BMC Anesthesiology

RESEARCH

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Association between thoracic epidural anesthesia and driving pressure in adult patients undergoing elective major upper abdominal surgery: a randomized controlled trial

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Abstract

Background Thoracic epidural anesthesia (TEA) is associated with a knowledge gap regarding its mechanisms in lung protection and reduction of postoperative pulmonary complications (PPCs). Driving pressure (ΔP), an alternative indicator of alveolar strain, is closely linked to reduced PPCs with lower ΔP values. We aim to investigate whether TEA contributes to lung protection by lowering ΔP during mechanical ventilation.

Methods In this prospective, randomized, patient and evaluator-blinded parallel study, adult patients scheduled for elective major upper abdominal surgery were assigned to either the TEA group with combined thoracic epidural anesthesia and general anesthesia (TEA-GA) ($n=30$) or the control group with only general anesthesia (GA) ($n=30$).

Measurements The primary outcome was the minimum ΔP determined based on positive end-expiratory pressure (PEEP) after intubation. Secondary outcomes included the incidence of PPCs within seven days, the minimum ΔP at various time points, blood gas analysis, intensive care unit (ICU) admission rates, length of hospital stay, and 30-day mortality rate.

Results The TEA group had a significantly lower minimum ΔP titrated based on PEEP compared to the control group (11.23 ± 2.19 cmH_2O vs. 12.67 ± 2.70 cmH_2O; $P=0.028$). Multivariate linear regression analysis showed that intraoperative TEA application (compared with its absence; unstandardized beta coefficient (B) = -1.289; $P=0.008$) significantly correlated with ΔP. The incidence of PPCs did not differ significantly between the two groups (8 of 30 [26.7%] vs. 12 of 30 [40%]; $P=0.273$), but the incidence of atelectasis in the TEA group was significantly lower than in the control group (5 of 30 [16.7%] vs. 12 of 30 [40.7%]; $P=0.012$). Multivariate logistic regression analysis indicated that

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ΔP was the only variable significantly associated with PPCs (Adjusted Odds Ratio [OR] = 2.190; 95% Confidence Interval [CI]: 1.300 to 3.689; $P = 0.003$).

Conclusion Compared to GA, TEA-GA can reduce intraoperative ΔP in patients undergoing major upper abdominal surgery, especially those undergoing laparoscopic surgery. However, compared to GA combined with ΔP-guided ventilation, TEA-GA combined with ΔP-guided ventilation does not reduce the risk of PPCs. There was no significant difference in the total use of various vasoactive drugs between the two groups.

Trial registration This study was registered in the Chinese Clinical Trial Registry (registration number ChiCTR2300068778 date of registration February 28, 2023).

Keywords Thoracic epidural anesthesia, Driving pressure, Postoperative pulmonary complications, Major upper abdominal surgery, Lung-protective ventilation

Background

Postoperative pulmonary complications (PPCs) are closely associated with higher mortality rates and can develop in up to 58% of major upper abdominal surgeries [1, 2]. Despite the increasing adoption of "lung-protective" measures, the overall incidence of PPCs remains high [3]. Therefore, it is necessary to adopt a range of lung-protective strategies to improve the prognosis of patients undergoing major upper abdominal surgery. Recent evidence suggests that driving pressure (ΔP) is the only significant mediator in protective ventilation parameters affecting PPCs [4]. ΔP is simply measured as plateau pressure (P_{plat}) - positive end-expiratory pressure (PEEP) or tidal volume (V_T)/respiratory system compliance (C_{RS}) [5] and serves as an alternative indicator of lung strain [4–6]. Multiple meta-analyses have shown that a minimum ΔP-guided individualized PEEP strategy can improve intraoperative oxygenation and reduce PPCs [4, 7, 8]. Moreover, several randomized controlled trials (RCTs) have confirmed that low ΔP can reduce the incidence of PPCs, particularly atelectasis, in open abdominal surgeries [9–11]. Low ΔP has become a mainstream trend in lung-protective ventilation. In major upper abdominal surgeries, monitoring and reducing ΔP to guide the setting of tidal V_T and PEEP during mechanical ventilation is very necessary.

Thoracic epidural anesthesia (TEA) regulates the conduction of thoracic sympathetic nerves, leading to vasodilation, increased visceral perfusion, and reduced afterload [12]. Given these physiological effects, TEA has advantages in reducing postoperative cardiac, pulmonary, renal, and gastrointestinal complications [13]. It significantly lowers the risk of postoperative pneumonia in patients undergoing thoracic and abdominal surgery and improves specific pulmonary function parameters and oxygenation [14]. Elefterion et al. reviewed patients who underwent elective non-cardiac surgery (primarily abdominal gastrointestinal surgeries) over the past decade. They reported that 86.2% of 1039 patients who received epidural anesthesia (mainly TEA) had no PPCs [15]. Studies by Park et al. [16] and Nishimori et al. [17] suggest that general anesthesia combined with TEA (TEA-GA) is associated with faster extubation, shorter intensive care unit stays, and favorable pulmonary outcomes after major abdominal surgery. The underlying pathophysiology and mechanisms remain unclear. Previous research focused on the significantly better analgesic effects of TEA compared to patient-controlled intravenous opioid administration, with pain relief from TEA improving postoperative respiratory function and arterial oxygenation [13, 14]. TEA also reduces central sympathetic stimulation, thereby favorably influencing organ perfusion and immune function [18, 19]. Currently, there is a lack of research evidence to demonstrate that TEA exerts lung-protective effects by lowering ΔP.

Hong et al. [20] proposed that TEA-GA could result in significantly lower peak inspiratory pressures and higher dynamic pulmonary compliance in patients undergoing laparoscopic abdominal surgery compared to those receiving GA alone. [20] At that time, ΔP, an essential respiratory mechanic parameter, was not proposed, so they did not establish a relationship between TEA-GA and ΔP. Based on the study by Hong et al., we hypothesize that in patients undergoing mechanical ventilation during major upper abdominal surgery under GA, TEA-GA can result in higher C_{RS} and functional residual capacity (FRC), leading to a lower ΔP compared to GA. On this basis, we conducted a randomized controlled trial hypothesizing that TEA-GA combined with ΔP-guided ventilation could significantly lower ΔP during mechanical ventilation in major upper abdominal surgery, thereby reducing PPCs and providing lung protection. This study aims to elucidate the protective mechanisms of TEA on PPCs through respiratory mechanics.

Methods

Study design and population

This prospective, randomized, patient and evaluator-blinded parallel study was conducted at The First Affiliated Hospital of Kunming Medical University. This study was registered in the Chinese Clinical Trial Registry before patient enrollment (registration number:

ChiCTR2300068778, principal investigator: Xuan Li; registration date: February 28, 2023). From April to October 2023, patients were screened for eligibility, and all eligible participants received written informed consent. This study adhered to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines [44].

This study recruited adult patients (age > 18 years) of American Society of Anesthesiologists (ASA) physical status I-III, of any gender, undergoing elective major upper abdominal surgery (liver, gallbladder or bile duct, pancreas, spleen, stomach, defined as surgeries lasting over 2 h) under general anesthesia. As our study involves the measurement of ΔP, PEEP titration, and the observation of PPCs, we excluded patients with recent or pre-existing pulmonary diseases. These conditions can alter lung compliance, airway resistance, and ventilation distribution, thereby impacting mechanical ventilation strategies and increasing the risk of barotrauma and volutrauma. Exclusion criteria included a history of upper respiratory or pulmonary infection within the past four weeks, chronic obstructive pulmonary disease (COPD, including all GOLD 1–4 stages), severe or uncontrolled bronchial asthma, preoperative pleural effusion requiring thoracic drainage, pulmonary bullae larger than 2 cm in diameter, preoperative CT findings of atelectasis, a history of severe restrictive pulmonary disease (e.g., pulmonary fibrosis, thoracic deformities with TLC and FVC < 80% of predicted values), and any prior thoracic surgery. Patients with lung nodules (presumed benign on preoperative CT) were not excluded. Other exclusion criteria included severe cardiovascular, renal, or hematopoietic disorders such as renal failure, leukemia, congenital heart disease; contraindications to epidural anesthesia, such as severe coagulopathy, infection at the puncture site, severe scoliosis, history of spinal trauma, allergy to local anesthetics; contraindications to the use of PEEP, such as raised intracranial pressure, hypovolemic shock, right ventricular failure. Exclusion criteria included actual mechanical ventilation duration < 60 min, conversion from laparoscopy to laparotomy, failure of epidural puncture or catheterization, and severe hypotension during surgery preventing continuation of combined TEA.

Randomization and blinding

An independent researcher responsible for randomization used Excel's "RAND" function to generate random numbers at a 1:1 ratio with a fixed block size of 4, randomly coding the TEA group and control group. The results of the randomization were placed in opaque envelopes, and allocation concealment was achieved using sealed, lightproof randomization envelopes. The attending anesthesiologist opened the envelope before anesthesia and implemented the anesthesia plan as specified in the envelope. Patients, the surgical team, and researchers collecting postoperative outcome data were blinded. The attending anesthesiologist performing the epidural catheterization, PEEP titration protocol, and collecting intraoperative data was aware of the group assignments and thus was not blinded.

Intervention

All participants underwent detailed preoperative examinations and were screened according to the exclusion criteria of this study. In the TEA group, thoracic epidural catheterization was performed 30 min prior to anesthesia induction. Patients were positioned laterally or sitting. The direct approach was chosen, using a 16-gauge Tuohy needle at the T7-8 or T8-9 interspace for epidural puncture. The epidural catheter was inserted cephalad 4–6 cm, and a test dose of 3 ml of local anesthetic (1% lidocaine with 1:200,000 epinephrine [5 μg/ml]) was administered through the catheter. After waiting for 5 min, if there were no signs of adverse reactions like inadvertent subarachnoid or epidural vein plexus drug entry, a single bolus of 1.25 mg/ml ropivacaine with 0.5 μg/ml sufentanil totaling 6 ml was administered, followed by the installation of an epidural pump starting at a rate of 6 ml/h (drug concentration: 1.25 mg/ml ropivacaine and 0.5 μg/ml sufentanil) for continuous intraoperative TEA. Fifteen minutes later, the anesthetic level was measured, using pinprick sensation to confirm the level of TEA blockade, ensuring a sensory blockade up to the T4 level. If the sensory blockade had not reached the T4 level, an additional 4 ml of local anesthetic was administered through the epidural catheter, and after waiting for 10 min, if the T4 level of sensory blockade was still not achieved, the patient was excluded from the study. After testing and adjusting the level, anesthesia induction was performed.

In the control group, epidural puncture and catheterization were similarly performed 30 min before anesthesia induction at the T7-8 or T8-9 interspace, with the same puncture site as the TEA group. A test dose of 3 ml of local anesthetic was pre-administered and, after a 5-minute wait and negative results, anesthesia induction commenced. No medication was given in the epidural space until the end of surgery when skin suturing began, at which point a single dose of 6 ml of local anesthetic (same concentration as in the TEA group) was administered. Postoperatively, patient-controlled epidural analgesia (PCEA) was conducted for 72 h (drug: 1.25 mg/ml ropivacaine and 0.5 μg/ml sufentanil, background dose 5 ml/h, bolus dose 4 ml, lockout interval 30 min).

Intraoperative anesthesia protocol and fluid management

Radial artery cannulation was performed for continuous arterial blood pressure (ABP) monitoring and intermittent blood gas analysis. A double-lumen high-flow

central venous catheter was inserted into the right internal jugular vein for central venous pressure (CVP) monitoring and intraoperative fluid administration. All patients received an intravenous bolus of 3 μg/kg fentanyl and 2–3 mg/kg propofol for induction of general anesthesia, followed by tracheal intubation after administration of 0.8 mg/kg rocuronium. Anesthesia maintenance involved combined intravenous and inhalational anesthesia, with an intravenous infusion of propofol at 3–4 mg/kg/h and remifentanil at 0.1–0.3 μg/kg/min, and inhalation of 1–2% sevoflurane in 50–80% oxygen/air mixture. Rocuronium was continuously infused throughout the surgery at a rate of 10 ug/kg/min. The depth of GA was controlled to maintain a bispectral index (BIS) between 40 and 60 (BIS monitor: Narcotrend, Germany). Neuromuscular blockade was monitored using a peripheral nerve stimulator, maintaining a muscle relaxation depth at one twitch response in a train-of-four (TOF) stimulation. At the end of the surgery, all patients were administered 2 mg/kg sugammadex to reverse residual neuromuscular blockade, transferred to the post-anesthesia care unit (PACU), and extubated when the ratio of the fourth twitch (T4) to the first twitch (T1) in the TOF response (TOFR) was ≥0.9. The epidural catheter was removed by an anesthesiologist from our institution's pain management department following the completion of PCEA. Before removal, coagulation function was assessed to confirm normalization. Postoperative coagulation dysfunction was defined as INR > 1.5, APTT > 40 s, or PLT count < 80×10^9/L. If any of these abnormalities were present, measures were taken to improve coagulation function prior to catheter removal.

For intraoperative fluid management, patients in the TEA group underwent volume assessment by the attending anesthesiologist prior to TEA administration. If low CVP, bowel preparation, prolonged fasting, or lack of preoperative IV fluid therapy indicated volume depletion, a preemptive infusion of 250–500 mL colloid solution (6% hydroxyethyl starch 130/0.4) was administered. During liver transection, the balanced crystalloid solution was infused at 1 mL/kg/h to maintain CVP below 5 cmH_2O. Following specimen removal, a 1:1 colloid replacement (with albumin if needed, using 20% human albumin) was initiated for blood loss and continued infusion of balanced crystalloid solution. Additional fluids were administered if systolic pressure fell below 90 mmHg or urine output was less than 25 mL/h. If surgical hemostasis was insufficient, additional plasma or platelets were infused upon consultation with the surgeon. For blood loss exceeding 400 ml during surgery and blood gas analysis indicated hemoglobin levels of < 80 g/L., packed red blood cells were transfused. For other upper abdominal surgeries, preoperative assessment of patients' volume reserves was conducted, infusing balanced saline solution or colloid at 5–10 ml/kg/h. Colloid infusions were primarily used for laparotomy surgeries, with the option of albumin infusion, and the need for plasma or packed red blood cell transfusion was evaluated based on intraoperative blood loss, aiming for zero balance. Total fluid volume on the day of surgery was maintained between 1.75 and 2.75 L. Intraoperative fluid management was adjusted flexibly based on patient blood pressure, heart rate, urine output, CVP, and blood loss, with detailed records of intraoperative fluid therapy (crystalloids, colloids, blood, and blood products).

Intraoperative mechanical ventilation protocol

After tracheal intubation, the patient was connected to an anesthesia machine (Anesthesia Machine A7, Mindray, China) and ventilated using volume-controlled ventilation (VCV). The V_T was set at 6–8 ml/kg of ideal body weight (IBW). An inspired oxygen fraction (FiO_2) of 0.4–0.8 was used based on intraoperative oxygenation to maintain SpO_2 > 97%. The inspiratory pause was set at 30%, with an inspiratory/expiratory ratio of 1/2 and a flow rate of 2 L/min. The initial respiratory rate was set at 12 breaths/min, then adjusted (within 10–20 breaths/min) to maintain end-tidal carbon dioxide ($EtCO_2$) levels between 35 and 45 mmHg. Both the TEA and conventional groups underwent individualized ΔP-guided PEEP titration trials. For laparoscopic surgeries, the titration started after pneumoperitoneum establishment and patient positioning. For laparotomy surgeries, titration began after opening the peritoneum and applying the abdominal retractor.

A manual alveolar recruitment maneuver (ARM) was performed using the anesthesia machine's reservoir bag, creating a continuous airway positive pressure of 30 cm H_2O for 15–20 s to increase peak airway pressure (P_{peak}) while keeping the P_{plat} <30 cm H_2O. This was followed by individualized ΔP-guided PEEP titration. A decremental PEEP titration method was used, employing the formula: $\Delta P = P_{plat}$ - PEEP, starting from 15 cm H_2O and decreasing in 1 cm H_2O steps to 0 cm H_2O (Zero PEEP, ZEEP). During PEEP titration, each PEEP step (15, 14, 13……0 cm H_2O) was maintained for 15 breathing cycles. The ΔP was calculated and recorded at the last breath of each PEEP level, selecting the PEEP level corresponding to the lowest ΔP to continue mechanical ventilation. The PEEP titration was stopped if any of the following were observed: (1) SpO_2 below 88%, (2) tachycardia > 140 beats/min, or bradycardia < 50 beats/min, or (3) any new arrhythmias. In laparoscopic surgeries, apart from this titration (T1), two more ΔP lowering titration procedures were conducted: when pneumoperitoneum is stopped for open specimen retrieval (T2) and when pneumoperitoneum is re-established for intraperitoneal hemostasis (T3).

Intraoperative haemodynamic protocol

Upon entering the operating room, initial ABP was recorded to establish baseline blood pressure, categorized as low (systolic blood pressure [SBP] < 90 mmHg or diastolic blood pressure [DBP] < 50 mmHg), normal (SBP = 90–129 mmHg and DBP = 50–79 mmHg), or high (SBP ≥ 130 mmHg or DBP ≥ 80 mmHg). Intraoperatively, fluid rates were adjusted or vasoactive drugs (norepinephrine, phenylephrine, ephedrine, dopamine, epinephrine) were administered to maintain the following blood pressure targets: in patients with low baseline blood pressure, maintain mean arterial pressure (MAP) ≥ 60 mmHg, keeping blood pressure within 100–120% of the baseline, ensuring it does not fall below the baseline value, and allowing a rise within ≤ 20%; in patients with normal baseline blood pressure, maintain MAP between 65 and 95 mmHg, keeping blood pressure within 80–120% of baseline (allowing changes ≤ 20% of the baseline value); in patients with high baseline blood pressure, maintain blood pressure within 80–110% of the baseline and ensure SBP is below 160 mmHg, with allowable reductions kept within 20% of the baseline. In the TEA group, if blood pressure dropped more than 20% below baseline and heart rate was > 70 beats/min, an intravenous bolus of 20 μg of norepinephrine or 2 μg of phenylephrine was administered, repeated up to five times. If the target blood pressure was still not reached after repeated boluses and the patient's heart rate remained > 70 beats/min, an infusion of norepinephrine at 0.25–1 μg/(kg.min) was started. If the blood pressure dropped more than 20% below baseline and heart rate was between 70 − 50 beats/min, a single bolus of 6–10 mg of ephedrine was administered, repeated up to three times. If blood pressure and heart rate continued to decrease, an infusion of phenylephrine at 0.1–0.5 μg/(kg.min) was started. If blood pressure dropped more than 30% below baseline and heart rate was < 50 beats/min, 20 μg of epinephrine was immediately injected intravenously, and an infusion of epinephrine at an initial rate of 0.05 μg/(kg.min) was started.In all patients, hemodynamic values below the target were immediately corrected. In the TEA group, if persistent hypotension or bradycardia occurred, epidural medication was immediately stopped, the patient was excluded from the study, and adverse reactions were actively managed.

Outcomes data

The primary outcome was the minimum ΔP achieved after ΔP-guided PEEP titration at the start of the surgery (T1) in both groups. The secondary outcome was the incidence of PPCs within seven days. PPCs include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, and aspiration pneumonia (Supplementary Table 1) [21]. The diagnosis of atelectasis, pleural effusion, and pneumothorax was made by radiologists (blinded to group assignment) based on routine chest X-ray examinations conducted on postoperative days 1 and 3. Respiratory system infection was diagnosed in patients presenting with fever, leukocytosis, and new infiltrates on chest X-ray, and aspiration pneumonia was diagnosed if there was a history of aspiration of gastric contents. Bronchospasm was diagnosed if patients presented with expiratory-dominant dyspnea during spontaneous breathing, accompanied by widespread wheezing on auscultation, required treatment with bronchodilators, and showed increased and disorganized pulmonary markings on CT imaging. The definition of respiratory failure is described in Supplementary Table 1 [21]. Other secondary outcomes include length of hospital stay, ICU admission rate, 30-day mortality rate, respiratory parameters, and blood gas analysis results.

Sample size estimation

This study conducted a pilot trial. Sample size calculation was based on the primary outcome, "minimum ΔP after PEEP titration." Considering that 67.3% of abdominal surgeries at The First Affiliated Hospital of Kunming Medical University are laparoscopic, we included three laparotomy patients and seven laparoscopic surgery patients in each group for the titration of the minimum ΔP, in accordance with this proportion. This approach was taken to avoid imbalances in baseline characteristics, such as surgical method, that could significantly affect ΔP and thus impact the accuracy of subsequent sample size calculations. In the pilot study, 20 patients were enrolled, with ten patients in each group as per the above-mentioned randomization method and proportion. The ΔP in the pilot trial were 10.5 ± 3.13 cmH_2O for the TEA group and 12.8 ± 3.42 cmH_2O for the control group. Based on these findings, the sample size was calculated using PASS software. Considering a Type I error (α = 0.05) and a power of 80% (β = 0.2, two independent samples t-test), the estimated sample size required was 54 (27 per group). The total sample size was increased to 60 (30 per group) to account for a potential 10% dropout rate.

Statistical analysis

The Shapiro-Wilk test was used to assess whether quantitative data conformed to a normal distribution. Quantitative data with normal distribution were expressed as mean ± standard deviation, and comparisons between the two groups were made using the two independent samples t-test. Skewed distribution quantitative data were represented by the median (M) and interquartile range (IQR), with comparisons between groups conducted using the Mann-Whitney U test. The $\chi 2$ test was used for comparisons of categorical data between the two groups. Multivariate analysis of quantitative data was conducted

using multiple linear regression, with Durbin-Watson tests utilized to test for autocorrelation in the data. Multivariate analysis of categorical data was performed using univariate and multivariate logistic regression analysis. We considered potential variables that could influence PPCs incidence—such as TEA application, ΔP, age, BMI, smoking history, preoperative liver and kidney function, and surgical approach—by including them in a univariate logistic regression analysis. Variables with $P<0.05$ from the univariate analysis were then included in a multivariate logistic regression analysis. The predictive performance of ΔP was evaluated using receiver-operating characteristic (ROC) curve analysis. In addition, the best cutoff to maximize sensitivity and specificity was calculated with its confidence interval (CI) by the method of bootstrap resampling. The aforementioned statistical analyses were carried out using SPSS 22.0 and Rstudio, with a significance level set at $\alpha=0.05$.

Result

Study population

The CONSORT flow diagram is depicted in Fig. 1. From April 2023 to October 2023, a total of 92 patients were assessed for eligibility, with 66 patients enrolled and randomized. In the TEA group, four patients were withdrawn from the study due to loss of follow-up, severe hypotension, and failure of epidural catheterization; in the control group, two patients were withdrawn due to failure of epidural catheterization. Consequently, a total of 60 patients (30 in each group) were included in the final analysis, with no other missing data. Patient characteristics are shown in Table 1. Except for serum albumin levels, both groups were balanced in all demographic and perioperative characteristics.

Primary outcome

The minimum ΔP after PEEP titration in the TEA group was significantly lower than in the control group (11.23±2.19 cmH_2O vs. 12.67±2.70 cmH_2O; $P=0.028$; Table 2; Fig. 2). Due to differences in surgical methods (laparotomy/laparoscopic), subgroup analyses were conducted based on the type of surgery. In laparoscopic surgeries, the minimum ΔP in the TEA group was significantly lower than that in the control group (11.95±1.91 cmH_2O vs. 13.57±2.44 cmH_2O; $P=0.023$; Table 2; Fig. 2). However, in laparotomy surgeries, there was no statistical difference in the minimum ΔP between the two groups (9.8±2.10 cmH_2O vs. 10.56±2.07 cmH_2O; $P=0.44$;

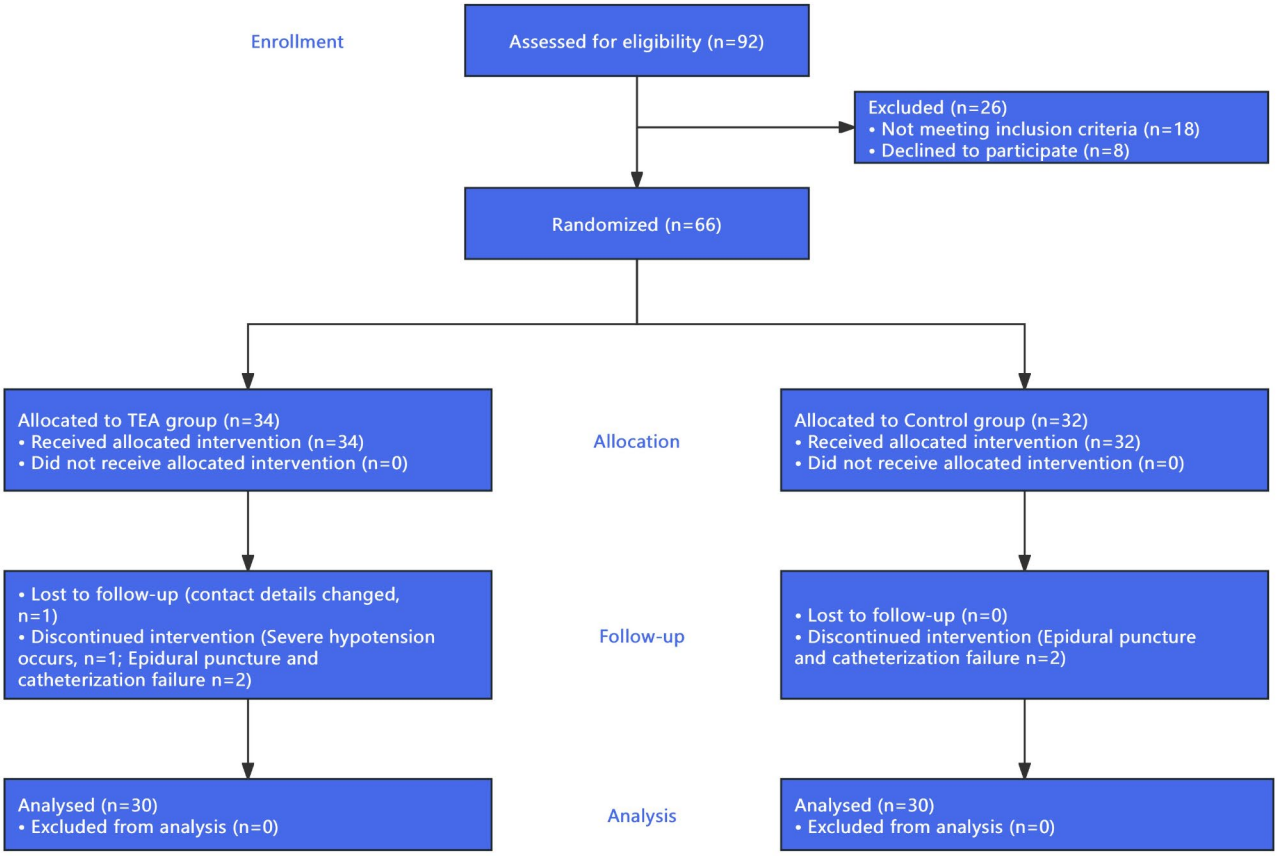

Fig. 1 CONSORT flow diagram. CONSORT indicates Consolidated Standards Of Reporting Trials; TEA: Thoracic epidural anesthesia

Table 1 Patients'baseline characteristics and surgical information

Characteristic	TEA group (*n* = 30)	Control group (*n* = 30)	*P* value
Age (years)	53 ± 19.99	55.6 ± 16.71	0.54[a]
Sex (male/female)	16/14	15/15	0.796[b]
Height (cm)	164 ± 8.53	162.4 ± 9.87	0.504[a]
Weight (kg)	62.7 ± 10.15	58.1 ± 11.31	0.103[a]
BMI (kg/m^2)	23.3 ± 3.17	22.01 ± 3.73	0.155[a]
Hemoglobin (g/L)	137.33 ± 23.79	129.53 ± 21.34	0.187[a]
Serum bilirubin (μmol/L)	11.5 [6.18–21.13]	10.8[7.68–17.15]	0.941[c]
Serum creatinine (μmol/L)	75.64 ± 12.31	73.15 ± 16.13	0.503[a]
Serum albumin (g/L)	43.17 ± 3.87	40.23 ± 5.11	0.015[a]
Left ventricle ejection fraction, %	70[60–74]	71.5[66–75]	0.332[c]
ALT	22.9[12.9–55.2]	25.8[15.4–52.4]	0.717[c]
AST	23.6[15.9–43.2]	24.9[20.5–40.8]	0.315[c]
Comorbidities			
Diabetes mellitu	3(10%)	2(28%)	0.64[b]
Hypertension	8(26.7%)	10(33.3%)	0.573[b]
Coronary artery disease	2(6.7%)	0(0%)	0.15[b]
Pulmonary hypertension	2(6.7%)	3(10%)	0.64[b]
Smoking status (Y/N)	8(26.7%)	9(30%)	0.774[b]
ASA physical status ≥ III	20/10	22/8	0.573[b]
NYHA Class	3[2–3]	3[2–3]	NA
Type of surgery			
Pancreatic	3(10%)	4(13.3%)	0.688[b]
Hepatobiliary	14(46.7%)	14(26.7%)	NA
Bile duct or gallbladder	2(6.7%)	2(6.7%)	NA
Gastric	11(36.7%)	10(33.3%)	0.787[b]
Laparoscopic	20(66.7%)	21(70%)	0.781[b]
Laparotomy	10(33.3%)	9(30%)	0.781[b]
Duration of anesthesia (min)	330.27 ± 127.28	321.53 ± 94.13	0.764[a]
Duration of surgery (min)	264.3 ± 112.92	254.87 ± 84.83	0.716[a]
Total fluid volume (mL)	1875[1587–2312]	1775[1350–2100]	0.263[c]
Crystalloid (ml)	796.67 ± 288.08	735 ± 360.83	0.709[c]
Colloid (ml)	869[713–1225]	912[708–1013]	0.313[c]
Estimated blood loss (mL)	136[57–234]	103[54–170]	0.145[c]
Infusion of blood product	5(16.7%)	6(20%)	0.739[b]
Urine output (mL)	325[263–515]	514[199–827]	0.464[c]
Vasoactive drugs needed (Y/N)	23/7	18/12	0.165[b]
Ephedrine(mg)	9.50 ± 7.60	7.50 ± 7.78	0.318[a]
Ehenylephrine(ug)	64.00 ± 62.40	59.00 ± 63.64	0.760[a]
Norepinephrine(ug)	0.53 ± 1.66	0.40 ± 0.81	0.610[a]
Dopamine(mg)	0	0	NA
Adrenaline(ug)	0	0	NA

Data are expressed as mean ± standard deviation, number (percentage), or median (interquartile range)

Abbreviations: TEA, thoracic epidural anesthesia; BMI, body mass index; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable

Statistical tests used: [a]Two independent samples t test; [b]χ2 test; [c]Mann-Whitney U test

Table 2 Primary outcome, minimum ΔP after PEEP titration and individualized PEEP

Variables	TEA group (*n* = 30)	Control group (*n* = 30)	*P* value
Primary outcome			
Minimum ΔP (cmH_2O)	11.23 ± 2.19	12.67 ± 2.70	0.028
Method of Surgery			
Minimum ΔP for laparoscopic surgeries (cmH_2O)	11.95 ± 1.91	13.57 ± 2.44	0.023
Minimum ΔP for laparotomy surgeries (cmH_2O)	9.80 ± 2.10	10.56 ± 2.07	0.439
Individualized PEEP	9.00[8.00–10.00]	9.00[8.00–10.00]	0.844
Method of Surgery Individualized PEEP for laparoscopic surgeries (cmH_2O)	9.50[9.00–10.00]	10.00[9.00-10.50]	0.512
Individualized PEEP for laparotomy surgeries (cmH_2O)	7.50[6.75-8.00]	7.00[7.00-8.50]	0.497

Data are expressed as mean ± standard deviation. TEA, thoracic epidural anesthesia; ΔP, driving pressure; PEEP, positive end-expiratory pressure

Table 2; Fig. 2). The optimal individualized PEEP between the groups was 9 [8–10] cmH_2O for the TEA group versus 9 [7–10] cmH_2O for the control group, there was no statistical difference in individualized PEEP after titration between the two groups (Table 2; Fig. 2).

Secondary outcomes

Within seven days postoperatively, there was no statistically significant difference in clinically meaningful PPCs between the TEA group and the control group (8 of 30 [26.7%] vs. 12 of 30 [40%]; $P=0.273$; Supplementary Table 2). The most common type of complication was atelectasis (TEA group, $n=5$; control group, $n=12$). The incidence of postoperative atelectasis in the TEA group was significantly lower than in the control group (16.7% vs. 40%; $P=0.045$; Supplementary Table 2). There were no statistically significant differences in length of hospital stay, 30-day mortality rate, and ICU admission rate between the groups (Supplementary Table 2).

At T1 (primary outcome) and T3, the ΔP in the TEA group was significantly lower than in the control group (T1: 11.95 ± 1.91 cmH_2O vs. 13.57 ± 2.44 cmH_2O; $P=0.023$; T3: 12.35 ± 1.60 cmH_2O vs. 14.00 ± 2.10 cmH_2O; $P=0.007$; Supplementary Table 3), with no statistical difference between the two groups in minimum ΔP at T2 (Supplementary Table 3). The C_{RS} in the TEA group was higher than in the control group at T1, T2 and T3. There were no differences between the groups in individualized PEEP after titration, P_{plat}, and P_{peak} at T1, T2 and T3 (Supplementary Table 3). Arterial blood gas analysis conducted 30 min after titration completion showed

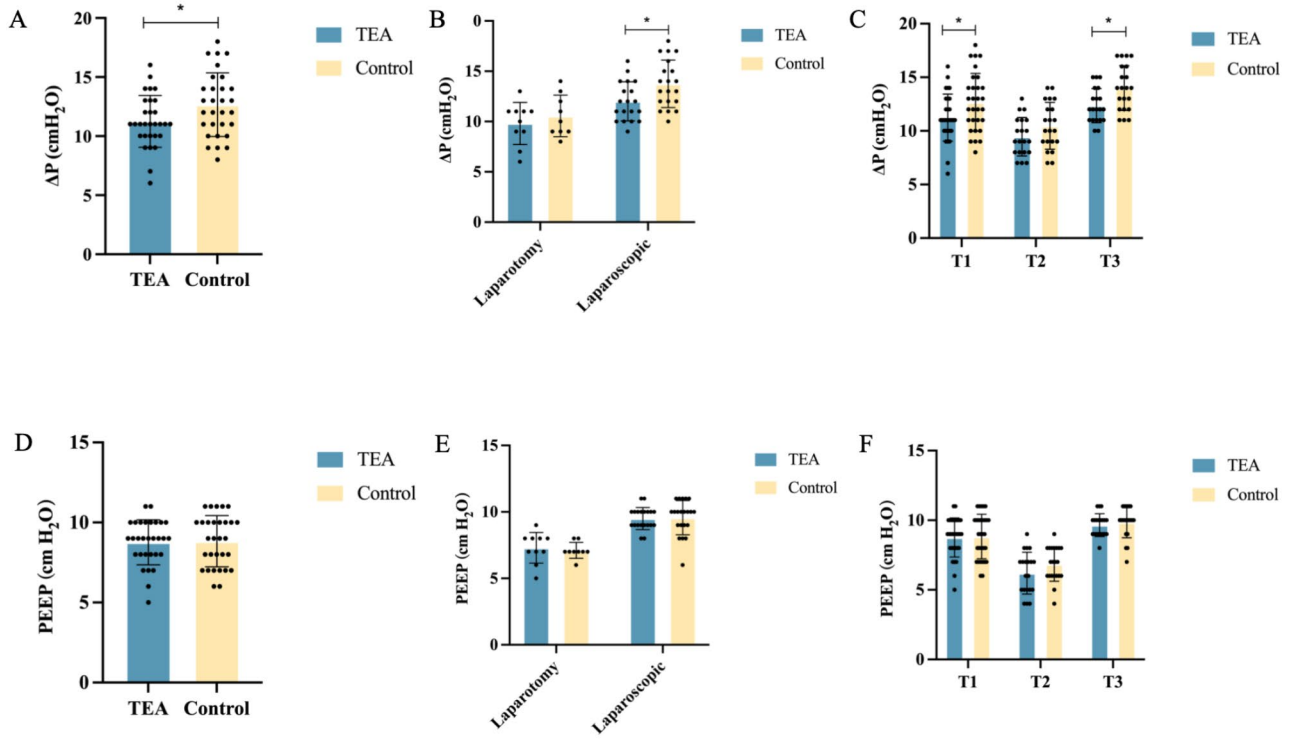

Fig. 2 Variables for ΔP and individualized PEEP. (**A**) ΔP; (**B**) ΔP under different surgical methods (laparotomy/laparoscopic); (**C**) ΔP under different time points; (**D**) individualized PEEP; (**E**) PEEP under different surgical methods (laparotomy/laparoscopic); (**F**) PEEP at different time points. Data are represented as mean ± SD. *, $P < 0.05$ versus the control group; T1, first titration; T2, when pneumoperitoneum is stopped for open specimen retrieval; T3, when pneumoperitoneum is re-established for intraperitoneal hemostasis

Table 3 Multiple linear regression model of the correlation between age, BMI, TEA application, sex, surgical method, preoperative cardiopulmonary comorbiditiesand minimum ΔP

Variables	B	*P* value	R^2	Constant	VIF	Durbin-Watson
Age	0.077	0.000	0.565	5.356	1.905	1.539
BMI	0.081	0.257			1.154	
TEA application	-1.289	0.008			1.049	
Sex	-0.672	0.156			1.046	
Surgical method	2.104	0.000			1.159	
Preoperative comorbidities	0.173	0.781			1.864	

Abbreviations: BMI, body mass index; TEA, thoracic epidural anesthesia; ΔP, driving pressure; B, unstandardized beta coefficient

that PaO_2 in the TEA group was significantly higher than in the control group (FiO_2: 0.4–0.8; 322.67 ± 67.083 vs. 283.33 ± 75.249; $P = 0.037$; Supplementary Table4).

Multiple linear regression analysis

In the multiple linear regression analysis, variables considered potentially related to the minimum driving pressure included age, BMI, gender, TEA application, type of surgery, and preoperative comorbidities, resulting in an adjusted R^2 of 0.565. The results indicated that variables significantly associated with minimum driving pressure were the application of TEA (compared to no intraoperative TEA use; unstandardized beta coefficient (B) = -1.289; $P = 0.008$; Table 3), age (B = 0.077; $P = 0.000$; Table 3), and surgical method (compared to laparotomy; B = 2.104; $P = 0.000$; Table 3), $R^2 = 0.565$.

Univariate and multivariate logistic regression analysis

Univariate logistic regression analysis revealed that variables significantly associated with PPCs included ΔP, age, smoking history, Preoperative comorbidities and left ventricular ejection fraction (LVEF) (Supplementary Table 5; Fig. 3A). Multivariate logistic regression analysis showed that driving pressure was the only variable significantly associated with PPCs. (Adjusted Odds Ratio [OR] = 2.190; 95% CI: 1.300 to 3.689; $P = 0.003$; Supplementary Table 5; Fig. 3B). For all patients (laparotomy/laparoscopic), the area under the ROC curve (AUC) for ΔP predicting PPCs was 0.83. The cut-off value for ΔP associated with the

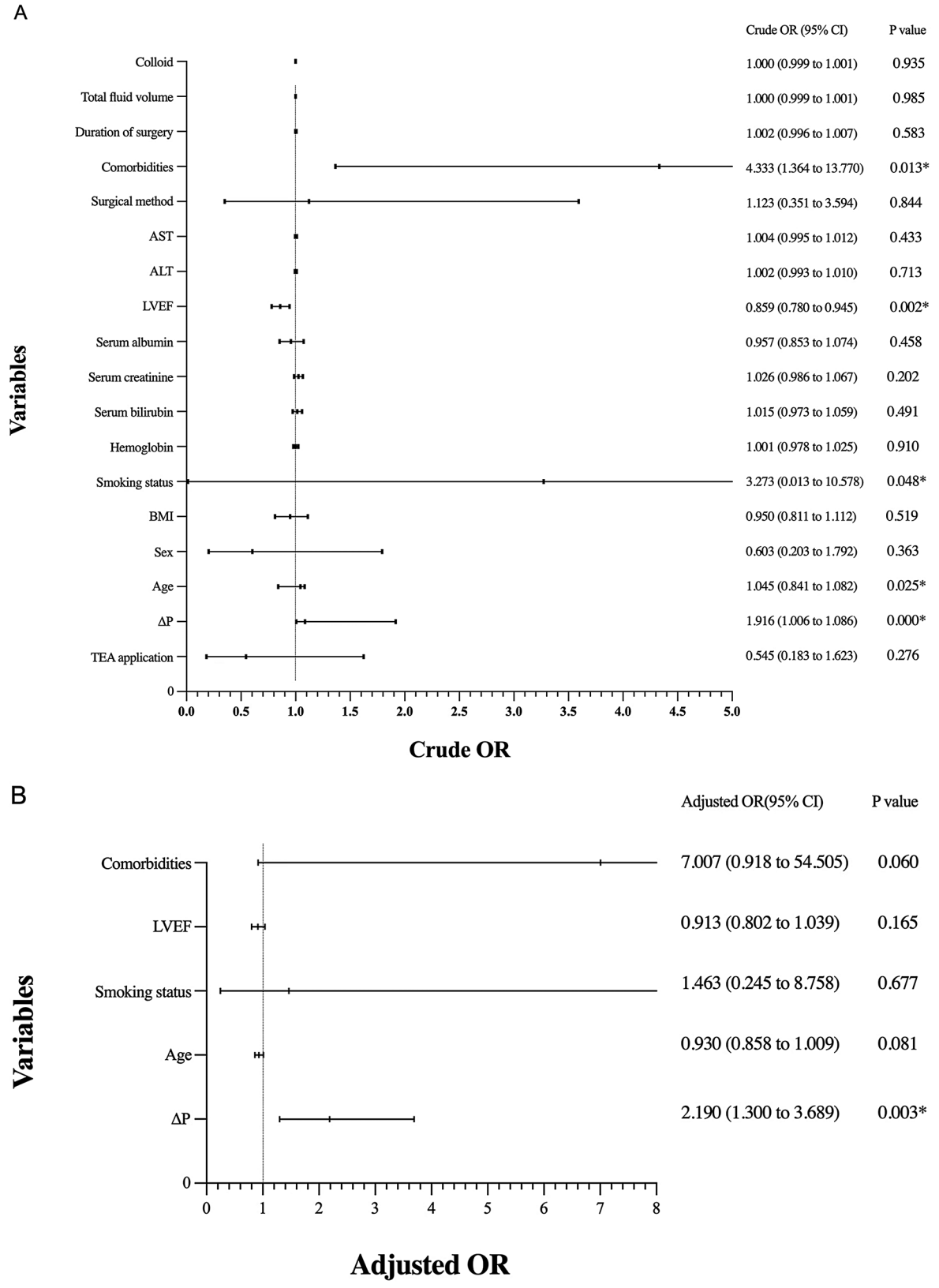

Fig. 3 Forest plot of the results of the univariate and multivariate logistic regression model of factors associated with postoperative pulmonary complications. (**A**) Forest plot of the results of the univariate logistic regression analysis; (**B**) Forest plot of the results of the multivariate logistic regression analysis

occurrence of PPCs, identified through ROC curve analysis, was 12.5 cmH_2O (95% CI: 0.707 to 0.950; Supplementary Fig. 1).

Discussion

This prospective randomized controlled trial tested the physiological effects of TEA-GA on patients undergoing elective major upper abdominal surgery with ΔP-guided ventilation (individualized PEEP titrated to the minimum ΔP). The main findings are: (1)TEA-GA significantly reduced patients' ΔP; (2) For laparoscopic patients, the effect of TEA in reducing ΔP persisted; (3) The impact of TEA-GA and minimal ΔP on post-extubation benefits is unclear; there was no statistical difference in PPCs between the two groups, but the incidence of atelectasis was lower in the TEA group; (4) Compared to GA, TEA-GA improved oxygenation and C_{RS}; (5) TEA application and age were significantly related to ΔP, and multivariate logistic analysis revealed ΔP as the only variable associated with PPCs. (6) A significant proportion of patients required vasoactive drugs during PEEP titration, but none needed continuous infusion throughout the surgery. There were no differences between the groups in the total use of vasoactive drugs, total fluid infusion, and urine output.

Prior to our study, there were no reports comparing the impact of TEA-GA versus GA alone on patients' minimum ΔP. Therefore, our research utilized a pilot trial, enrolling ten patients per group (three laparotomy, seven laparoscopic) according to the proportion of laparoscopic surgeries at our hospital to calculate the sample size based on the difference in minimum ΔP between groups. The final patient enrollment in our study had a laparoscopic surgery ratio of TEA group vs. control group (66.7% vs. 70%, $P=0.781$, Table 1), similar to the pilot trial's laparotomy/laparoscopic ratio (67.3%), thus validating the accuracy of our pilot trial's sample size estimation. In the initial study design, we planned to conduct subgroup analyses to investigate whether the effect of TEA-GA on ΔP varied between different types of surgeries, which is why we did not exclusively include patients undergoing a single type of surgery.

Several potential mechanisms can explain the result of TEA-GA reducing ΔP. Firstly, although both groups received continuous rocuronium infusion and muscle relaxation was monitored using a nerve stimulator, the more profound motor nerve blockade produced by TEA in the TEA group could improve ΔP. Sundberg et al. demonstrated that the impact of TEA on respiratory mechanics is primarily associated with direct motor blockade of intercostal and abdominal muscles [22]. We ensured that the anesthetic level in all patients in the TEA group reached T4. The intercostal nerves, which provide chest wall sensation and coordinate the movement of external intercostal muscles, can be blocked by TEA, either in their afferent or efferent pathways (or both), resulting in paralysis of these muscles [13]. The motor blockade in intravertebra anesthesia is typically 1–4 segments lower than the sensory level, so our level would paralyze the intercostal motor nerves at least up to T8. During mechanical ventilation, this effect not only reduces the need for additional non-depolarizing muscle relaxants but more importantly, increases chest wall compliance due to a more profound motor blockade, a key factor in reducing ΔP. Moreover, while the primary mechanism of TEA is to provide central afferent nerve conduction blockade to paralyze motor nerves [13], which is different from the action of neuromuscular blocking agents at the skeletal muscle neuromuscular junction, there is evidence suggesting that local anesthetics absorbed from the epidural space into systemic circulation and reaching the intercostal neuromuscular junctions may act on motor nerve terminals [22, 23]. Local anesthetics may disrupt neuromuscular transmission by inhibiting acetylcholine release, blocking or modifying acetylcholine receptors, or directly suppressing muscle excitability, thus achieving a "pseudo-neuromuscular blocking agent" effect [24–27]. This leads to systemic stabilization of the neuromuscular junctions. The systemic absorption of local anesthetics is another contributing factor to the more severe motor nerve blockade in the TEA group. Therefore, the deeper level of muscle relaxation in the TEA group, due to direct motor nerve paralysis and systemic neuromuscular stabilization caused by the circulation of local anesthetics, resulted in higher chest wall compliance and increased lung compliance. This increased FRC is the main reason the TEA group achieved a lower ΔP compared to the control group.

The clinical benefits of TEA can be partly explained by the physiological impacts of afferent nerve conduction blockade on various aspects of surgical pathology. The mechanism by which TEA reduces PPCs remains unclear [14], with previous hypotheses focusing on TEA's excellent analgesic effects [28], vasodilation following thoracic sympathetic nerve blockade leading to increased visceral perfusion and reduced afterload [18, 29], and potential reduction in the release of inflammatory cytokines [19]. Based on our main findings, we propose that in addition to these mechanisms, TEA may offer lung protection by reducing ΔP during mechanical ventilation (MV). ΔP provides an easily obtainable surrogate marker for lung strain that is relevant to the entire lung. The minimum ΔP, aimed at achieving maximal C_{RS}, can help avoid lung overdistention or atelectasis [30], thereby reducing the risk of volutrauma and barotrauma to the lung tissues [6, 31]. The lung-protective effect guided by minimal ΔP is reflected in this approach. Our multiple linear regression analysis significantly supports this hypothesis, with TEA

application being significantly related to the magnitude of ΔP. The initial identification of ΔP as a predictor of survival in patients with Acute Respiratory Distress Syndrome (ARDS) by Amato et al. demonstrated that P_{plat}, V_T, and PEEP do not affect survival in ARDS patients unless their changes affect ΔP. They reported a 3.4% increase in morbidity for each 1 cmH_2O increase in ΔP. [5] In patients undergoing general anesthesia with MV, Neto et al. identified ΔP as the only significant mediator in protective ventilation parameters affecting PPCs, with an odds ratio (OR) of 1.16 [4]. Zhang et al. showed that ΔP-guided ventilation significantly reduced PPCs in patients undergoing open upper abdominal surgery compared to traditional protective ventilation. [9] Although numerous studies have reported evidence of ΔP reducing PPCs, our study did not find that TEA-mediated lower ΔP significantly reduced the incidence of PPCs within seven days postoperatively. Similar to findings by Park et al. [6] (thoracic surgery) and Li et al. [32] (cardiac surgery), our results suggest that a lower ΔP does not substantially reduce PPCs. This could be due to the inclusion of both laparotomy and laparoscopic surgeries in our study, as subgroup analysis showed no significant difference in ΔP between TEA and control groups in laparotomy, but a difference in laparoscopic surgery. Amato et al. [5] proposed that ΔP has a more substantial lung-protective effect when the size of ventilated lung tissue is significantly reduced (e.g., reduced compliance, as in establishing pneumoperitoneum or even ARDS). [5] Homogenizing patient populations might yield different conclusions; further RCTs are awaited to confirm this. On the other hand, both groups in our study used postoperative PCEA. TEA has been shown to significantly increase FRC and improve the reduction in FRC, vital capacity (VC), and postoperative diaphragmatic dysfunction after abdominal surgery [33, 34]. Thus, patients in both groups might have benefited postoperatively from TEA's improvement in lung function, not resulting in significant differences in PPCs. However, we found that the incidence of postoperative atelectasis was lower in the TEA group, supporting conclusions by Mini et al. [10] and Zhang et al. [9] This suggests that the essence of minimal ΔP is still to reduce lung strain while increasing FRC and compliance, impacting morphological clinical outcomes like atelectasis. However, such morphological changes alone may not be sufficient to alter more considerable clinical outcomes like PPCs. Our study's limitation of small sample size and a 7-day postoperative observation window might not be sufficient to yield statistically significant differences, though univariate and multivariate logistic regression analysis still showed a significant association between ΔP and PPCs, highlighting the importance of larger samples on outcomes. Lastly, our inclusion of patients with healthy preoperative lungs and the homogenized use of TEA postoperatively, which has been shown to reduce pro-inflammatory cytokines (PG-2, IL-6, TNF-α, even Troponin I) in upper abdominal surgery [19], might explain why we found no differences in postoperative pulmonary infections between the groups.

Our study used a decremental PEEP titration method following lung recruitment. Spadaro et al. [37] compared incremental PEEP titration and decremental PEEP titration following lung recruitment in thoracic surgery patients. They found that both strategies improved shunt and reduced ΔP, but the decremental titration group achieved lower ΔP and increased PaO_2/FiO_2 ratio. [37] Due to the hysteresis effect in the lungs, decremental titration from a high PEEP level after lung recruitment can keep the alveoli open at lower ΔP [6]. Decremental PEEP titration following systematic lung recruitment is a more commonly used technique [38], which was the reason for our study's choice. A concern might be that lung recruitment and high PEEP could lead to alveolar overdistension and reduce cardiac output, impacting hemodynamics [39]. We limited lung recruitment (P_{plat} <30 cmH_2O) and titrated PEEP to minimize ΔP, thus reducing the risk of overdistension. However, the impact of decremental titration on hemodynamics should not be overlooked. Although previous studies suggested the hemodynamic impact of lung recruitment maneuvers during mechanical ventilation is negligible [40, 41], in our study, vasoactive drugs were still needed to maintain blood pressure, even in the control group, which did not use TEA. More than half of the patients in both groups required vasoactive drugs, mostly during titration, and it is unclear whether this was due to the titration itself, peri-intubation hypotension (PIH), TEA, preexisting comorbidities, or a combination of these factors. Fortunately, hypotension mainly occurred during the first titration and could be corrected with vasoactive drugs. After titration, neither individualized PEEP levels nor TEA application had a noticeable effect on MAP, allowing cessation of vasoactive drugs.

Although TEA not only reduced ΔP during mechanical ventilation but also improved oxygenation through sympathetic blockade and improved pulmonary blood perfusion, it is necessary to clarify TEA's safety. We must acknowledge that the need for vasoactive drugs during titration in the TEA group was partly due to TEA-induced thoracic sympathetic blockade and autonomic imbalance. A few patients experienced bradycardia, which could be improved with ephedrine, suggesting preoperative volume expansion preparation in such patients. No patients experienced severe hypotension or bradycardia requiring epinephrine correction. Additionally, TEA may impact postoperative respiratory function [13, 14], but no patients in our follow-up complained of postoperative respiratory difficulty; instead, they

were satisfied with the excellent postoperative analgesic effects. Regarding TEA's impact on postoperative respiratory function, Oh et al. reported that TEA-GA with postoperative PCEA maintained diaphragm inspiratory amplitude (DIA) unchanged postoperatively [34], while those with only GA and postoperative patient-controlled intravenous analgesia (PCIA) had significantly reduced DIA on the first postoperative day. Several studies confirm that TEA improves postoperative diaphragmatic dysfunction, enhancing diaphragmatic activity [34, 42, 43]. This might be partly due to pain relief and the transfer of respiratory effort from the thoracic muscles, partially paralyzed by TEA, to the diaphragm, the primary muscle for respiration [13]. Finally, the success rate of TEA procedures could be a lot higher. Unfortunately, there have been no significant updates in practices to improve TEA puncture success rates in recent years. Overall, with a guaranteed success rate, the safety of TEA is testable. Amato et al. demonstrated that a $\Delta P > 15$ cmH_2O is associated with increased mortality in ARDS [5], with the current safe range for ΔP estimated between 14 and 18 cmH_2O [30]. In our titration process, we observed that for patients undergoing laparotomy, ΔP levels exceeding 13 cmH_2O, and for those undergoing laparoscopic, ΔP exceeding 17 cmH_2O, correlated with C_{RS}<40 mL/cmH_2O and P_{peak} >28 cmH_2O in most cases. Using ROC curve analysis on 60 patients, we determined ΔP cut-off value of 12.5 cmH_2O, beyond which the risk of PPCs significantly increased.

Considering that C_{RS} may increase over the duration of MV, we chose subsequent time points for further reducing ΔP at T2 (when pneumoperitoneum is stopped for open specimen retrieval) and T3 (when pneumoperitoneum is re-established for intraperitoneal hemostasis). These repeated titration procedures were specific to the laparoscopic group, as no equivalent targeted time points were identified in laparotomy. We observed that ΔP decreased at T2 compared to T1 for both groups, which is understandable given the increased FRC after pneumoperitoneum cessation. However, the difference in ΔP between the two groups diminished at T2, even becoming smaller than the ΔP difference at T1 in laparotomy. Subgroup analysis showed no significant difference in ΔP between the groups during laparotomy, suggesting the significant effect of TEA in reducing ΔP may be more applicable to high-risk populations for atelectasis, such as with pneumoperitoneum or ARDS. Notably, our study included only 19 patients who underwent laparotomy, and this small sample size may limit the ability to detect statistically significant differences. We look forward to future RCTs with larger samples focused on a single surgical approach to confirm whether TEA-GA can further reduce ΔP in laparotomy patients. At T3, when pneumoperitoneum was re-established, ΔP increased compared to T1 in both groups, but the difference in ΔP between the groups remained statistically significant. A large multicenter RCT conducted by Park et al. [6] on thoracic surgery patients, involving three repeated titrations (at the start of MV, at the start of one-lung ventilation, and at re-initiation of double-lung ventilation), also found an increase in ΔP and diminishing group differences over time after 45 min of one-lung ventilation. Park et al. concluded that it is still unclear if other strategies can continuously drive and maintain the reduction of ΔP. From our study results, it seems uncertain whether there are better strategies to further reduce ΔP in prolonged MV (with our study's average surgery duration nearing 300 min). However, TEA-GA indeed provided significantly lower ΔP compared to GA alone, and this effect was enduring.

In our study, nearly two-thirds of the patients underwent laparoscopic surgery, where pneumoperitoneum can significantly disrupt lung function [45]. Firstly, diaphragmatic elevation and reduced thoracic volume lead to decreased C_{RS} and a reduction in FRC; both CRS and FRC are directly related toΔP. Additionally, increased ventilation pressures raise P_{plat} and ΔP. We found that ΔP rose by 2.15cmH_2O in laparoscopic patients in the TEA group and by 3.01cmH_2O in the control group compared to laparotomy. Logistic regression analysis confirmed that ΔP is directly associated with the incidence of PPCs. However, ΔP differences alone do not imply that the risk of PPCs in laparoscopic surgery is higher than in laparotomy, as PPCs are also influenced by postoperative pain, with laparoscopy offering a minimally invasive advantage. Nevertheless, laparoscopic patients are subject to tremendous mechanical stress and strain from intraoperative mechanical ventilation, increasing the risk of VILI compared to open surgery. Upper abdominal surgeries often employ a head-up tilt of 20°-30° (reverse Trendelenburg position), which can mitigate the effects of pneumoperitoneum. This position reduces thoracic pressure on the diaphragm, allowing it to descend, thereby expanding thoracic volume, improving FRC and C_{RS}, and ultimately reducing ΔP. If we were to include patients undergoing lower abdominal or pelvic surgeries, the minimum ΔP threshold might increase.

Our study is essential in several aspects. Firstly, the mechanism by which TEA-GA provides lung protection and reduces PPCs has yet to be determined. We introduced ΔP, a crucial respiratory mechanic parameter, and demonstrated that intraoperative application of TEA could reduce the average ΔP by 1.44 cmH_2O compared to control ΔP-guided ventilation. The results of the multiple linear regression analysis further confirmed that TEA application significantly impacts ΔP, suggesting that the benefits of TEA might be realized through lowering ΔP. Secondly, ΔP-guided ventilation is a simple yet optimized strategy for PEEP titration. Combining

this with TEA, we found that these two protective measures could significantly and enduringly reduce ΔP in patients undergoing major upper abdominal surgery. It is known that an increase of 1 cmH_2O in ΔP is associated with an increased major morbidity rate (by 3.4%) and an increased risk of PPCs. Our multivariable logistic regression analysis echoed this result, highlighting the potential clinical significance of integrating TEA with ΔP-guided ventilation to optimize patient outcomes in upper abdominal surgeries.

This study has several limitations. First, the accuracy of the results from the pilot trial might not be entirely representative due to its small sample size and the fact that the proportion of laparoscopic surgeries specific to our hospital may differ in other contexts; Among the 60 patients, only 19 underwent open surgery. One limitation of a small sample size is that it may be insufficient to detect statistically significant differences. This insight provides direction for future studies, suggesting either the inclusion of patients with a single surgical approach or grouping by surgical type to further investigate the effect of TEA combined with general anesthesia on the minimum ΔP. This suggests future research directions, such as focusing on a single surgical method or considering the surgical approach as a factor in studying the impact of TEA-GA on ΔP. Second, we didn't perform subsequent ΔP reductions in laparotomy surgery patients due to unstandardized time points and a smaller number of these patients, which makes it challenging to assess whether interventions could have a long-term significant impact on ΔP in these cases. Third, the timing for retitration of PEEP was based on key surgical moments, and changes in C_{RS} over time necessitate further investigation to identify optimal PEEP titration timing in major upper abdominal surgeries. Fourth, our decision to use decremental PEEP titration, though based on referenced studies, may lead to different outcomes in optimal PEEP and ΔP due to differences in patient populations and surgical methods. The 6–8 ml/kg IBW V_T was chosen based on lung-protective ventilation guidelines. However, a lower V_T might be more appropriate for patients with individualized PEEP undergoing major upper abdominal surgeries. Fifth, although we tested the sensory level of TEA in patients before anesthesia induction to ensure it reached T4, we could not measure the sensory level of TEA during general anesthesia. Fluctuations in the anesthesia level could potentially interfere with the measurement of ΔP. Sixth, our PCEA protocol was continued for three days postoperatively, during which most patients reported satisfactory analgesic effects. Since the observation window for PPCs extended to seven days post-surgery, we did not monitor pain levels beyond the PCEA period. Any differences in pain levels after this timeframe could potentially interfere with the measurement of PPCs outcomes. Seventh, we believe that the mechanism by which TEA reduces ΔP is primarily related to its alteration of chest wall compliance. Factors influencing ΔP include both lung and chest wall compliance. Regarding the compliance of the lungs themselves, the blocking effect of TEA on visceral nerves may also have an impact. However, this may require direct assessment of transpulmonary pressure, which we did not measure in our patients. Finally, considering the potential for technical errors in postoperative lung function tests due to patient fatigue and lack of cooperation, which could reduce the accuracy of these tests, we did not conduct lung function tests after surgery. As a result, we could not determine if there were differences in lung function between the groups. Therefore, we did not quantitatively assess the safety of using TEA in the enrolled patients.

Conclusion

In conclusion, combining TEA-GA and ΔP-guided ventilation significantly reduces ΔP and improves oxygenation compared to using GA with ΔP-guided ventilation alone. This approach does not cause significant harm in patients undergoing major upper abdominal surgery, such as hemodynamic fluctuations. The lower ΔP did not impact PPCs, when using ΔP-guided ventilation in clinical practice, it is important to be aware of the limitations of the specific equations and values used, and consider their impact on patient outcomes. The lung-protective mechanism of TEA may be realized through the reduction of ΔP. Further research is needed to validate the value of combining TEA with ΔP-guided ventilation in other surgical settings.

Abbreviations

ASA	American Society of Anesthesiologists
ARDS	Acute Respiratory Distress Syndrome
ARM	Alveolar recruitment maneuver
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BIS	Bispectral Index
B	Unstandardized Beta Coefficient
C_{RS}	Respiratory System Compliance
CVP	Central Venous Pressure
CI	Confidence Interval
CONSORT	Consolidate Standards of Reporting Trials
ΔP	Driving Pressure
DLV	Double Lung Ventilation
DIA	Diaphragm Inspiratory Amplitude
DBP	Diastolic Blood Pressure
$EtCO_2$	End Tidal Carbon Dioxide
EPCO	European Perioperative Clinical Outcome
EIT	Electrical Impedance Tomography
FRC	Functional Residual Capacity
FiO_2	Fraction of Inspired Oxygen
GA	General Anesthesia
IBP	Invasive Blood Pressure
IBW	Ideal Body Weight
ICU	Intensive Care Unit
LPV	Lung Protective Ventilation
LVEF	Left Ventricular Ejection Fraction

MAP	Mean Arterial Pressure
MP	Mechanical Power
NA	Not Applicable
OR	Odds Ratio
PEEP	Positive End-Expiratory Pressure
PPCs	Postoperative Pulmonary Complications
PaO_2	Arterial Partial Pressure of Oxygen
P_{plat}	Plateau Pressure
P_{peak}	Peak Airway Pressure
PACU	Postanesthesia Care Unit
PIH	Peri-intubation Hypotension
RCT	Randomized Controlled Trial
RR	Respiratory Rate
SBP	Systolic Blood Pressure
TEA-GA	General anesthesia combined with thoracic epidural anesthesia
TEA	Thoracic Epidural Anesthesia
TOF	Train-Of-Four
TOFR	The ratio of the fourth twitch to the first twitch in the TOF response
VT	Tidal Volume
VC	Vital Capacity
VILI	Ventilator-Induced Lung Injury

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02808-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

The authors would like to thank statistician Xiaoye He for her indispensable help in data analysis. In addition, the author Dr. Xuan Li wants to thank, in particular, the accompany and support from Xinyi He over the past months. I miss the feeling of being accompanied at that time, then you appear, at the moment when I most need encouragement. Although now i'm just passing through, that the past will exist in another form in my life.

Author contributions

XL, YF and JH: Conceptualization, Methodology, Writing–original draft. XL, YY, QY, YZ: Investigation; Methodology; Project administration. XL, YY, YF: Supervision; Validation; Visualization. All authors contributed to the article and approved the submitted version.

Funding

The authors are particularly grateful to the financial support by Science and Technology Department of Yunnan Province project fund (Grant No: 202401AY070001-230; 202101AY070001-133).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki, ethical approval for this study ([2022] Ethics L No. 309) was provided by the Ethics Committee of The First Affiliated Hospital of Kunming Medical University, on December 29, 2022.

Competing interests

The authors declare no competing interests.

Concent for publication

Not applicable.

CONSORT guidelines

This study adhered to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines [44]. The CONSORT checklist related to the study can be found in the supplementary files.

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Received: 18 August 2024 / Accepted: 12 November 2024
Published online: 27 November 2024

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