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Research Article

The Stepwise Slow Titration of Positive End-Expiratory Pressure Before the End of General Anaesthesia Improves Lung Mechanics in Children: A Randomized Open Label Clinical Trial

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Abstract

Background: Intraoperative application of positive end-end-expiratory pressure (PEEP) is recommended in mechanically ventilated children since it improves lung mechanics. However, inadequate level of applied pressure can increase risk of barotrauma. **Objectives:** To assess the impact of titrated PEEP on lung mechanics in mechanically ventilated children under general anaesthesia. **Methods:** This was an open label, single Tertiary Centre randomized controlled clinical trial. The study population included 70 preschool children, ASA I and II, scheduled for orthopaedic, reconstructive, abdominal or urological surgery. Children with upper respiratory tract infection, allergic to chosen anaesthetics, cardiorespiratory comorbidities were excluded. Patients were randomly assigned either to receive intraoperative PEEP titration form 5 - 11 cmH₂O 20 minutes before the end of anaesthesia (intervention group) or to be ventilated until the end of anaesthesia conventionally with a positive end-expiratory pressure of 3 cmH₂O (control group). Main outcomes: changes in dynamic lung compliance (Cdyn), peak airway pressure (PIP), mean airway pressure (Paw) between groups at the end of surgery; changes in PIP and Paw during PEEP titration and desaturation in interventional group during PEEP titration.

Results: Seventy preschool children were recruited and analysed. Intraoperative positive end-expiratory pressure titration improved Cdyn in the intervention group comparing to control (Δ Cdy -3.2 vs. 0.63; P < 0.001). PIP and Paw were higher in interventional group (Δ PIP -0.57vs. 0.11; P < 0.001, and Δ Paw -0.63 vs. 0.0; P < 0.001) and desaturation was not observed in interventional group.

Conclusions: Stepwise titration of PEEP up to 11 cmH₂O improves subsequent lung mechanics without causing of barotrauma.

Keywords: Barotrauma, Positive End-Expiratory Pressure, Pediatric Patients

1. Background

Decrease in functional residual capacity (FRC) and atelectasis formation are well documented consequences of general anaesthesia. Longer duration and deeper levels of anaesthesia, high inspired oxygen fraction, lack of PEEP and muscle paralysis potentiate FRC reduction (1-5). Positive consequences of applied PEEP during general anaesthesia and mechanical ventilation refer as slowdown of alveolar de-recruitment and improvement of lung compliance (6-9). On the other hand, application of excessive PEEP can produce pneumothorax as well as hemodynamic instabillity. Current recommendations advocate use of PEEP 3 -5 cmH₂ in children with healthy lungs and also PEEP titration to prevent alveolar collapse (10). However, it is not stated how much PEEP we should titrate in order to improve lung function. This is due to lack of studies in children both healthy and sick (10). This research is a substudy of clinical trial (no.: NCT03745443) that investigated PEEP effect on lung function: oxygenation, ventilation, intrapulmonary shunting, lung mechanics and hemodynamics in preschool children. In previous paper we presented that PEEP titration in preschool children with healthy lungs during general anaesthesia up to 11 cmH₂O improves oxygenation, reduces alveolar-arterial gradient without compromising hemodynamic stability (11).

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2. Objectives

In this paper we will address to effects of the same slow PEEP titration on lung mechanics.

3. Methods

Methodology as well as study protocol were described in previous published paper but we will repeat it in the following text (1). We conducted a prospective, open label, randomized clinical trial in 70 children age 3 - 7 scheduled general anaesthesia for elective non-cardiothoracic surgery. Following ethical approval of our National Tertiary Health Care Centre (Institute for Mother and Child Health Care Ethic Committee, Institute for Mother and Child Health Care, Serbia, Chairperson K. Sedlecky, registration number No 8/30, November 2017), and after obtaining informed consent from parents/legal guardians, the subjects were recruited between January-June 2017. The study was performed in compliance with Declaration of Helsinki. Inclusion criteria were: age 3 - 7 years, ASA I and II, children undergoing orthopaedic, reconstructive, abdominal or urological surgery. Exclusion criteria were: present cardiac comorbidity and respiratory comorbidity, current or recent (up to 4 weeks) upper airway infection, children scheduled for cardiothoracic surgery and contraindication to anaesthetics used in study protocol. After triage recruits were randomly assigned in a 1:1 ratio, using "sealed envelope" technique into two groups; interventional (n = 35) and control (n = 35). The box containing 70 envelopes with allocation instruction (paper with group; I, interventional group; C, control group) was used to allocate patients randomly. Anaesthetist in charge pulled the envelope from the box and allocated patient to interventional or control group. General anaesthesia and intraoperative monitoring were the same in both groups. Midazolam 0.1 mg/kg i.v. was used for premedication 30 minutes before induction. We combined inhalation and intravenous induction using thiopental 5 mg/kg, fentanyl 3 mcg/kg, sevoflurane 1%, O₂/air (35:65) and rocuronium 1 mg/kg. For Anaesthesia maintenance air/oxygen mixture (65%:35%), sevoflurane 1.5% - 2%, fentanyl 2 mcg/kg and rocuronium were used. Ventilator settings were the same in both groups (Datex Ohmeda, Avance CS2, GE anaesthesia machine) except in interventional group when trial intervention was performed: pressure control mode (PCV), inspiratory pressure (Pinsp) to achieve tidal volume of (Vt) 6 - 8 mL/kg, respiratory rate (RR) adjusted to keep endtidal CO₂ (EtCO₂) 35 - 45 mmHg, PEEP 3 cmH₂O. Intraoperative respiratory monitoring included: peripheral oxygen saturation (SpO₂), capnography, EtCO₂, Pinsp, peak airway pressure (PIP), mean airway pressure (Paw) and dynamic

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lung compliance (Cdyn), partial pressures of CO₂ and O₂. Due to goals of our clinical trial mentioned in Introduction and well known effect of PEEP on filling pressures we monitored invasive blood pressure (IBP) and EKG. All investigated variables were continuously monitored during anaesthesia in both groups using monitoring incorporated in anaesthesia machine. Twenty minutes before the end of surgery the trial intervention was performed in interventional group (11).

3.1. Trial Intervention

In the interventional group, 20 minutes before the end of surgery the PEEP was increased by 2 cmH₂O on every 5th breath up to 11 cmH₂O. Ventilation was maintained with a PEEP of 11 cm H₂O for 2 minutes. The PEEP was then reduced by 2 cm of H₂O at every 5th breath until a plateau of 5 cmH₂O was reached. Ventilation with a PEEP of 5 cmH₂O was maintained until extubation. The total time required for this intervention was approximately 5 minutes. The control group was ventilated with a baseline PEEP setting (3 cmH₂O) until extubation. The criteria for aborting the experiment were: hypotension (defined as SBP < 70 mmHg and MAP < 55 mmHg.), bradycardia (defined as heart rate \leq 60/min), desaturation (defined as SpO₂ < 94%) and a sudden rise in PIP and/or PIP above 30 cmH₂.

3.2. Study Outcomes

Our primary outcome was change in Cdyn. Secondary outcomes were changes in PIP, Paw and cases of desaturation in interventional group during PEEP titration. We obtained measurements for analysis in 2 time points defined as: TI, 20 minutes before the end of surgery; and TII, before extubation. We monitored Cdyn, Paw, PIP, and desaturation during PEEP titration in interventional group.

3.3. Statistical Analysis

Since this is a substudy, as stated in Introduction section, the sample used here is the same in previously published paper (11). In brief, calculation of the sample size was based on expected effect of PEEP on PaO_2/FiO_2 with $\alpha = 0.05$ and study power of 80%. This parameter was discussed in previously published paper (11). The number needed was read from statistical tables and there were 30 participants per group (12). A further 5 were added in each group to compensate for dropouts. We needed 35 participants per group. All data were analysed using IBM-SPSS 20.0 (IBM Corp, New York, USA) software. The results were presented as mean and standard deviation with CI 95% or proportions. To evaluate size effects that PEEP titration caused, delta value (Δ) was used and compared between groups. The differences between groups were tested using

independent *t*-test at given endpoints. Within the interventional group variation of variables were explored using ANOVA. All tests were 2-tailed and a P < 0.05 was considered statistically significant.

4. Results

The demographic data of the study groups are presented in Table 1. There were no differences between groups regarding age, gender, body weight and type of surgery. The participant flow is shown in the CONSORT flow diagram (Figure 1). Of 486 children scheduled for surgery between January 2017-June 2017, 271 were younger than 3 or older than 7 years of age, 113 refused participation, 10 had upper respiratory tract infections, 7 had a chronic heart or lung condition and 15 didn't show up for surgery. Recruited participants (n = 70) finished the study and were analysed, there were no dropouts.

Table 1. Characteristics of Patients ^a						
	Group	PValue				
	Interventional	Control	i value			
Age, y	4.9 ± 1.5	5.1 ± 1.6	0.728			
Body weight, kg	18.8 ± 5.2	19.4 ± 5.3	0.682			
Gender, male	19 (54)	25 (71)	0.138 ^b			
Type of surgery			0.328 ^b			
Abdominal	12 (34)	10 (29)				
Urology	7(20)	14 (40)				
Orthopedics	7(20)	5 (14)				
Reconstruc- tive surgery	9 (26)	6 (17)				

 a Values are expressed as No. (%) or mean \pm SD. $^b\chi^2$ test.

4.1. Main Outcomes

The outcomes Cdyn, PIP, Paw are presented in Table 2 and Figures 2 and 3 and 4. We used delta (Δ) to evaluate effect size PEEP titration caused and compared it between groups. Independent *t*-test for delta between groups revealed that there was a statistically significant difference in the magnitude of change in investigated parameters between the groups and all were P < 0,001: Cdyn (Δ TI-TII I group -3.2 vs C group 0.63); PIP (Δ TI-TII I group -0.57 vs C group 0.11) and Paw (Δ TI-TII I group -0.63 vs C group 0.0). The changes in lung compliance, PIP, Paw during PEEP titration in the Interventional group are presented in Figures 2-4.

[able 2. Outcome Variables Between Interventional and Control Group ^a , ^b						
		Interventional	Control	Pc		
Cdyn						
	TI	30.1 (27.4 - 32.8)	27.8 (24.9 - 30.6)	0.225		
	TII	33.4 (30.1 - 36.7)	27.1 (24.3 - 30.0)	0.005		
	Δ TI-TII	- 3.2 (-4.51.9)	0.63 (0.25 - 1.01)	< 0.001		
PIP						
	TI	10.9 (10.5 - 11.3)	10.6 (9.9 - 11.4)	0.530		
	TII	11.5 (11.2 - 11.8)	10.5 (9.8 - 11.3)	0.020		
	Δ TI-TII	- 0.57 (-0.90.3)	0.11 (0.0 - 0.2)	< 0.001		
Paw						
	TI	7.14 (6.8 - 7.5)	6.1 (5.8 - 6.5)	< 0.001		
	TII	7.8 (7.6 - 7.9)	6.1 (5.8 - 6.5)	< 0.001		
	Δ TI-TII	- 0.63 (-0.90.3)	0.0 (0.0 - 0.0)	< 0.001		

^aValues are expressed as mean (95% CI).

^bTI-20 minutes before the end of surgery; T II -before extubating.

^cIndependent samples *t*-test.

5. Discussion

In this research we found out two things: first, lung compliance improved after PEEP titration in interventional comparing to control group at the end of surgery, and second, maximal PEEP level of 11 cmH₂ did not cause increase in airway pressure that could lead to pneumothorax.

We used dynamic lung compliance as a marker of lung mechanics (13). Dynamic lung compliance is measured in presence of gas flow and is inversely related to PIP: [(Cdyn = Vt/(PIP - PEEP)]. Therefore, changes in respiratory mechanics can be spotted immediately, at bedside. This is very important in clinical setting since it enables clinician to estimate effect of treatment immediately. As we demonstrated, lung compliance improved in interventional group comparing to control after PEEP titration at the end of surgery. Similar results exist in available literature. In experimental studies on animals, with and without induced lung injury, PEEP titration of 5, 10, 15 or 20 cmH₂O caused the increase of lung compliance (14-16). Recent study in adult patients ASA I and II, without cardiorespiratory comorbidity demonstrated that application of PEEP from 4 up to 12 cmH₂O improved lung compliance (17). Substudy of the PROVHILO trial also demonstrated that in adult patients without cardiorespiratory comorbidities lungs became more compliant when PEEP 12 cmH₂O was applied (18). When it comes to children with healthy lungs and idea of preventive role of PEEP literature data are limited. Recently, Cruces et al. (19) demonstrated that application of PEEP 5 cmH₂O in children up to

CONSORT 2010 Flow Diagram



15 years (median 4 years) resulted in improvement of respiratory compliance. Similar studies, mostly using PEEP 4 - 5 cmH₂O, were also published earlier. Due to experimental data in lung model, we know that improvement in lung compliance is a result of reduction in non-aerated and poorly aerated airspaces (20). Titration of PEEP up to 15 cmH₂O reduced surface of collapsed and poorly aerated airspaces from 31% with 0 PEEP to 7% with initial recruitment happening at a PEEP less than 10 cmH_2O (20). As much PEEP affects these lung regions, it also increases volume of already normally aerated alveoli which can lead to overdistension. Experimental studies in animals demonstrated overdistension with a PEEP of 9 cmH₂O but not with a PEEP 7 - 8 cm $H_2O(21, 22)$. On the other hand, analysis from PROVHILO substudy concluded that incidence of overdistension between groups (comparing PEEP 12 and $2 \text{ cmH}_2\text{O}$) wasn't significant, in only one patient overdistension was observed (21). In our study, during the slow step up PEEP titration, the lung compliance increased reaching the maximum at a PEEP of 11 cmH₂O. After 2-minute ventilation on PEEP 11 cmH₂O there was clinically insignificant fall of compliance by 9%. It is possible that this was because of overdistension according to mentioned experimental data (20). Further investigation and measurements of lung mechanics are needed in order to draw conclusion form this observation. For now, we can state that overall effects of stepwise up and down PEEP titration from 5 - 11 cmH₂O had a positive effect. The dynamic compliance in the interventional group at the end of surgery was better than that of the control group.

Awareness of potential risk of barotrauma among clinicians limits to some extent application of high PEEP. Elevated PIP and Paw have been implicated as being traumatic for lung parenchyma. High PIP is associated with pneumothorax, whereas elevated Paw is associated with pneumothorax and reduction in cardiac output (23). In the case





of tension pneumothorax, insidious complication of mechanical ventilation, PIP will rise and dynamic lung compliance will fall. In clinical practice, in order to induce such trauma, besides PEEP, set inspiratory pressure has to be high too (since, in pressure control mode, PIP is sum of inspiratory pressure and PEEP). As experimental data show, distension pressures that could induce barotrauma are greater than ones applied in everyday practice. Even with PEEP of 20 cmH₂, high inspiratory pressure over 60 cmH₂ was the factor that caused pneumothorax among laboratory animals (24). One of the safety limitations of our study was sudden rise in PIP above 30 cmH₂0. In our study, maximal PIP was 17 cmH₂O and maximal PEEP level used was 11 cmH₂. During PEEP titration, as stated in methodology section, we didn't change preset inspiratory pressure, which was adjusted to achieve Vt 6 - 8 mL/kg, so the only factor that could influence PIP was PEEP titration. No desaturation or pneumothorax was observed in investigated group.



Therefore, we interpreted that presented PEEP titration in children with healthy lungs came out as safe.

The limitation of our study is open label design. There was no possibility for blinding because of the randomization design which means that anaesthetist in charge had to know on whom and when to perform the PEEP maneuver.

5.1. Conclusions

Administration of staggered PEEP from $5 - 11 \text{ cmH}_2O 20$ minutes before end of anaesthesia in Anaesthetized ventilated children without cardiorespiratory comorbidity improved lung compliance without posing a risk of barotrauma and subsequent pneumothorax.

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Footnotes

Authors' Contribution: Ana Dragoljub Mandras developed. the idea, protocol, collected and analyzed data, wrote, and prepared the manuscript and is guarantor. Maja Sujica, Nikola Stankovic, Sladjana Vasiljevic and Vesna Milojkovic recruited the patients and collected data. Dusica Simic did the drafting of manuscript.

Clinical Trial Registration Code: The clinical trial registration code was NCT03745443 (www.clinicaltrials.gov).

Conflict of Interests: Part of this study regarding oxygenation, intrapulmonary shunt and hemodynamic effect was published in Iranian Journal of Pediatrics (doi: 10.5812/ijp.92269).

Ethical Approval: The ethical approval code was no.: 8/30, 2017, www.imd.org.rs/institut/eticki-odbor.

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Informed Consent: The procedure was explained in details to parents or legal guardians. Parents/legal guardians had to fill prepared statement and sing consent for study. Informed consent template was prepared in accordance to WHO criteria (https://www.who.int/ethics/reviewcommittee/informed_consent/en/).

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