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ORIGINAL ARTICLE

Effects of positive end-expiratory pressure/recruitment manoeuvres compared with zero end-expiratory pressure on atelectasis in children

A randomised clinical trial

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BACKGROUND Atelectasis is a common postoperative complication. Peri-operative lung protection can reduce atelectasis; however, it is not clear whether this persists into the postoperative period.

OBJECTIVE To evaluate to what extent lung-protective ventilation reduces peri-operative atelectasis in children undergoing nonabdominal surgery.

DESIGN Randomised, controlled, double-blind study.

SETTING Single tertiary hospital, 25 July 2019 to 18 January 2020.

PATIENTS A total of 60 patients aged 1 to 6 years, American Society of Anesthesiologists physical status 1 or 2, planned for nonabdominal surgery under general anaesthesia ($\leq$2 h) with mechanical ventilation.

INTERVENTIONS The patients were assigned randomly into either the lung-protective or zero end-expiratory pressure with no recruitment manoeuvres (control) group. Lung protection entailed 5 cmH_2O positive end-expiratory pressure and recruitment manoeuvres every 30 min. Both groups received volume-controlled ventilation with a tidal volume of 6 ml kg^{-1} body weight. Lung ultrasound was conducted before anaesthesia induction, immediately after induction, surgery and tracheal extubation, and 15 min, 3 h, 12 h and 24 h after extubation.

MAIN OUTCOME MEASURES The difference in lung ultrasound score between groups at each interval. A higher score indicates worse lung aeration.

RESULTS Patients in the lung-protective group exhibited lower median [IQR] ultrasound scores compared with the control group immediately after surgery, 4 [4 to 5] vs. 8 [4 to 6], (95% confidence interval for the difference between group values −4 to −4, Z = -6.324) and after extubation 3 [3 to 4] vs. 4 [4 to 4], 95% CI −1 to 0, Z = −3.161. This did not persist from 15 min after extubation onwards. Lung aeration returned to normal in both groups 3 h after extubation.

CONCLUSIONS The reduced atelectasis provided by lung-protective ventilation does not persist from 15 min after extubation onwards. Further studies are needed to determine if it yields better results in other types of surgery.

TRIAL REGISTRATION Chictr.org.cn (ChiCTR2000033469).

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Introduction

Postoperative pulmonary complications (PPCs) are common in adult patients undergoing surgery, with an incidence of 11 to 59%, and it leads to prolonged hospitalisation, lower long-term survival and even death.[1–5] In recent years, in order to accelerate the rehabilitation of surgical patients, the concept of intraoperative lung-protective ventilation has attracted increasing attention. However, it has yielded inconsistent results. It is not clear whether the temporary gains in either lung mechanics or oxygenation using lung-protective ventilation persist into the postoperative period, even when performed shortly before extubation.

In adults, lung recruitment ventilation has been demonstrated as effective in reducing pulmonary complications after cardiac surgery,[6] surgery in obese patients[7,8] and

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endoscopic surgery,[9,10] as well as in increasing oxygenation[11,12] However, adequate positive end-expiratory pressure (PEEP) was demonstrated as sufficient to minimise atelectasis in patients undergoing nonabdominal surgery without the need for lung recruitment.[13] Additionally, compared with low PEEP ($\leq$2 cm H_2O), high PEEP (12 cm H_2O) combined with lung recruitment during open abdominal surgery does not protect against PPCs.[14] In one study, an increase in driving pressure resulting from increased PEEP was related to a greater degree of PPCs.[15]

It remains controversial whether lung-protective ventilation is protective against PPCs in healthy American Society of Anesthesiologists (ASA) physical status 1 or 2 paediatric patients; this constitutes the core of the debate on the utility of intra-operative protective ventilation.[16]

In paediatrics, lung-protective ventilation has been proved useful in improving oxygenation[17] as well as reducing the incidence of anaesthesia-induced atelectasis.[18–20] However, its beneficial effects on postoperative atelectasis remain unclear.[20]

Although computed tomography (CT) of the chest has become the gold standard for lung examination, it is not optimal for routine examination of critically ill patients due to risks posed by the radiation and the required transportation of patients. Compared with chest radiography and CT, lung ultrasound is simple, noninvasive and time- and cost-effective, making it suitable for monitoring changes in lung ventilation.[21] In this trial, the efficacy of lung-protective ventilation in children at low risk of atelectasis was evaluated by monitoring the changes in lung aeration during both the intra-operative and postoperative periods. The primary outcome of our study was lung ultrasound score (LUS) after extubation. The secondary outcomes were other respiratory complications, systemic complications and a failure to recover sufficiently to be discharged from hospital after 2 days.

Methods

The study was conducted in accordance with the Declaration of Helsinki[22] after approval by the ethics committee of Shanghai Children's Hospital, Shanghai, China on 24 July 2019 (approval number: 2019R044-F01). The trial was registered at chictr.org.cn (trial number: ChiCTR2000033469). Written informed consent was obtained from the parents or guardians of the children. This single-centre, prospective randomised controlled trial was conducted at a tertiary teaching children's hospital affiliated to Shanghai Jiao Tong University in China from 25 July 2019 to 18 January 2020. The enrolment and allocation of patients is summarised in the CONSORT flow diagram (Fig. 1).

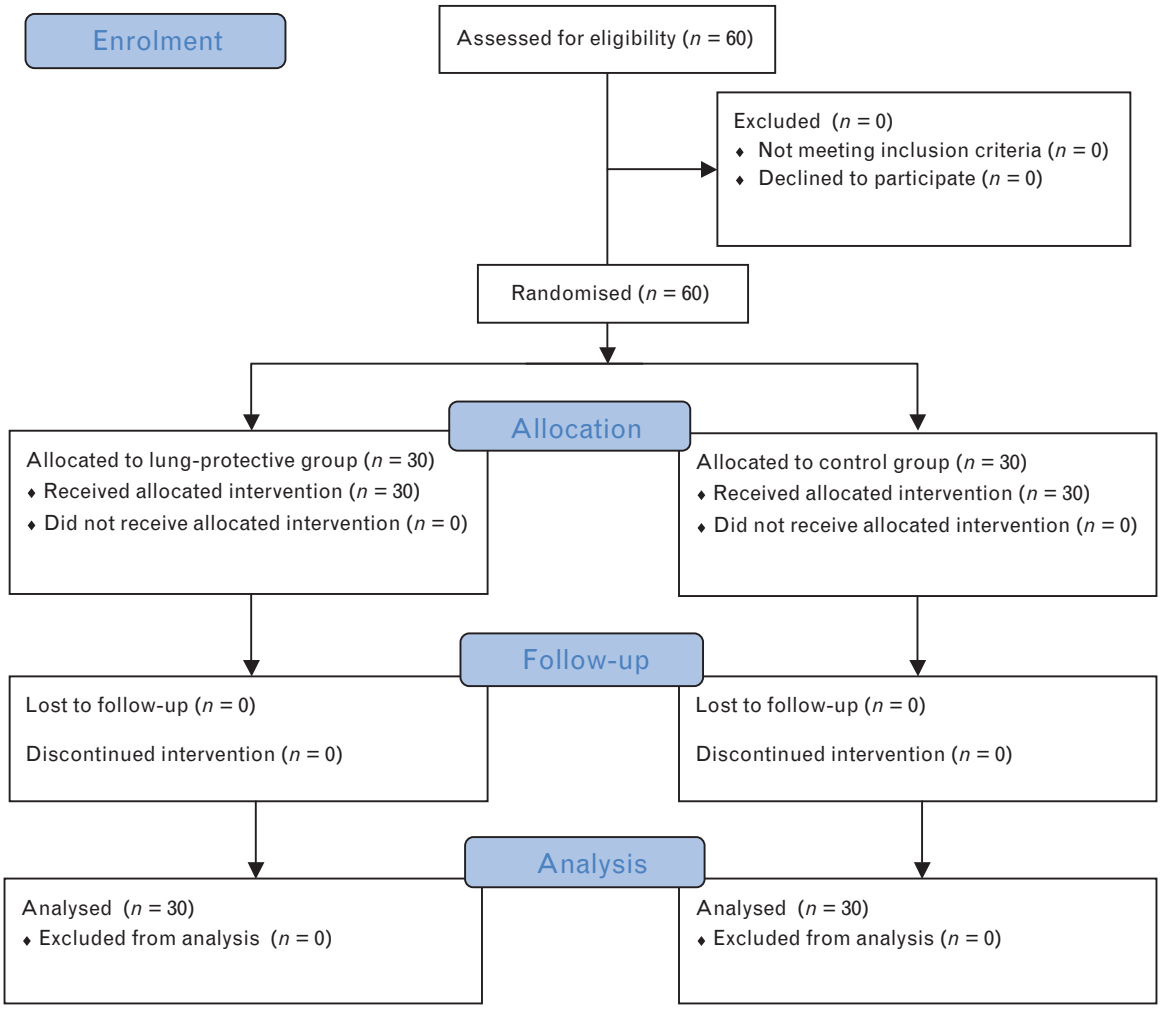
Healthy ASA 1 or 2 paediatric patients aged 1 to 6 years who received mechanical ventilation during general anaesthesia ($\leq$2 h) for nonabdominal surgery were included. The exclusion criteria were ASA physical status higher than 2, planned surgery expected to last >2 h, pre-operative oxygen saturation (SpO_2) <96%, respiratory infection within 2 weeks before surgery, pulmonary comorbidity, pre-operative anaemia, abdominal and/or chest surgery, emergency surgery, pre-operative lung ultrasound abnormality, overweight or obese patients or participation in other trials.

Computer-generated sealed-envelope randomisation was performed to assign patients in a 1 : 1 ratio to one of two parallel arms, receiving different mechanical ventilation protocols: lung-protective ventilation or zero end-expiratory pressure (control; with no recruitment manoeuvres). One investigator (SZ) opened the envelopes and carried out the different mechanical ventilation protocols. That investigator did not participate in other aspects of the trial. The Patients and Data Safety and Monitoring Board were also blinded to the random allocation.

Each patient underwent the first lung ultrasound in the preparation room before anaesthesia induction and those with lung ultrasound abnormalities were excluded from the study. The patients were monitored continuously using ECG, pulse oximetry, capnography, noninvasive measurement of blood pressure and the bispectral index (BIS) (Medtronic plc, Dublin, Ireland). All patients received a standardised general anaesthetic protocol that included pre-oxygenation (without continuous positive airway pressure), intravenous fentanyl 2 $\mu g\,kg^{-1}$, propofol 3 $mg\,kg^{-1}$, rocuronium 0.6 $mg\,kg^{-1}$ and tracheal intubation with a cuffed tracheal tube of appropriate size when the BIS was lower than 60 and the jaw was relaxed. The pressure of the tracheal intubation cuff was maintained at 20 to 30 cmH_2O. All patients received only crystalloid fluids 6 to 10 $ml\,kg^{-1}\,min^{-1}$ during the operation. Propofol was used for maintenance of anaesthesia. The neuromuscular block was reversed before emergence using intravenous neostigmine 0.05 $mg\,kg^{-1}$ and atropine 0.02 $mg\,kg^{-1}$. All patients received volume-controlled ventilation using the same type of mechanical ventilator (Avance CS2; GE Healthcare, Milwaukee, Wisconsin, USA). Lung recruitment manoeuvres were performed before tracheal extubation only in the lung-protective ventilation group. The tracheal tube was removed when a train-of-four ratio of >0.9 was confirmed, when spontaneous breathing was adequate and the patient was fully awake. After extubation, patients spontaneously breathing room air were transferred supine to the postanaesthesia care unit (PACU) for 1 h of observation. Thereafter, patients were continuously monitored in the ward for 24 h postoperatively using pulse oximetry.

In the control group, the lungs were ventilated with a tidal volume of 6 $ml\,kg^{-1}$ actual body weight, with no

Fig. 1 CONSORT study flow diagram



PEEP or recruitment manoeuvres. The fraction of inspired oxygen was set to 1.0 during pre-oxygenation and 0.4 during ventilation. Air was used for maintenance and the inspiration:expiration ratio was 1 : 2 in both groups. The end-tidal partial pressure of carbon dioxide was maintained at 4.7 to 6.0 kPa (35 to 45 mmHg) by adjusting the respiratory rate in both groups.

In the protective ventilation group, the lungs were ventilated with a tidal volume of 6 ml kg^{-1} actual body weight with 5 cmH_2O PEEP. Recruitment manoeuvres were performed immediately after induction of anaesthesia, every 30 min intra-operatively, after any disconnection from the ventilator and immediately before tracheal extubation.[14] Recruitment manoeuvres were performed, in pressure-controlled mode, with a constant driving pressure of 15 cmH_2O. PEEP was increased in steps of 5 cmH_2O, from 5 to 15 cmH_2O, every three breaths. The target recruitment pressure of 30 cmH_2O was maintained for 10 breaths.[18]

The primary outcome was the LUS.[21,23–25] Lung ultrasound was performed using a Logiq e ultrasound machine (FUJIFILM SonoSite Inc., Bothell, Wisconsin, USA) with a 4 to 10 MHz linear transducer. As reported previously, peri-operative atelectasis predominantly affects the dependent and dorsal parts of the lung directly above the diaphragm.[26] Therefore, to avoid bias, all lung ultrasounds were performed in the lateral position by one anaesthetist (ZJ) and one ultrasound technician (YJ).

According to a systematic protocol for lung ultrasound examination,[21,23–25] each hemithorax was divided into anterior, lateral and posterior regions using three longitudinal lines (parasternal, anterior and posterior axillary); these were further subdivided into six regions each using two axial lines (one above the diaphragm and the other 1 cm above the nipples). The probe was placed parallel to the ribs for scanning and placed vertically for longitudinal scanning. The probe was also placed obliquely in the

longitudinal direction for maximum visibility of atelectasis near the pleura.

Lung ultrasound was performed at eight specific intervals: immediately before induction of anaesthesia (T0), immediately after induction (T1), immediately after the surgical procedure (T2), immediately after tracheal extubation (T3) and 15 min (T4), 3 h (T5), 12 h (T6) and 24 h after extubation (T7). For the LUS, we applied an aeration score from 0 to 3 that was previously described for paediatric and adult patients.[21,23–25] The four levels of aeration were as follows:

Normal aeration (N): lung sliding (the respiratory movement of the visceral pleura relative to the fixed parietal pleura) and A-lines (repetitive, horizontal reverberation artefacts generated by air within the lungs, separated by regular intervals).
Moderate loss of lung aeration (B1): multiple, well-defined B-lines (vertical, dynamic and laser-like echoic lines, originating from the pleural line or from small, subpleural consolidations reaching the lowest edge of the screen).
Severe loss of lung aeration (B2): multiple coalescent B-lines that occupy the whole lung image (so-called 'white lung').
Complete loss of aeration (C): anaesthesia-induced atelectasis, defined as localised sonographic consolidation (subpleural tissue-like pattern). Air bronchograms may be observed as hyperechoic branching structures within such consolidations.[21]

For a given thoracic area, an LUS was allocated as follows: $N = 0$, $B1 = 1$, $B2 = 2$ and $C = 3$.

The secondary outcomes were other respiratory complications, systemic complications and a failure to recover sufficiently to be discharged after 2 days. The incidence of desaturation (defined as $SpO_2 < 95\%$) was compared between the two groups during the procedure and period of ventilation, as well as in the PACU. We also assessed whether side effects, including hypotension (<80% of baseline blood pressure), were more likely following recruitment manoeuvres.

Statistical analysis

Our primary hypothesis was that the use of lung-protective ventilation would prevent the development of atelectasis during general anaesthesia. The sample size was calculated on the basis of previous studies in which the mean LUS before emergency was 4 ± 4.1 points lower in the lung-protective ventilation group compared with that in the control group.[26,27] We calculated that a total sample size of 51 patients would provide 80% power (for $\alpha = 0.05$) to detect a difference of four points between the two groups when allowing for a dropout rate of 20%.

Data are expressed as n (%), mean ± SD or median [IQR] depending on the distribution of the data. For comparisons among continuous variables, Student's t-test was used for normally distributed data and the Mann–Whitney U-test for nonnormally distributed data. Comparisons between categorical variables were performed using the χ^2-test or Fisher's exact test, as appropriate. All comparisons were two-tailed. A P value < 0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York, USA) was used for statistical analyses.

Results

Patient enrolment started on 25 July 2019. In total, 60 patients were randomly assigned to the control ($n = 30$) or lung-protective ventilation ($n = 30$) group (Fig. 1). Baseline characteristics did not differ between the groups (Table 1).

Primary outcome

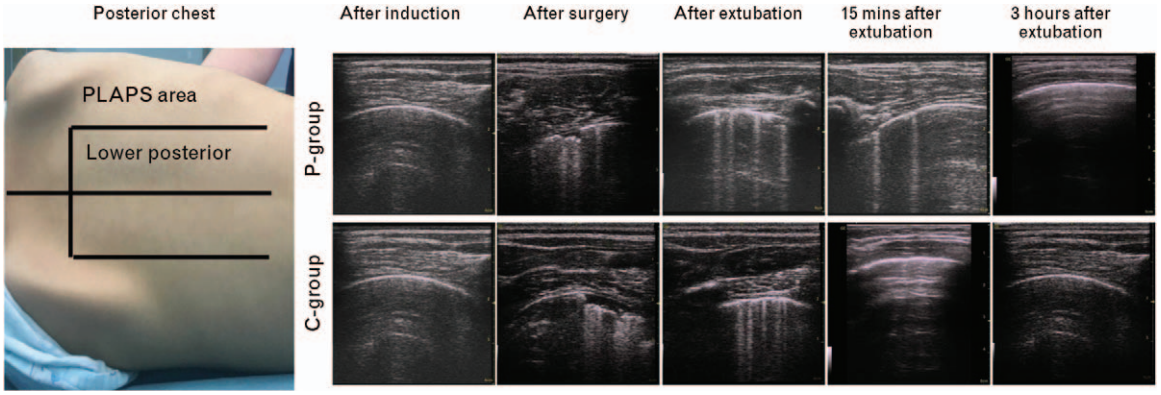
There was no difference in the LUS before (time point T0) and immediately after (time point T1) induction of

Table 1 Comparisons of baseline characteristics in both groups

	Lung-protective group ($n = 30$)	Control group ($n = 30$)
Age, months	56.0 [40.4 to 64.1]	48.7 [28.2 to 62.9]
Male/female	13/17	16/14
Body mass index, kg m^{-2}	15.1 [14.8 to 15.4]	15.2 [14.9 to 15.5]
ASA physical status		
1	20	26
2	10	4
Type of surgery		
Concealed penis repair	15	12
Fracture	5	7
Torticollis surgery	1	3
Inguinal hernia repair	1	2
Thyroglossal duct cyst operation	3	1
Strabismus surgery	5	5
Duration of surgery, min	57.7 ± 16.1	64.4 ± 14.1
Mechanical ventilation duration, min	81.2 ± 17.0	87.5 ± 14.6
PACU stay, min	43.7 ± 7.0	44.5 ± 5.0

Values are mean ± SD, mean (range), median [IQR] or number. ASA, American Society of Anesthesiologists; PACU, postanaesthesia care unit.

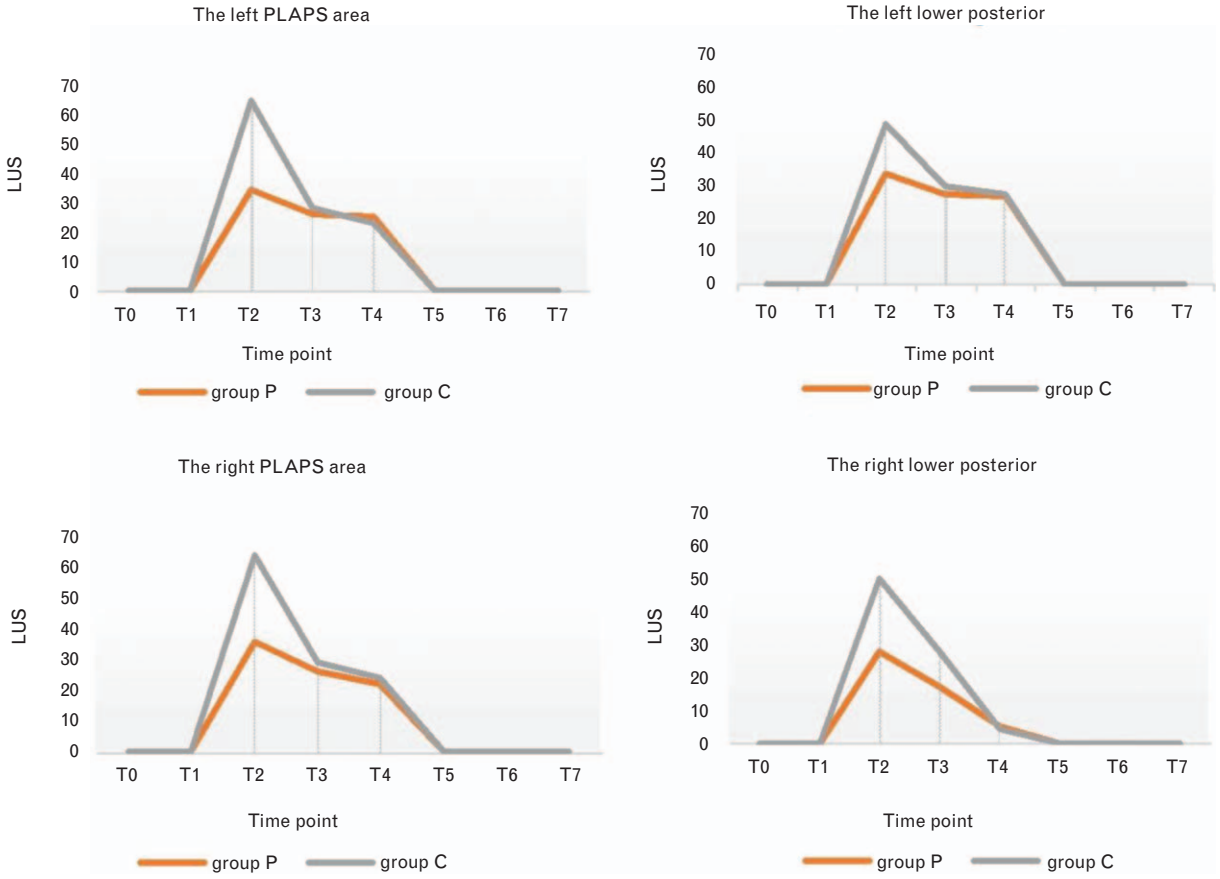
Fig. 2 Lung ultrasound images of one representative patient in the posterior chest wall at different time points



C-group, control group; P group, lung-protective ventilation group. See text for details.

anaesthesia in either group. After induction of anaesthesia, lung aeration deteriorated in both groups. The LUS was higher in the control group immediately after surgery (time point T2, 8 [4 to 6] vs. 4 [4 to 5], 95%CI for the difference between group values (−4 to −4), $Z = -6.324$) and after extubation (time point T3, 4 [4 to 4] vs. 3 [3 to 4]), 95% CI (−1 to 0), $Z = -3.161$] than in the protective ventilation group. Lung aeration improved in both groups

Fig. 3 Temporal evolutions of the lung ultrasound score



T0, before induction of anaesthesia; T1, after induction; T2, immediately after surgery; T3, immediately after extubation; T4, 15 min after extubation; T5, 3 h after extubation; T6, 12 h after extubation; T7, 24 h after extubation; group C, control group; group P, lung-protective ventilation group. PLAPS, posterolateral alveolar and/or pleural syndrome.

Table 2 Temporal evolution of lung ultrasound score in posterolateral alveolar and/or pleural syndrome and lower posterior area

LUS score	Lung protective group ($n = 30$)	Control group ($n = 30$)	Z	95% CI
Left PLAPS area				
Pre-operative	0 [0 to 0]	0 [0 to 0]	0	0
After anaesthesia induction	0 [0 to 0]	0 [0 to 0]	0	0
Immediately after surgery	1 [1 to 1]	2 [1 to 3]	−5.431	−1 to −1
Immediately after intubation	1 [1 to 1]	1 [1 to 1]	−0.853	0 to 0
15 min after intubation	1 [1 to 1]	1 [0.75 to 1]	−0.640	0 to 0
3 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
12 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
24 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
Left lower posterior area				
Pre-operative	0 [0 to 0]	0 [0 to 0]	0	0
After anaesthesia induction	0 [0 to 0]	0 [0 to 0]	0	0
Immediately after surgery	1 [1 to 1]	1 [1 to 2]	−3.207	−1 to 0
Immediately after intubation	1 [1 to 1]	1 [1 to 1]	−1.026	0 to 0
15 min after intubation	1 [1 to 1]	1 [1 to 1]	−0.399	0 to 0
3 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
12 h after extubation	0 [0 to 0]	0 [0 to 0]		
24 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
Right PLAPS area			0	0
Pre-operative	0 [0 to 0]	0 [0 to 0]	0	0
After anaesthesia induction	0 [0 to 0]	0 [0 to 0]	0	0
Immediately after surgery	1 [1 to 1]	2 [2 to 3]	−5.049	−1 to −1
Immediately after intubation	1 [1 to 1]	1 [1 to 1]	−1.209	0 to 0
15 min after intubation	1 [0 to 1]	1 [1 to 1]	−0.605	0 to 0
3 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
12 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
24 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
Right lower posterior area				
Pre-operative	0 [0 to 0]	0 [0 to 0]	0	0
After anaesthesia induction	0 [0 to 0]	0 [0 to 0]	0	0
Immediately after surgery	1 [1 to 1]	2 [1 to 2]	−4.179	−1 to 0
Immediately after intubation	1 [0 to 1]	1 [1 ti 1]	−3.252	−1 to 0
15 min after intubation	0 [0 to 0]	0 [0 to 0]	−0.359	0 to 0
3 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
12 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
24 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
Posterior chest regions				
Pre-operative	0 [0 to 0]	0 [0 to 0]	0	0
After anaesthesia induction	0 [0 to 0]	0 [0 to 0]	0	0
Immediately after surgery	4 [4 to 5]	8 [4 to 6]	−6.324	−4 to −4
Immediately after intubation	3 [3 to 4]	4 [4 to 4]	−3.161	−1 to 0
15 min after intubation	3 [2 to 3]	3 [2 to 3]	−0.390	0 to 0
3 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
12 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0
24 h after extubation	0 [0 to 0]	0 [0 to 0]	0	0

LUS scores are median [IQR]. PLAPS, posterolateral alveolar and/or pleural syndrome.

15 min after extubation, with no difference between the two groups (time point T4, 3 [2 to 3] vs. 3 [2 to 3], 95% CI (0 to 0), $Z = -0.390$). Lung aeration returned to normal (LUS = 0) from 3 h after extubation in both groups. Temporal ultrasound images in the posterior chest wall are displayed in Figure 2. Temporal evolutions of the LUS per group are indicated in Figure 3. LUSs are summarised in Table 2.

Secondary outcomes

No other intra- or PPCs or hypoxaemia were observed in either group. All patients recovered sufficiently to be discharged after 2 days. A total of 23 patients in the lung-protective ventilation group developed arterial hypotension and required vasopressors during the recruitment manoeuvres. All episodes of arterial hypotension were transient and arterial blood pressure was restored soon after recruitment.

Discussion

Our randomised controlled trial demonstrated that atelectasis was the most common pulmonary complication in healthy ASA 1 or 2 paediatric patients. Aeration loss peaked immediately after tracheal extubation. Aeration gradually improved thereafter and was fully restored 3 h after extubation, irrespective of the intra-operative ventilation strategy. Lung-protective ventilation yielded better aeration compared with nonlung-protective ventilation after surgery was completed; however, the benefit was not significant from 15 min after extubation onwards. Furthermore, recruitment manoeuvres can lead to haemodynamic instability. Therefore, drawing conclusions

regarding the importance of an intra-operative lung-protective ventilation strategy for children at low risk for atelectasis is challenging.

The results of our study allow for more comprehensive interpretation of the findings of two trials performed with children and infants, in which tidal volumes of 6 and 8 ml kg^{-1}, as well as 5 cm H_2O PEEP, were compared with a lung-protective strategy using recruitment manoeuvres.[18,24] Those trials demonstrated that the lung-protective strategy lowered the incidence of atelectasis during capnoperitoneum and at the end of surgery. However, the design of those trials did not allow for the provision of information on the progression of atelectasis after extubation. As a result, those trials did not clarify whether the observed benefits were short or long lived.[10,18] Therefore, we designed the present trial to allow us to track the evolution of atelectasis until 24 h after surgery. We revealed that intra-operative lung-protective ventilation decreased aeration loss during general anaesthesia, but that this effect did not persist after tracheal extubation. Another study demonstrated that recruitment manoeuvres could reduce the incidence of atelectasis in anaesthetised children.[28] However, all subjects in that study breathed spontaneously during the procedure. Tidal volume cannot be controlled when patients breathe spontaneously while inhaling sevoflurane. A different tidal volume might have affected the atelectasis. Therefore, their result should be interpreted with caution. To date, it is not clear whether temporary improvements in either lung mechanics or oxygenation gained using recruitment manoeuvres persist into the postoperative period, even when the manoeuvres are performed shortly before extubation.[29] Hence, we suggest that recruitment manoeuvres should be utilised only when clearly indicated.

Low tidal volume is the important part of the lung-protective strategy. In one study, stress and strain of mechanically ventilated patients with acute respiratory failure were decreased during anaesthesia by reducing tidal volume from 10 or 15 to 6 ml kg^{-1} ideal body weight.[30] For patients with acute respiratory failure, end-expiratory lung volume (EELV) is very low (baby lung).[31] A tidal volume of 10 ml kg^{-1} could cause a substantial increase in strain in such cases, leading to lung injury. However, for healthy subjects during anaesthesia, EELV was reduced by an average of 0.41, which caused an increase in strain of no more than 21 to 29%.[14]

Thus, a concept derived from patients in intensive care may not be of similar importance in patients with healthy lungs undergoing anaesthesia.

Our study has several strengths. In previous studies, lung ultrasound evaluation was performed usually before or shortly after tracheal extubation; however, the change in LUS was not reported. In this study, we chose eight time points, from anaesthesia induction to 24 h after surgery, and observed the dynamic changes of lung ultrasound images under different ventilation protocols. The occurrence and progression of atelectasis at different time points and in different lung regions were investigated. We discovered that atelectasis was short lived, even when the lung-protective ventilation strategy was not applied, and it did not cause a decline in oxygenation. Lung recruitment can improve ventilation at 15 min after extubation; however, the benefit in our study was temporary and recruitment manoeuvres can lead to haemodynamic instability.

Our study also has several limitations. First, we did not include patients undergoing laparoscopic surgery, those who were morbidly obese or those undergoing abdominal surgery, who might have benefited from an intra-operative lung-protective ventilation strategy. Second, we did not measure arterial partial pressure of oxygen because of ethical restrictions.

In conclusion, PEEP and recruitment manoeuvres reduce intra-operative aeration loss; however, this benefit does not persist 15 min after extubation. Lung aeration improved shortly after surgery even without PEEP and recruitment manoeuvres. However, further studies are needed to determine the benefit of lung-protective ventilation in patients undergoing other types of surgery.

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Conflicts of interest: none.

Presentation: none.

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