

Continuous Positive Airway Pressure During General Anesthesia Induction For
Elective Pediatric Surgery: Randomized Clinical Trial

NCT03432390

02/28/2018

General anesthesia can be defined as a transient stage of drug-induced unconsciousness through its actions on molecular receptors^{1,2}. Little is known about its mechanisms, but this state is supposed to be an adaptive phenomenon as sleep¹. It is a reversible condition that has specific behavioral and physiological patterns (unconsciousness, amnesia, analgesia, and akinesia). It consists of three phases: induction, maintenance and emergency or awakening².

Anesthetic induction is the period in which the administration of hypnotic drugs (venous, inhalational or a combination of both) begins ^{2,3}. At this stage, an irregular breathing pattern progresses to apnea. Ventilatory assistance is then initiated by the anesthesiologist, usually through a face mask and reservoir bag^{2,4}.

Inhalation induction is a safe, feasible and well-accepted patient technique widely used in children or, exceptionally, in adults with difficult venous access. However, it is not a risk free method. Complications such as cough, laryngospasm, salivation, induction failure and voluntary apnea may increase the morbidity of the anesthetic procedure^{3,5}.

The effects of general anesthesia on the respiratory system are well established. Among them, there is a greater predisposition to airway obstruction and collapse. Its mechanisms are not clearly known, although some associations have been documented (ventilatory muscle relaxation, anesthesia dose-effect relationship and airway patency impairment) ^{6,7}. Loss of respiratory muscle tone due to anesthetic induction is related to lower airway collapse, reducing functional residual capacity (CRF) ⁷.

Another additive explanation for airway collapse is the pharmacological impact of drugs used for sedation and hypnosis in processes that control both the efferent motor pathways of the pharyngeal muscles and the mechanoreceptor afference⁶.

Inhalational anesthetics exacerbate dynamic airway collapse, especially in the soft palate, and are directly associated with the administered dose of the drug. Sevoflurane acts by reducing the inspiratory phasic activity of the genioglossus muscle without compromising its tonic activity. Even

at sedative levels, sevoflurane modifies airway dimensions, reducing its patency especially on inspiration⁶.

As with inhaled drugs, venous anesthetics also act on the respiratory system. Propofol reduces the cross-sectional area of the upper airway, a reduction that has been shown to be maximum at the base of the tongue when sedative doses are used. Induction with this agent reduces the electromyographic activity of the genioglossus muscle⁶.

During the apnea period following general anesthesia induction, oxygen stores (O₂) are being consumed which may result in hypoxemia⁸. Oxyhemoglobin desaturation is faster in patients with reduced O₂ transport capacity, ie, those with reduced CRF, partial oxygen pressure (PaO₂), arterial oxygen content and cardiac output, or increased oxygen uptake (VO₂).) ⁹.

General anesthesia appears as a major risk factor for mortality in pediatric surgical patients, and problems with airway management in patients with comorbidities appear to add life-threatening risk to this population¹⁰. Pediatric patients, in turn, have more frequent episodes of desaturation during induction (4-10%) ^{5,8,11,12}. Children undergoing a greater number of tracheal intubation attempts, considered to have a difficult airway, are at greater risk of desaturation, which, if left untreated, naturally evolves to hypoxemia¹². The occurrence of this during airway manipulation in children may be accompanied by even more serious complications such as cardiopulmonary arrest (CRP) and death¹¹.

Decreasing oxyhemoglobin saturation to levels less than or equal to 95% induces changes in hemodynamic parameters such as systolic index [ratio of heart index (systolic volume x heart rate / body surface area) and heart rate], which indicates a reduction in blood pressure. heart function¹³.

Data from a five-year tertiary hospital study (12,158 surgeries) document respiratory events accounting for 29% of perioperative cardiac arrest in children. This share rises to more than half (56%) when analyzing anesthesia-related data. All CRP attributed exclusively to the anesthetic act were induction¹⁴.

Another study (10,649 anesthetics) conducted through a questionnaire with data from a period of six years points to problems in airway management as the major cause of anesthesia-related CRP¹⁵. Proper anatomical characteristics may contribute to the occurrence of hypoxemia in perioperative children, such as: 1) proportionally large head and tongue; 2) adenoid and tonsil hypertrophy; 3) smaller and narrower hypopharynx; 4) higher larynx at neck height; 5) inclined vocal cords, not at right angles; 6) inverted U-shaped epiglottis; and 7) smaller airway radius compared to adults, which imposes more airflow resistance according to Poiseuille's law ($R = 8\eta L / \pi r^4$). All these factors imply daily challenges to airway manipulation, either during ventilation or during intubation¹⁶. In infants, airway closure occurs during general anesthesia induction, primarily in the anterior-posterior direction, and is uniform throughout the pharynx, which changes in older children in whom the epiglottis is the point of greatest narrowing⁶.

The physiological characteristics of pediatric patients, such as lower CRF, higher VO_2 , higher carbon dioxide (CO_2) production and higher incidence of respiratory complications during the induction period when O_2 supply is interrupted, also contribute to the decrease in saturation. oxygen by hemoglobin^{9,11,16,17}. Age also has a linear correlation with the duration of apnea before oxyhemoglobin desaturation, as well as the lower the patient's weight, the higher the incidence of severe episodes of the event^{8,11}. The risks of obstruction and desaturation appear to be higher in children under three years⁶.

One of the strategies used by the anesthesiologist to prevent this complication is pre-oxygenation, which offers O_2 at levels above those usually breathed by the patient in order to increase their stocks. This strategy allows prolonging the time before oxyhemoglobin desaturation^{9,11,18}. In theoretical models, O_2 body reserves (lung, plasma and hemoglobin) may increase by more than two and a half times when the inspired fraction of that gas (FiO_2) is equal to 1. This increase is mainly at the expense of the alveolar fraction. in CRF, the body's main oxygen reservoir^{8,17}. This, associated with VO_2 and cardiac output, is responsible for the availability of O_2 to the patient⁸.

Preoxygenation, despite the benefits, may also contribute to the occurrence of oxyhemoglobin desaturation. Microatelectasis and ventilation / perfusion (V / Q) disturbance are documented during anesthesia induction under different FiO₂. Alveolar recruitment maneuvers and use of end-expiratory airway pressure (PEEP) can reverse and prevent the occurrence of these events, respectively^{7,8}. Other preventive strategies, such as apneic oxygenation, have also been studied, but it is not yet known which technique is ideal^{19,20}.

A variation of noninvasive ventilation, Continuous Positive Airway Pressure (CPAP) is a ventilation mode in which the patient breathes spontaneously through a pressurized circuit²¹. In patients with obstructive sleep apnea, in which its use is already well established, benefits such as improved sleepiness and severity of the disease, improvement in cardiovascular outcomes, as well as a reduction in blood pressure, and additional indirect effects such as an improvement in endurance, were evidenced. insulin therapy in non-diabetics²²⁻²⁴.

From the ventilatory point of view, its benefits are demonstrated by the improvement in alveolar gas exchange, minimization of atelectasis formation and increase of both functional residual capacity and tidal volume²¹. Improvements in peripheral oxygen saturation, peak respiratory flow and reduction in both frequency and respiratory work have been evidenced in patients during asthma attacks²⁵.

In the pediatric population, CPAP is widely studied in patients with bronchiolitis as an alternative to controlled mechanical ventilation due to its effects on small airways (alveolar opening, prevention of atelectasis and increased functional residual capacity) ^{26,27}. A study conducted with patients between three months and five years of age with respiratory distress also showed a potential benefit through reduced respiratory rate²⁸.

There is evidence that CPAP can be effective in minimizing the deleterious effects of pre-oxygenation under high FiO₂ by maintaining lung volume⁷. Its use in ventilation during general

anesthesia induction still requires well-conducted studies to support its routine practice, but research in adults shows encouraging results^{29,30}.

In patients without comorbidities, candidates for major surgery, the longer apnea before desaturation and the highest PaO₂ values in those who received CPAP during anesthetic induction were significant. The use of CPAP also reduced the time to return to normal baseline saturation after apnea²⁹.

The use of CPAP was also related to higher PaO₂ and lower carbon dioxide blood pressure values (PaCO₂) in obese in anesthetic induction. There were no episodes of hypoxemia in these patients, unlike those who did not use the continuous positive pressure technique³⁰.

The aim of this study is to evaluate the effectiveness of CPAP during anesthetic induction in increasing apnea time until hemoglobin saturation drops to 95% in children undergoing general anesthesia for elective surgery.

Primary hypothesis

- The use of CPAP in preschoolers' pulmonary ventilation during general anesthesia induction for elective surgery delays the occurrence of oxyhemoglobin desaturation during apnea.

Secondary hypotheses

- Oxyhemoglobin saturation values in pulse oximetry in apneic patients in similar periods during anesthetic induction are higher in those using CPAP;
- Time to recovery of normal oxyhemoglobin saturation levels in pulse oximetry after apnea is shorter in patients using CPAP;
- The frequency of complications (laryngospasm, hypoxemia, bradycardia, cardiopulmonary arrest, death) is lower in patients using CPAP.

General objective

To evaluate the effectiveness of CPAP during anesthetic induction in increasing apnea time until hemoglobin saturation drops to 95% in children undergoing general anesthesia for elective surgery.

Specific objectives

In children undergoing general anesthesia for elective surgery who will undergo CPAP or standard circular circuit ventilation during anesthetic induction, compare:

PRIMARY OUTPUT:

The time between onset of apnea and 95% drop in oxyhemoglobin saturation between groups.

Secondary Outcome:

Oxyhemoglobin saturation values on pulse oximetry during anesthetic induction at different times between groups;

Time to recovery of oxyhemoglobin saturation levels in pre-apnea pulse oximetry between groups;

The frequency of complications (laryngospasm, hypoxemia, bradycardia, cardiopulmonary arrest, death) between the groups.

Study Design

This is a randomized, phase III, parallel clinical trial in pediatric patients undergoing elective surgery.

Study site

The study will be developed in the operating room of the Clinical Hospital of the Federal University of Pernambuco (HC-UFPE).

The HC-UFPE Pediatric Surgery Service performs about 15-20 surgeries per week on an elective basis; The team consists of six surgeons and three resident physicians; and has a room in the operating room in four weekly shifts where it performs procedures on children from birth to 18 years.

Study Period

The study will be conducted from January 2018 to June 2018.

Study Population

Preschool pediatric patients undergoing elective surgery in the operating room of Hospital das Clínicas.

Sample

Sampling

A non-probabilistic convenience sample will be obtained, composed of preschool children who will be submitted to general anesthesia for elective surgery, following the inclusion and exclusion criteria of the study.

Sample size

Sample size calculation was performed using Openepi software, version 3.01 (Dean AG, Sullivan KM, Soc. MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. [Www.OpenEpi.com](http://www.OpenEpi.com), updated 2013/04/06, accessed 2017/07/11), using difference of means. The first parameter used was the mean time in apnea that patients exposed to the intervention took to achieve a pulse oximetry oxygen saturation of 95% (166 ± 47 seconds) 20. The second parameter was the average time in apnea that patients not exposed to the intervention took to reach a pulse oximetry oxygen saturation of 95% (131 ± 39 seconds) 20. Considering a significance level of 5% and a power of 90%, 64 patients (32 in each group) will be needed. However, with possible losses due to post-randomization exclusion (around 10%), this number will be increased to 72 (36 in each group).

Randomization Procedure

The randomization table will be generated on the computer using the Random Software Allocation program. After randomization, opaque envelopes numbered sequentially from 1 to 72 will then be prepared according to the random number table. The allocation concealment will be respected.

Criteria and procedures for selecting, capturing and following participants

Inclusion criteria

Preschool children;

ASA I or II;

Children undergoing general anesthesia for elective surgery;

Exclusion Criteria

Pre-existing parenchymal lung disease;

Cyanotic or oxyhemoglobin-saturated children less than 95% before anesthetic induction;

Recent history (<4 weeks) or duration of upper respiratory tract infection;

Participant Capture and Follow-Up Procedures

Participants will be captured by an undergraduate student who will not participate in the data collection. He will be solely responsible for capturing participants, applying the eligibility criteria using a checklist (Appendix 1) and requesting the signature of the IC. This stage will take place at the entrance to the operating room where patients and caregivers, coming from the outpatient clinic after weighing and measuring, await surgery. Subsequently, it will deliver to the principal researcher the envelope referring to the participant, which will contain the group to which he / she has been allocated.

Allocation will be by sequentially numbered, otherwise identical, sealed envelopes, each containing a 2 inch by 2 inch paper with a written code that will designate the intervention group or the comparative group. There will be no detectable differences in size or weight between intervention group envelopes and comparative group envelopes. Envelopes will be opaque and opened sequentially only after the patient information assigned to them has been written to them. The envelope opening will occur before the patient enters the operating room so that the study setting can be set.

The lead researcher will be responsible for the entire procedure, along with the anesthesiologist responsible for the surgery. Data collection in turn will be performed by a student of scientific initiation responsible only for data collection without knowledge of the group to which the patient will be allocated (CPAP system will be selected before the student enters the room for collection).

A flowchart (CONSORT) will be completed with study progress throughout the phases of a two-group parallel intervention study (participant selection, intervention allocation, follow-up, and data analysis) (Figure 1).

All medical records of the participants involved in the study will be identified by self-adhesive labels containing the research name, registration number, study identification number and the group in which it was allocated.

Terms, Variables and Concepts

Control Variables (for sample characterization)

Age

Weight

Height

Sex

Physical state according to ASA

Surgery type

Independent Variable

CPAP Usage

Dependent Variables

Time between onset of apnea and 95% drop in oxyhemoglobin saturation (Time 1);

Oxyhemoglobin saturation on pulse oximetry during anesthetic induction at different times;

Frequency of complications: laryngospasm, hypoxemia, bradycardia, cardiopulmonary arrest, death;

Time to recover oxyhemoglobin saturation levels in pre-apnea pulse oximetry (Time 2);

Procedures, tests, techniques and exams

Performing Anesthesia:

Patients selected for the study will be admitted to the operating room and will receive regular monitoring (cardioscope, oximeter, noninvasive blood pressure and capnography).

Inhalation induction will be with 8% sevoflurane, 60.5% inspired oxygen fraction under fresh gas flow of 4l / min (2l oxygen and 2l compressed air) until loss of eyelid reflex. The anesthetic concentration will then be reduced to 4%. A face mask coupled to the anesthesia machine will be used, fixed to the patient through an elastic band.

After adequate ventilation is verified through the correct positioning of the face mask and capnography curve present, peripheral venous access with venous catheter number 20, 22 or 24G will be obtained for hydration and propofol infusion at a dose of 3.5mg / kg to induce apnea in patients in both groups.

CPAP Realization

Patients will be submitted soon after monitoring the technique described on the envelopes delivered at the entrance to the operating room.

In the CPAP group, it will be applied to the anesthesia device (Dräger Fabius GS) using a circular system. This system consists of two corrugated tubes coupled at one end to a Y-piece, connected to the patient's face mask, and at the other end to the anesthesia machine which, in addition to providing fresh gas flow, has a carbon dioxide absorber called lime. soda. The latter allows the system to be circulated by removing CO₂ from the air supplied to the patient, warms and humidifies the gas mixture. A pressure relief valve (pop-off valve), which prevents gas loss by the patient-device system when closed, is an integral part of the anesthesia device. It has several markings (0-70cmH₂O), is manually manipulated and can be open (0cmH₂O), ie without any pressure being supplied to the patient's airway or closed. In the closed position, there will be continuous positive pressure being delivered to the patient's airway. The pressure that will be used in this group will be 10cmH₂O.

In the Open System group, the system will remain with the valve in the open position, ie 0cmH₂O.

In both groups, patients will spontaneously ventilate from the outset with the technique defined at the time of allocation.

After the apnea begins, the time will be timed and periodically (every 10 seconds), the oxyhemoglobin saturation through the pulse oximeter will be recorded for a maximum time limit of five minutes in order to catch a minimum saturation of 95% in both groups.

The entire anesthetic procedure will be attended by the anesthesiologist who accompanies the patient and will be at his discretion as soon as the study is over.

Procedures for data collection

Data Collection Instrument

Data will be collected using a standard, pre-coded form for data entry into the computer (Appendix 3). Information on categorical variables will be pre-coded and continuous variables will be expressed at their own numerical value and only at the time of analysis will the results of some of these be categorized.

These forms will be properly stored in specific file folders, before and after typing and analysis, under the responsibility of the researcher, who will fill them out at different times, before, during and after the surgical procedure.

Data collect

Data will be collected by an independent researcher who will be present in the operating room, fill out the form with patient identification data and study variables and will not interfere with the anesthetic procedure to be performed.

The time from the moment of cessation of respiratory movements and decay of the capnography curve will be timed. The measurement will take place until the pulse oximetry is recorded at 95%. Assisted ventilation will then be instituted (in the Open System group, the pop-off valve will be manually closed to 10cmH₂O). At this time, there will be a new timing of the time until pulse oximetry reading of the value of 100% or the value obtained immediately before the beginning of apnea.

Data Processing and Analysis

Data Processing

Typing in the specific database created in the excel program will be performed twice, at different times and by different people, obtaining at the end a listing to correct any typing errors, under the supervision of the researcher himself.

In case of inconsistencies or lack of data when the listings are reviewed, the corresponding archived forms will be consulted, according to the patient's registration number.

Upon completion of the entry of all forms in the database, the final revision will be performed and the missing data will be completed by the above mentioned processes. The definitive database thus created will then be used for statistical analysis in the STATA program, being also submitted to tests of consistency and cleaning of the information, generating backups.

Data analysis

Data analysis will be performed by the researcher and the responsible statistician (supervised by her advisor), using the STATA program.

Descriptive statistical analysis will be performed through measures of central tendency and dispersion for quantitative variables and frequency distribution for qualitative variables. For comparison of paired samples, a non-parametric method, Wilcoxon's t-test will be used.

Student's t-test will be used for two independent samples, previously considering the Kolmogorov-Smirnov normality test for each sample, and for non-normality, the nonparametric Mann-Whitney U test will be used. Quantitative variables according to the time of their performance will be used analysis of variance for repeated units (ANOVA), if they present a normal distribution, or Wilcoxon if normality is not present. For categorical variables, Fisher's exact test or Chi-square will be used when necessary.

Relative Risk and its 95% confidence interval, in addition to the Number Needed to Treat and Benefit (NNT) or the Number Needed to Treat or Harm (NNH) where relevant, will also be calculated.

Ethical aspects

The research will respect human rights and the principles of bioethics (Autonomy, Non-Maleficence, Charity, Justice and Equity). Confidentiality and confidentiality in the collection and archiving of collected data will be respected.

The terms of National Council of Health Resolution No. 466 of December 12, 2012 for human research will be followed as well as the Declaration of Helsinki. In addition, the project will be submitted to the Research Ethics Committee of the proposing institution, the data will only be collected after such submission and approval of the committee, and the children of the study will only be included after the parents or guardians have signed the free and informed consent form. Clarified (IC, Appendix 2).

The study will be registered in ClinicalTrials.gov and will not offer any additional risks or discomforts beyond those inherent to the anesthetic-surgical procedure itself, as well as no adverse effects that contraindicate the use of CPAP during induction have not been reported in the literature. In contrast, the few existing studies report respiratory improvement with the use of this intervention. All research procedures will be performed by trained and qualified professionals for both pediatric anesthesia and CPAP.

The informed consent form (Appendix 2) will provide the guardians with all information regarding the advantages and disadvantages of using both techniques; emphasize that no procedures no longer routinely performed by the team will be performed; It will include the right to refuse to participate in the study, as well as the guarantee of assistance to those who do not accept it, without compensation from the institution or from the researchers. They will undertake to publish the study, regardless of the results obtained.

Interest conflicts

This research will be free of conflict of interest, private or institutional. There will be no funding from the pharmaceutical industry or representatives of any research object used.

Informed Consent Form

We request your permission to invite your child _____ {or minor under your responsibility} to participate, as a volunteer, in the Continuous Positive Airway Pressure during General Anesthesia Induction survey. FOR ELECTIVE PEDIATRIC SURGERY: RANDOMIZED CLINICAL TEST. Before you can decide whether or not to participate, you need to know the benefits, risks and consequences of your participation.

This document is called the Informed Consent Form (ICF) and is named after you should only participate in the research after you have read and understood this statement. Please read the information carefully and talk to the responsible researcher and research team about any questions you may have. If there is a word or term you do not understand, talk to the person responsible for obtaining this consent for further clarification. If you prefer, talk to your family, friends, and medical staff before making a decision. Once you have received all the information, you may provide your consent by initialing and / or signing both copies, one from the responsible researcher and one from the research participant.

If you do not agree, there will be no penalty for you or the child you are responsible for, and it will be possible for you to withdraw consent at any time, also without any penalty.

This is a research, which is the responsibility of researcher Jayme Marques dos Santos Neto, who is an anesthetist and is studying a technique to help the breathing of children during surgery. The researcher's address is: Avenida Boa Viagem, 306 apt. 701, Pina, Recife-PE Zip Code 51011-000; telephone (81) 996212977. Dr. Jayme is doing a Master's dissertation and is being advised by also Anaesthesiologist Dr. Flávia Augusta of Orange Lins da Fonseca e Silva, Phone 81994197979, email orangeflavia@gmail.com

RESEARCH INFORMATION:

Your child is being asked to participate in research that will study the effect of a breathing aid during the onset of anesthesia. We call this technique Continuous Positive Pressure (CPAP).

For the child to have surgery, he needs to receive general anesthesia. To do this, she breathes using a silicone or plastic mask that is attached to the anesthesia machine. The gas that comes from the anesthetic device contains the medicine that makes the child sleep. This technique is popularly known as “smelling”, but is actually General Anesthesia, and is commonly used in virtually all anesthesia in children. CPAP is done the same way. The only difference to usual ventilation is that in CPAP the anesthesia machine provides a pressure that can help (is what we want to find out) better breathing.

Two groups will be formed in which one child will receive CPAP and the other child will receive usual ventilation. We don't know which group your child will be in. Her participation is not required. The aim of this project is to know if CPAP at the beginning of anesthesia improves the child's safety and if the oxygen in her blood remains at normal levels any longer.

Your child's participation ends as soon as she returns to the initial condition in the study when her surgery will then be performed. We want to make it clear that this is not a new method that is already being used and is considered a safe technique. In previous studies, no side effects or complications were found.

It is hoped that as a result of this study, the use of CPAP at the onset of anesthesia may be increasingly encouraged, improving the quality of anesthetic care. All anesthesia will have the participation of the anesthesiologist responsible for the surgery and the researcher who will be present throughout the study period, thus increasing the vigilance over the procedures performed on your child.

Undesirable effects are likely to occur in any research study, such as embarrassment in signing this term, despite all possible precautions, and can happen without your own or the researchers' fault. If your child experiences undesirable effects such as associated harm from your participation in this study, immediate and full professional assistance will be provided.

Possible advantages for your child are more oxygen in her blood, less chance of problems at the beginning of anesthesia, increased safety time for her if any problems also occur at the beginning of anesthesia and faster recovery if she stops breathing.

The information of this research will be confidential and will be disclosed only in scientific events or publications, with no identification of volunteers, except among those responsible for the study, ensuring confidentiality about the participation of the volunteer. The data collected in this research, through forms, will be stored in archive folders, under the responsibility of the researcher, at the address informed above, for a period of at least 5 years.

You will not pay anything and will not receive any payment for him / her to participate in this research, as it must be voluntary, but compensation is also guaranteed in cases of damage, evidently resulting from his / her participation in the according to a judicial or extra-judicial decision. If necessary, expenses for participation will be borne by the researchers (reimbursement for transportation and food).

If you have any questions regarding the ethical aspects of this study, you may consult the IMIP Research Ethics Committee Involving Human Beings at: Rua dos Coelhos, 300, Boa Vista. IMIP Research Directorate, Orlando Onofre Administrative Building, 1st Floor tel: 2122-4756 - Email: comitedeetica@imip.org.br. The CEP / IMIP is open from Monday to Friday, from 07:00 to 11:30 in the morning and from 13:30 to 16:00 in the afternoon.

Researcher's signature

CONSENT OF THE RESPONSIBLE FOR THE PARTICIPATION OF THE VOLUNTEER

I, _____, CPF _____, the undersigned, responsible for _____, authorize your participation in the study. I was duly informed and informed by the researcher about the research, the procedures involved in it,

as well as the possible risks and benefits arising from his / her participation. I have been assured that I can withdraw my consent at any time without this leading to any penalty or interruption of your follow-up care for me or the minor concerned.

Place and date _____

Signature of Responsible: _____