatus (hours)	26.1 ±7.7	31.4 ±7.1	<0.001
Postoperative ileus (%)	5 (5.2)	14 (14.3)	0.032
<b>Time to nasogastric tube removal (hours)</b>	54.2±8.6	62.6±10.4	<0.001
<b>QoR-40 Score</b>			
Emotional status	38 [32 to 41]	38 [32 to 40]	0.953
Physical comfort	53 [50 to 56]	50 [44 to 53]	0.026
Psychological support	28 [25 to 32]	27 [24 to 30]	0.121
Physical independence	18 [16 to 21]	15 [13 to 20]	0.001
Pain	30 [28 to 31]	28 [28 to 30]	0.002
Total	165 [152 to 177]	158 [144 to 169]	0.026
<b>Length of hospital stay (days)</b>	5 [5 to 6]	6 [5 to 7]	<0.001

**Note:** Data are mean ± SD, median [IQR] or n (%).

**Abbreviations:** PPC, postoperative pulmonary complication; ARDS, acute respiratory distress syndrome; MEQ, morphine equivalents; PACU, post-anesthesia care unit; QoR-40, quality of recovery-40 scores.

obvious differences at any time points (Figure 3B). Group lidocaine had a lower CC-16 concentration than group control at T<sub>4</sub> (15.2 (11.3 to 20.4) vs 19.5 (13.7 to 23.9) ng mL<sup>-1</sup>, Figure 3C).

### Postoperative Total Opioid Consumption (MEQ)

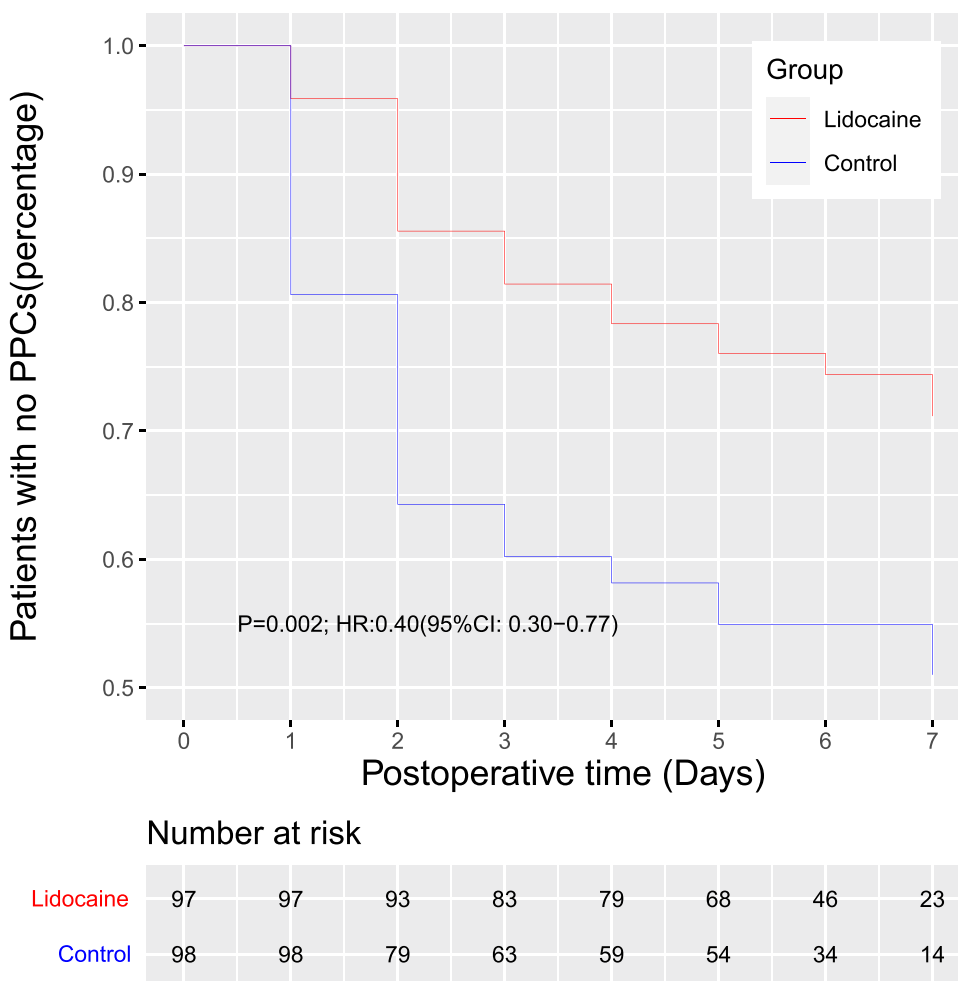
The total postoperative opioid consumption in group lidocaine was less than that in group control (102.7±21.3 vs 141.4 ±22.9 mg, difference: -38.7, 95% CI: -44.9 to -32.4; *P*<0.001) (Table 2).

### Postoperative Pain Level

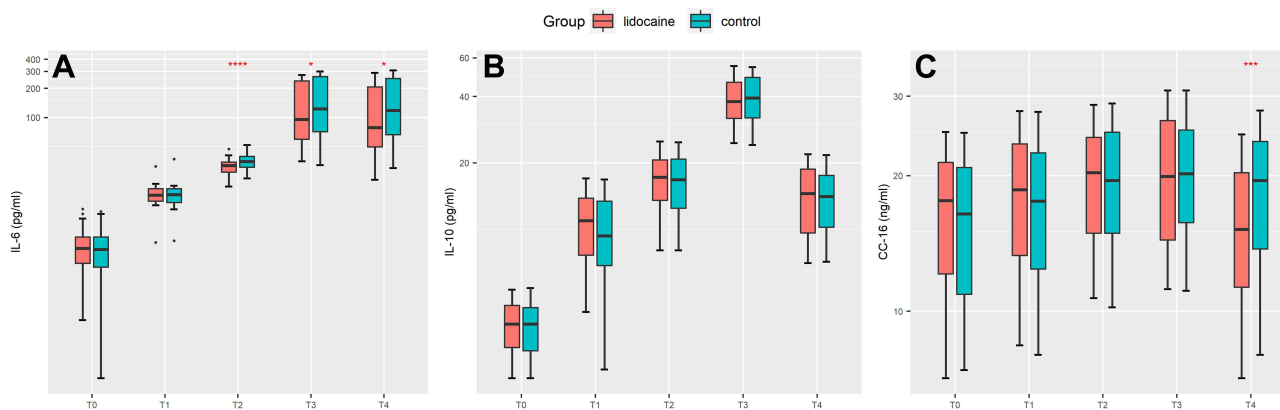
The comparison of VSA scores between group lidocaine and group control at various time points only showed a difference at 4 hours postoperatively (2.9 ±1.0 vs 4.0 ±1.4, difference: -1.1, 95% CI: -1.5 to -0.8; *P*<0.001) (Table 2).

### Gastrointestinal Recovery

The time of first defecation or bowel movements in group lidocaine was 6.3 hours (95% CI: 3.9 to 8.7) earlier than that in group control (*P*<0.001). And the time of first flatus was also shorter in group lidocaine (26.1 ±7.7 vs 31.4 ±7.1 hours, difference: -5.0, 95% CI: -7.3 to -3.2; *P*<0.001). In addition, the incidence of postoperative ileus was lower in group lidocaine, compared with group control (5.2% vs 14.3%, relative risk: 0.36, 95% CI: 0.14 to 0.96, absolute risk reduction: -9.1%, *P*=0.032). Consistent with these results, removal time of nasogastric tube was also earlier in the lidocaine group (54.2±8.6 vs 62.6±10.4 hours, difference: -8.4, 95% CI: -12.2 to -4.6; *P*<0.001) (Table 2).



**Figure 2** Patients with no PPCs at 7 postoperative days. No PPCs was defined as no PPCs occurred within 7 postoperative days or before discharge, whichever came sooner.



**Figure 3** Concentrations of inflammatory factors at different time points. **(A)** Concentrations of IL-6; **(B)** concentrations of IL-10; **(C)** concentrations of CC-16. \* $P < 0.05$ ; \*\* $P < 0.02$ ; \*\*\* $P < 0.001$ . IL-6, interleukin-6; IL-10, interleukin-10; CC-16, Clara cell protein-16; T<sub>0</sub>, pre-induction of anesthesia; T<sub>1</sub>, 1 hour after ventilation; T<sub>2</sub>, 2 hours after ventilation; T<sub>3</sub>, the end of surgery; T<sub>4</sub>, 24 hours after surgery. All of the y-axis were log<sub>2</sub> transformed.



## Quality of Recovery

Compared with group control, the total QoR-40 score in group lidocaine was higher at 24 hours postoperatively (165 (152 to 177) vs 158 (144 to 169), difference:7, 95% CI:4 to 13;  $P=0.026$ ). To be specific, the scores of physical comfort, physical independence, and pain domains in group lidocaine were higher than those in group control (53 (50 to 56) vs 50 (44 to 53), difference:3, 95% CI:2 to 5,  $P=0.026$ ; 18 (16 to 21) vs 15 (13 to 20), difference:3, 95% CI:2 to 4,  $P=0.001$ ; 30 (28 to 31) vs 28 (28 to 30), difference:2, 95% CI:1 to 4,  $P=0.002$ , respectively). However, there were no obvious differences in emotional status and psychological support domains (Table 2).

## Length of Hospital Stay

The median length of hospital stay in group lidocaine was shorter than that in group control (5 (5 to 6) vs 6 (5 to 7), difference: -1, 95% CI: -1 to 0,  $P<0.001$ ) (Table 2).

## Parameters Reflecting Pulmonary Function and Mechanics and Hemodynamics

There was interaction of group and time on driving pressure ( $P=0.032$ ). The simple effects of the group were analyzed. The driving pressure between the two groups was similar at each time point (Table 3). The interaction of group and time was not statistically significant on Cdyn ( $P=0.831$ ), RI ( $P=0.130$ ),  $PO_2/FiO_2$  ( $P=0.422$ ), heart rate ( $P=0.980$ ), and MAP ( $P=0.485$ ). The main effects of the group were analyzed. Cdyn, RI, and  $PO_2/FiO_2$  were similar between the two groups. Compared with group control, the heart rate and MAP were not affected by infusion lidocaine (Table 3).

## Adverse Events

There were no significant lidocaine-related adverse events during the entire trial.

## Discussion

In this prospective, double-blind, randomized controlled trial, we found that intravenous infusion of lidocaine could significantly reduce the incidence of PPCs within 7 days postoperatively in patients undergoing major abdomen surgical procedures, shortened lengths of hospital stays, and improved patient prognosis. Possible underlying mechanisms maybe include inhibiting inflammation, reducing opioid consumption, and promoting gastrointestinal motility. In the present study, the total incidence of PPCs seems higher (35.9%) than those in previous studies.<sup>22,23</sup> It may be because the patients we included were at intermediate to high risk of PPCs (ARISCAT  $\geq 26$ ).

**Table 3** Secondary Outcomes: Intraoperative Variables Reflecting Lung Function and Hemodynamics

	Group	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	P-value
<b>ΔP (cm H<sub>2</sub>O)</b>	<b>Lidocaine (n=97)</b>		7.1 ±1.1	13.5 ±1.5	7.7 ±1.1	
	<b>Control (n=98)</b>		7.0 ±1.1	13.4 ±1.4	7.9 ±0.9	
	<b>P-value</b>		0.601	0.533	0.118	
<b>PaO<sub>2</sub>/FiO<sub>2</sub> (mm Hg)</b>	<b>Lidocaine (n=97)</b>	434 ±31	436 ±26	436 ±24	438 ±23	0.421
	<b>Control (n=98)</b>	430 ±30	433 ±25	435 ±24	436 ±22	
<b>RI</b>	<b>Lidocaine (n=97)</b>	0.95 ±0.11	0.94 ±0.09	0.94 ±0.09	0.95 ±0.09	0.690
	<b>Control (n=98)</b>	0.95 ±0.11	0.92 ±0.10	0.94 ±0.10	0.94 ±0.09	
<b>Cdyn (mL cmH<sub>2</sub>O<sup>-1</sup>)</b>	<b>Lidocaine (n=97)</b>		36.2 ±3.4	35.6 ±2.8	40.6 ±4.5	0.072
	<b>Control (n=98)</b>		35.5 ±3.8	35.2 ±3.4	39.8 ±5.3	
<b>Heart rate (bpm)</b>	<b>Lidocaine (n=97)</b>	64.1 ±6.0	64.7 ±5.7	64.3 ±5.4	64.0 ±5.8	0.585
	<b>Control (n=98)</b>	64.4 ±6.1	64.7 ±5.9	64.7 ±5.5	64.4 ±6.2	
<b>MAP (mm Hg)</b>	<b>Lidocaine (n=97)</b>	98 ±13	83 ±9	83 ±8	82 ±8	0.846
	<b>Control (n=98)</b>	97 ±12	84 ±10	82 ±8	83 ±9	

**Note:** Data are reported as mean ± SD.

**Abbreviations:** PaO<sub>2</sub>, partial pressure of Oxygen; FiO<sub>2</sub>, fraction of inspiration Oxygen; RI, respiratory index (A-aDO<sub>2</sub>/PaO<sub>2</sub>, A-aDO<sub>2</sub>=PAO<sub>2</sub>-PaO<sub>2</sub>=713FiO<sub>2</sub>-PaCO<sub>2</sub>/0.8-PaO<sub>2</sub>); Cdyn, dynamic lung compliance (Vt/(Pmax-PEEP); ΔP, driving pressure (P<sub>plat</sub>-PEEP); bpm, beat per minute; MAP, mean arterial pressure.

Risk factors for PPCs development are numerous, including systemic inflammatory response after surgery, side effects of opioids, postoperative inadequate analgesia, and changes of respiratory mechanics.<sup>4</sup> All these entities are ameliorated by the administration of i.v. lidocaine.<sup>24</sup>

Intravenous administration of lidocaine showed analgesic effect, and reduced postoperative pain, especially in the early postoperative period.<sup>25,26</sup> In our present study, i.v. lidocaine effectively reduced postoperative pain, although the VAS scores were significantly lower only at 4 hours postoperatively. This may be because the PCA we used had background infusion. The analgesia effect of i.v. lidocaine resulted in reducing opioid consumption. Previous studies showed that intraoperative i.v. lidocaine reduced morphine consumption in patients undergoing open radical prostatectomy and open gastrectomy.<sup>26,27</sup> Similar results were found in the present study. The total opioid consumption was much lower in group lidocaine than that in group control, so the side effects induced by opioids, such as respiratory depression, were reduced.

In addition to analgesia, the anti-inflammatory effects of lidocaine have been extensively studied.<sup>8–10</sup> The systemic inflammatory response is an important factor in PPCs. Lidocaine was reported to activate protein kinase C to reduce endotoxin-induced leukocyte adhesion and granulocyte-mediated phagocytosis through G-protein coupled signal pathways.<sup>28</sup> The anti-inflammatory effect of lidocaine was also reflected in blocking neutrophil activation and inhibiting inflammatory cytokines and proteolytic enzyme release.<sup>11,29</sup> In the present study, i.v. lidocaine significantly prevented IL-6 release during operation. Besides, the level of CC-16 in plasma was significantly lower in group lidocaine than in group control at 24 hours postoperatively. CC-16 protein, a homodimer protein synthesized and secreted by lung epithelial cells, is a specific biomarker of the damage of Clara cell and alveolar-capillary permeability. It can reflect early alveolar epithelial permeability changes induced by subclinical lung injury<sup>30,31</sup> by leaking from damaged lung epithelial barrier to blood.<sup>32</sup> These results suggested that i.v. lidocaine presents lung protective effects by inhibiting inflammation and protecting alveolar epithelial and alveolar-capillary barriers.

Interestingly, although the previous study<sup>33</sup> found that intravenous lidocaine could improve the respiratory mechanics of patients undergoing thoracoscopic surgery during operation, however, in our present study, it was not improved by i.v. lidocaine. This may be due to the different types of surgery (abdominal surgery vs thoracic surgery). Thoracoscopic surgery maybe have a greater impact on respiratory mechanics than laparoscopic surgery. In addition, we stratified patients according to the type of surgery and adopted standard lung protection ventilation strategies. Although the anti-inflammatory effect of lidocaine had benefits on lung function, it was not enough to affect the intraoperative respiratory mechanics. So, the improvement of respiratory mechanics was not obvious.

PPC is a composite outcome measure, the rate of atelectasis in group lidocaine was significantly lower than that in group control. This is mainly because of the benefits of i.v. lidocaine (pain relief, reduced opioid consumption, anti-inflammatory effects) could promote deep breathing and coughing, which is of great significance for reducing postoperative atelectasis.<sup>4</sup> In addition, a previous study showed that patients with a nasogastric tube had a higher risk of atelectasis.<sup>34</sup> The rapid recovery of gastrointestinal function in group lidocaine allowed the nasogastric tube to be removed earlier, which may be another important reason for the decrease in the incidence of postoperative atelectasis. However, the incidence of other PPCs (Respiratory infection, Pleural effusion, Pneumonia, Respiratory failure, ARDS) decreased in group lidocaine, but the difference was not statistically significant. This may be due to our insufficient sample size. Because sample size calculation was based on the primary outcome measure (the incidence of PPCs). Since PPCs are a composite indicator, the incidence of single PPC is lower than that of PPCs, lower incidence means less difference between the two groups, so a larger sample size may be required to meet the same power and level of the test.

In this study, we observed that i.v. lidocaine had a promoting effect on gastrointestinal recovery. Previous study and meta-analyses showed that i.v. lidocaine could reduce the time to first bowel movement and the incidence of ileus.<sup>35,36</sup> The main reasons may include reducing opioid consumption and inhibiting systemic inflammation. Inflammation plays a crucial role in sustaining postoperative ileus,<sup>37</sup> lidocaine may mediate its beneficial effects on promoting gastrointestinal recovery by anti-inflammatory. The rapid recovery of gastrointestinal function allowed the nasogastric tube, which is closely related to atelectasis, to be removed earlier, and thus promote patients' early recovery.

Taking together, i.v. lidocaine reduced the incidence of PPCs, promoted patients' recovery, and shortened the length of hospital stay by inhibiting systemic inflammation, relief pain, reducing opioid consumption, and promoting gastrointestinal recovery.

There are some limitations in our research. First, we did not measure the blood concentration of lidocaine. This is because the dose we used is similar to others. Previous studies<sup>38–40</sup> found that after a bolus of 1.5 mg kg<sup>-1</sup> with 1.0–2.0 mg kg<sup>-1</sup> h<sup>-1</sup> continuous infusion of lidocaine, the average plasma concentration of lidocaine was 1.60–2.05 µg mL<sup>-1</sup>, which is far lower than the concentration of 5.0 µg mL<sup>-1</sup> that produces toxic reactions<sup>41</sup> and is therefore considered to be safe. Second, we did not continue i.v. lidocaine for a longer time after surgery, this is mainly because of concerns about the safety of patients after returning to the ward. Third, we only enrolled patients at an intermediate/high risk for PPCs undergoing major abdominal surgery, these findings cannot be generalized to more patients. Finally, long-term effects of i.v. lidocaine were not observed. Hence, further multi-center, large-sample randomized trials are needed to investigate the long-term impact of lidocaine infusion on surgery patients.

## Conclusions

In summary, our results suggest that perioperative lidocaine administration can reduce the incidence of PPCs in patients with intermediate/high risk of PPCs under major abdominal surgery. In addition, i.v. lidocaine can also relieve early pain level (postoperative 4 hours), promote gastrointestinal recovery, improve the quality of recovery and shorten the length of hospital stay. These findings may provide a new strategy of lung protection for patients with intermediate/high risk of PPCs during the perioperative period.

## Data Sharing Statement

The authors will share participant data, such as blood pressure, heart rate, and pain scores and so on. No other study-related documents will be available. Emails could be sent to the address below to obtain the shared data: wangxh\_77@163.com. The data will be accessible from the publication date.

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## Disclosure

The authors report no conflicts of interest in this work.

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