RESEARCH PROTOCOL

Current Practice of Ventilation Strategies in Children undergoing General Anesthesia and Associations with Postoperative Pulmonary Complications - a Multicenter Prospective Cohort Study

The BIG APPLE investigators

Correspondence
David van Meenen, MD PhD
Department of Anesthesiology
Amsterdam University Medical Centers, location 'AMC'
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands
Email: d.m.vanmeenen@amsterdamumc.nl

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Coordinating investigator(s)	David van Meenen, MD PhD Department of Anesthesiology Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands Email: d.m.vanmeenen@amsterdamumc.nl & Jorinde Polderman, MD PhD Department of Anesthesiology Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands Email: j.a.polderman@amsterdamumc.nl
Principal investigator(s)	David van Meenen, MD PhD Department of Anesthesiology Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands Email: d.m.vanmeenen@amsterdamumc.nl & Jorinde Polderman, MD PhD Department of Anesthesiology Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands Email: j.a.polderman@amsterdamumc.nl
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STEERING COMMITTEE

Steering Committee	
Jorinde A.W. Polderman, MD PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	Jan van Wijk, MD Erasmus MC Rotterdam, the Netherlands
David M.P. van Meenen, MD, PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	Ignacio Malagon, MD, PhD Radboud MC Nijmegen, the Netherlands
Marcus J. Schultz, MD, PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	Nicola Disma, MD, PhD IRCCS Istituto Giannina Gaslini Genoa, Italy
Markus W. Hollmann, MD, PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	Britta von Ungern-Sternberg, MD, PhD Perth Children's hospital Perth, Australia
Markus F. Stevens, MD PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	Walid Habre, MD, PhD Geneva University Hospital Geneva, Switzerland
Lonneke Staals, MD, PhD Erasmus MC Rotterdam, the Netherlands	Thomas Riva, MD, PhD Universitatsspital Bern Bern, Switzerland
Sabrine Hemmes, MD, PhD Antoni van Leeuwenhoek Amsterdam, the Netherlands	

SUMMARY

Rationale

Postoperative pulmonary complications (PPCs) are common in children undergoing general anesthesia and are associated with prolonged stay in the hospital and high costs. Development of PPCs is associated with ventilator settings in adult patients undergoing general anesthesia. Data on perioperative ventilator settings in children are lacking, leaving the anaesthetist without guidance. Consequently, the current standard of care in perioperative mechanical ventilation in children is expected to be extremely heterogeneous, leading to ventilation with higher levels of energy than necessary. Therefore, it is highly necessary to evaluate the current practice in perioperative ventilation in children and to determine associations with PPCs.

Objective

The aims of this study are to:

- determine the incidence of PPCs in pediatric patients;
- describe the practice of ventilatory support in children undergoing general anesthesia;
- describe geo-economic differences/variations in ventilatory support and development of PPCs in children undergoing general anesthesia;
- identify potentially modifiable factors that have independent associations with development of PPCs, hospital length of stay and ICU admittance; and
- develop a risk score for the development of PPCs comparable to the ARISCAT score.

Study design

Multicenter international observational cohort study.

Study population

Patients ≤16 years of age undergoing invasive ventilation for general anesthesia in the operating room.

Main study endpoints

The primary endpoint is the incidence of PPCs. Secondary outcomes are the ventilator settings, ventilation parameters, length of hospital stay and ICU admittance.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Prospective collection of demographic data, ventilation settings and ventilation parameters, and outcomes means the risks are negligible and the burden is minimal.

1. INTRODUCTION AND RATIONALE

Numerous children receive anesthesia for a surgical procedure worldwide. Their breathing is often supported by mechanical ventilation. Contrary to the general perception, postoperative pulmonary complications (PPCs) are the most common complication in children undergoing general anesthesia and are associated with prolonged stay in the hospital and high costs.(1, 2) Development of PPCs is associated with ventilator settings in adult patients undergoing general anesthesia.(3, 4) It is unknown whether these associations also apply in children.

Most recommendations are extrapolated from studies in adults and some studies in children with acute respiratory distress (ARDS). However, the healthy lungs of our surgical pediatric population differ anatomically, physiologically and immunologically from the lungs of the healthy adult population. Moreover, they also differ significantly from the sick lungs of the pediatric patients with ARDS.

Currently, there is a paucity of data on practice perioperative ventilator settings in children. Consequently, the current standard of care in perioperative mechanical ventilation in children is expected to be extremely heterogeneous, possibly leading to deleterious ventilation settings and parameters. Therefore, it is highly necessary to evaluate the current practice in perioperative ventilation in children and to determine associations with PPCs.

2. OBJECTIVES & HYPOTHESES

2.1. Objectives

The aims of this study are to:

- determine the incidence of PPCs in pediatric patients;
- describe the practice of ventilatory support in children undergoing general anesthesia;
- describe geo-economic differences/variations in ventilatory support and development of PPCs in children undergoing general anesthesia;
- identify potentially modifiable factors that have independent associations with PPCs, hospital length of stay and ICU admittance; and
- develop a risk score for the development of PPCs comparable to the ARISCAT score.

2.2. Hypotheses

We will test the following hypotheses:

- the incidence of PPCs in pediatric patients decreases with age;
- practice of ventilatory support varies substantially;
- there are large geo-economic differences/variations in practice of ventilatory support;
- potentially modifiable factors related to ventilation have independent associations with outcome in critically ill pediatric patients, including PPCs, hospital length of stay and ICU admittance; and
- A score using preoperative variables can predict the development of postoperative pulmonary complications

3. STUDY DESIGN

Investigator–initiated, prospective, international, multicenter, observational study of a random-sample cohort of pediatric patients undergoing any in-hospital surgical procedure with general anaesthesia and mechanical ventilation during a continuous 14-day period of recruitment.

4. STUDY POPULATION

4.1. Population (base)

Pediatric patients undergoing general anesthesia.

4.2. Inclusion criteria

Patients are eligible if:

- aged ≤ 16 years;
- undergoing general anesthesia
- airway management with tube or LMA; and
- connected to mechanical ventilator.

4.3. Exclusion criteria

The following patients will be excluded:

- patients undergoing surgical procedures involving extra-corporal circulation;
- patients receiving ventilation with high frequency jet ventilation or high frequency oscillatory ventilation;
- sedation without airway management in the form of a endotracheal tube or a supraglottic airway device; and
- (rigid) bronchoscopic procedures with maintenance of spontaneous ventilation.

4.4. Sample size calculation

In previous studies, the reported prevalence of PPCs ranges between 4 and 53%, depending on age.(1, 2) Using a conservative estimate of 5% PPCs, in order to provide a sample of 100 events, inclusion of at least 2000 children is required. We defined 5 age groups: neonates up to 44 weeks postmenstrual age or up to 60 weeks post menstrual age if born premature (GA <37 weeks), 1 month to 1 year, 1 to 3 years, 3 to 6 years and 6 to 17 years. Therefore, to be able to do stratified analyses in 5 age groups, a sample of 10000 patients is needed. This will allow for inclusion of up to 10 covariates (including but not limited to mechanical ventilation settings, fluid loading and blood transfusion,) in a mixed effect model to analyze the effect on postoperative pulmonary complications. For a logistic regression analysis, the number of events divided by the number of predictor variables should be at least 10.

5. METHODS

5.1. Study endpoints

5.1.1. Primary endpoint

The main study endpoint is incidence of postoperative pulmonary complications (PPCs) in the first five postoperative days.

5.1.2. Secondary endpoints:

Secondary parameters are type of airway management; Tid; ventilation settings and parameters including tidal volume (V_T); peak inspiratory pressure (PIP); plateau pressure (Pplat); positive end-expiratory pressure (PEEP); fraction of inspired oxygen (FiO_2); inspiration to expiration ratio (I:E); inspiration time; set and total respiratory rate (RR); compliance (Crs); driving pressure (ΔP); and the mechanical power of ventilation (MP).

Clinical outcome measures: Saturation of peripheral oxygen (SpO_2), and end-tidal carbon dioxide ($EtCO_2$); intraoperative complications, hospital length of stay; and ICU admittance.

5.2. Data to be collected

All data to be collected are part of standard clinical care.

5.2.1. Patient characteristics

- age (weeks or months);
- sex (male or female);
- height (cm);
- weight (kg);
- gestational age at birth (weeks);
- surgical specialty;
- type of surgery; and
- duration of procedure.

5.2.2. Medical status

- Comorbidities (bronchopulmonary dysplasia, asthma/bronchiolitis, other pulmonary pathology, chronic ventilation, cyanotic congenital heart disorder, acyanotic congenital heart disorder, single ventricle physiology with palliative surgery, neuromuscular disease, oncologic, organ transplant, mental retardation);
- Current physical condition (preoperative saturation; recent/current upper /lower respiratory infection).

5.2.3. Intraoperative data

Collected after induction:

- Type of airway management: intubation or tracheostomy (invasive); supraglottic airway device; size of tube or supraglottic airway device.

Collected 15 minutes after incision:

- Ventilator settings: including but not restricted to: adult / pediatric / neonatal breathing circuit; minimization of deadspace: ventilation mode, expiratory tidal volume (V_Te) or inspiratory tidal volume (V_{Ti}) (only in case V_Te is not available); PEEP; PIP or Pplat; level of pressure support above PEEP (only in spontaneously breathing patients); FiO_2 (%); set and measured RR; I:E ratio; or inspiration time; SpO_2; $EtCO_2$; fresh gas flow; use of active humidification; Mean arterial pressure (invasive or non-invasive (MAP mmHg); heart rate (HR in bpm).

Collected during the duration of the procedure:

- Anesthesia related: anesthesia maintenance with halothane/desflurane/N2O/isoflurane/sevoflurane/propofol/ketamine/dexmedetomidine, use of regional technique (epidural, caudal, peripheral nerve block), use of neuromuscular block, reversal of neuromuscular block before extubation;
- Intraoperative complications possibly related to the mechanical ventilation strategy: oxygen desaturation (SpO2 < 90%), hypercapnia (etCO2 > 6.0), laryngospasm, bronchospasm, aspiration, need for unplanned recruitment maneuvers, cardiac arrest.

5.2.4. Follow–up

PPCs will be collected on Day 0 (end of surgery until 11.59 pm) and on Day 1, 2, 3, 4 and 5 postoperatively (each day goes from 0.00 AM to 11.59 PM). Data collection will be finalized on the day of hospital discharge or on Day 5, if the patient is still hospitalized. Length of hospital stay and admission to the pediatric intensive care unit will be recorded (planned and unplanned).

PPCs are defined as follows:

- Invasive mechanical ventilation after discharge from the operating room.
    - If yes, specify if the MV was previously planned;

    - If not planned, specify if the ventilatory support was maintained when leaving the operating room or if the patient was re-intubated.
- respiratory failure defined as: PaO2 < 8 kPa or SpO2< 90% despite oxygen therapy, with a need for non-invasive ventilation (NIV) after surgery (after discharge from the operating room);
- unplanned oxygen therapy with FiO2 > 0.6, due to PaO2< 8 kPa or SpO2< 90% in room air. This includes HIGH flow nasal oxygen or non-rebreathing mask. Excluding oxygen given as standard care, e.g. directly after arrival in the post anesthetic care unit);
- unplanned oxygen therapy with FiO2 < 0.6, due to PaO2< 8 kPa or SpO2< 90% in room air. This includes LOW flow nasal oxygen. Excluding oxygen given as standard care, e.g. directly after arrival in the post anesthetic care unit
- need for bronchodilators postoperatively in the PACU or at the ward;
- pneumonia (presence of a new or progressive radiographic infiltrate, consolidation or cavitation, and one of the following: (1) fever > 38 °C, (2) leukocytosis or leucopenia (WBC count > 12000 cells µl-3 or < 4000 cells µl-3 plus 2 of the following: (a) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, (b) new onset or worsening cough, or dyspnoea, or tachypnoea, (c) rales or bronchial breath sounds, (d) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand).);
- ARDS (defined according to Montreux definition(5) in case of age < 44 weeks of gestational age or PALICC definition(6) in case of age ≥ 44 weeks of gestational age);
- pneumothorax (air in pleural space with no vascular bed surrounding the visceral pleura on the chest radiograph).

5.3. Randomization, blinding and treatment allocation

To prevent that large centers, > 300 expected subjects, are overrepresented, we will offer centers with a large case-load, defined as >300 subjects within the inclusion criteria in the study period, to reduce their inclusions with 50% by using a provided randomization program which will select patients in a 1:1 ratio

5.4. Study procedures

A physician from each participating country will be appointed as national coordinator. The researcher will enroll patients in the study. Informed consent will be obtained if this is required by local legislation. As this study is purely observational, patients will not be subjected to any procedures or interventions outside of standard care.

5.5. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

5.6. Replacement of individual subjects after withdrawal

There will be no replacement of an individual subject after withdrawal.

6. SAFETY REPORTING

6.1. Temporary halt for reasons of subject safety

N.A.

6.2. AEs, SAEs and SUSARs

N.A.

6.3. Data Safety Monitoring Board (DSMB) and Safety Committee

N.A.

7. STATISTICAL ANALYSIS

7.1. Descriptive statistics

Descriptive statistics will be used to describe baseline characteristics, ventilation settings and parameters. Categorical variables will be expressed as n (%), continuous variables as median [IQR]. Categorical variables will be compared between groups using Chi^2 and continuous variables using Kruskal-Wallis test were appropriate. A p-value < 0.05 is considered statistically significant. Data will be analyzed with R (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org). No or minimal losses to follow–up for the primary and secondary outcomes are anticipated. In case of missing data, we will adjust complete–case analysis.

7.2. Visualization of endpoints

The primary endpoint, incidence of PPCs, will be analyzed using descriptive statistics and reported for the predefined age groups. Patient outcomes will be described, visualized using Kaplan Meier curves and differences between groups will be analyzed using time to event analysis, such as cox proportional hazards PPCs and length of hospital stay. Geo-economics differences in ventilator settings will be compared using propensity weighted cohorts. To develop a risk prediction score for the development of PPCs a logistic regression model will be constructed using a backward stepwise selection procedure in which the presence of a PPC is the dependent variable.

7.3. Associations between ventilation settings, parameters and outcome

Propensity score matching will be used to adjust for confounding and univariate and multivariate analyses will be used to identify associations of predefined ventilation settings and parameters with outcome.

8. ETHICAL CONSIDERATIONS

8.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013), with Good Clinical Practice (GCP).

8.2. Recruitment and consent

The investigator will enroll patients in the study. If required by local legislation informed consent by the patient and/or parents will be obtained by the investigator.

8.3. Benefits and risks assessment, group relatedness

This study does not result in any risk or burdens to patients.

8.4. Compensation for injury

Since the study is purely observational and no research related interventions will take place, participating in the study is without risk.

8.5. Incentives

There is no financial incentive for subjects to participate in this study.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1. Handling and storage of data and documents

Handling of personal data will comply with the General Data Protection Regulation. All collected data will be transcribed by investigators into Castor electronic data capture. Castor edc. is a secure web-based software platform designed to support data capture for research studies. Access to Castor edc. will be granted only to data collecting staff of participating centers, in accordance with the procedures outlined in the present protocol. Each participating center is granted access only to the patient data it has generated and recorded in the Castor database. The data will be recorded using an encrypted data connection (HTTPS) in input masks via a web browser or mobile app. Transcription will only take place in a secured environment. Directly identifying personal data will be separated from the research data and replaced by an assigned code. The directly identifying data will only be used to contact the patients if necessary and will only be available to the local investigators. Access to the assigned codes linked with personal data will be controlled with password protection. The passwords will only be given to directly involved investigators. Any data leaks will be reported to all parties within 1 working day after discovery of the leak.

9.2. Monitoring and Quality Assurance

In order to minimize the number of errors and missing data we will use standard operating procedures. Accuracy and consistency checks will be carried out by ad hoc checking by investigation coordinators.

9.3. Amendments

N.A.

9.4. Annual progress report

N.A.

9.5. Temporary halt and (prematurely) end of study report

N.A.

9.6. Public disclosure and publication policy

The study protocol will be registered on Clinicaltrials.gov before start of the study. The results of the study will be published in (inter–) national scientific journals and guidelines. The project leader will have final responsibility for the decision to submit for publication. The results will be published in a peer-reviewed journal. Final decision on publishing the results will be kept by the steering committee of the study. Authors of the publication will be team members of the steering committee who contributed to the

design, conduct or analysis of the study and who approved of the final version of the manuscript, plus the BIG APPLE investigators. All participating investigators will be collaborator of this group and will be included on all publications from the BIG APPLE database. Local PIs agree not to individually publish or present the results they obtain from the participation in this multicenter study before the publication of the main results of the study. According to FAIR data principles, the pooled dataset will be available for all members of the BIG APPLE collaboration on request for secondary analyses after judgement and approval of scientific quality and validity by the Steering Committee.

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