University of Thessaly
School of Medicine
Laboratory of Biomathematics

M.Sc. Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics

Master Thesis

A protocol for a Randomized Controlled Clinical Trial for assessing the effectiveness of Alveolar Recruitment Maneuver in Improvement of Lung Compliance during Laparoscopic Surgery in Children

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Μεταπτυχιακή Διπλωματική Εργασία

Πρωτόκολλο για μια Τυχαιοποιημένη Ελεγχόμενη Κλινική Δοκιμή για την εκτίμηση της αποτελεσματικότητας του Χειρισμού Κυψελιδικής Επιστράτευσης στη βελτίωση της Πνευμονικής Ενδοτικότητας κατά τη διάρκεια της Λαπαροσκοπικής Χειρουργικής σε Παιδιά

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Επιβλέπων καθηγητής
Χατζηχριστοδούλου Χρήστος

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Study Title

A phase II Randomized Controlled Clinical Trial to assess the effectiveness of Alveolar Recruitment Maneuver (RM) in Improvement of Lung Compliance during Laparoscopic Surgery in Children

Indication studied

The investigators will test the hypothesis that RM during Abdominal Laparoscopic Surgery in Children aged 1-14 years improves lung compliance and gas exchange. The investigators will apply RM as a Sustained Inflation (at a pressure level of 30 cm H_2O for 30 seconds) in pediatric patients under Pressure Controlled Ventilation (PCV) after deflation of pneumoperitoneum.

Brief description

This will be an Interventional, Prevention, Parallel Assignment, Double-blind (patient, care-giver, outcomes Assessor), Randomized, Safety / Efficacy Study. We will use two parallel groups of children aged 1-14 years who are scheduled for elective Abdominal Laparoscopy

Trial Site, Patient Enrollment, Start and Completion Date

Trial Site: General Hospital of Thessaloniki “Papageorgiou”
Enrollment: 30 patients
Study Start day: XXXXXXX
Primary Completion date: XXXXXXX
Study Completion date: XXXXXXX

Protocol Identification

ClinicalTrials.gov Identifier: XXXXXXX
Study ID Number: XXXXXXX

Principal Investigator

XXXXXXX

Sponsor

General Hospital of Thessaloniki “Papageorgiou”, Ring Road, Pavlos Melas, Thessaloniki, 56403

Ethics

The Institutional Review Board will review and approve the study.
This study will be performed in compliance with good clinical practice (GCP): International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH Harmonised Tripartite Guideline - Structure and Content of Clinical Study Reports

Patient Information and Consent

Written informed consent will be obtained from minors’ parents or patients’ legally acceptable representatives. Patients will be informed about the trial to the extent compatible with their understanding and, if capable, patients should sign and personally date informed consent form.

Protocol version

Version: 5.6 (21/9/2017)

Abbreviations

ASA	American Society of Anesthesiologists Physical Status classification system
BMI	Body Mass Index
CO_2	Carbon dioxide
IAP	Intra-abdominal pressure
IBW	Ideal Body Weight
MinV	Minute Ventilation
MV	Mechanical Ventilation
PACU	Post-Anesthesia Care Unit
PCO_2	Partial Pressure of Carbon Dioxide
PCV	Pressure-controlled Ventilation
PEEP	Positive end-expiratory pressure
$P_{et}CO_2$	End-tidal carbon dioxide concentration
pH	Power of Hydrogen
PI	Principal investigator
PIP	Peak Inspiratory Pressure
PO_2	Partial Pressure of Oxygen
PO_2 / FiO_2	Arterial Oxygen Partial Pressure to Fraction of Inspired Oxygen
RM	Recruitment Maneuver
RR	Respiratory Rate
SI	Sustained Inflation
SpO_2	Peripheral Oxygen Saturation
Vt	Expiratory Tidal Volume

Abstract

Introduction

Pneumoperitoneum and increase in Intra-abdominal Pressure in Children Laparoscopy reduces diaphragmatic excursion and shifts the diaphragm cranially, resulting in the reduction in Lung Compliance and Functional Residual Capacity and Ventilation – Perfusion (V/Q) mismatch leading, finally, to atelectasis, hypoxemia and hypercapnia. In a prospective randomized double-blind clinical trial, the investigators will test the hypothesis that alveolar Recruitment Maneuver (RM) during Laparoscopy in children aged 1-14 years improves Lung Compliance. The primary endpoint of the study will be the improvement in dynamic lung compliance (Com_{dyn}) (dv/dp) while the improvement in gas exchange (increase in PO_2, PO_2/FiO_2, and decrease in PCO_2) will be the secondary endpoint of the study.

Materials and Methods

Children undergoing Abdominal Laparoscopy will prospectively be assigned to one of two groups. During the operation, patients In both groups, will be ventilated with Pressure-Controlled Ventilation (PCV) with Positive End-Expiratory Pressure (PEEP) 5 cm H_2O and titration to achieve Tidal Volume (Vt) 6-7 ml/kg and End-tidal CO_2 ($EtCO_2$) 35-40 mmHg. In the RM group, 3 minutes after deflation of pneumoperitoneum, the investigators will apply RM as a Sustained Inflation with CPAP 30 cm H_2O for 30 seconds, by setting Manual / Spontaneous Ventilation Mode and the Adjustable Pressure Limitation (APL) Valve to 30 cm H_2O. In both groups, lung compliance will be measured (dynamic compliance) as dv/dp (ml/cm H_2O). Measurements (including hemodynamics and blood gas) will be assessed after a stabilization period of Mechanical Ventilation (MV), as baseline before surgical incision, during the pneumoperitoneum, after deflation, after RM and in Post-Anesthesia Care Unit (PACU). A power analysis will be conducted in order to compare Dynamic Lung Compliance (dv/dp) between the two study groups. The improvement in Dynamic Compliance will be the Primary Endpoint of the study. Children will be assigned in a 1:1 ratio to one of the two groups using software-generated blocks.

Results and Discussion

Data will be presented as mean value (+/- SD) and $p < 0.05$ will be considered significant. The investigators will use Mixed Analysis of Variance to make comparisons between and within groups. At time points before RM is performed, there should be no significant differences in Lung Compliance between the two groups ($p > 0.05$). The investigators will use two-sample t-test as supplementary analysis in order to compare the two groups at each time point, while chi-square test for categorical variables and two-sample t-test for continuous variables for patient and procedural characteristics differences between the two groups will be used. In the RM group, according to similar studies, we expect to detect a significant increase in lung Compliance after RM in comparison to control group where RM will not be applied. In the RM group, the investigators estimate that Dynamic Lung Compliance will be significantly increased compared to baseline compliance too. There should be no significant differences in demographics between the two groups. The investigators expect that there will be no statistical or/and clinical significant differences in patients' hemodynamics and blood gas measurements.

Introduction

Recruitment Maneuver – Definition

Alveolar recruitment maneuver (RM) is a technique using sustained airway pressure increase aiming at recruiting collapse alveoli, increasing lung area available for gas exchange and consequently improving arterial oxygenation.

General Anesthesia, Atelectasis and Recruitment Maneuver

Mechanical ventilation (MV), during General Anesthesia (GA), should not be considered as a simple and neutral intervention, without potential serious consequences in patient's homeostasis. In fact, Positive Pressure MV is increasingly recognized as a potentially harmful intervention that can cause lung damage (Ventilator-Induced Lung Injury – VILI) and respiratory muscle injury (Ventilator-Induced Diaphragm Dysfunction - VIDD).

Between the several mechanisms that have been postulated to describe the development of VILI, Atelectasis plays an important role, as in the presence of atelectasis, MV may harm the alveolar units by repetitive collapse and reopening, a condition that is called atelectrauma[1].

Atelectasis develops in as much as 90% of patients undergoing general anesthesia[2] and can be present to different degrees after surgery, maybe for days. It occurs in the dependent parts of the lungs and the development of atelectasis is associated with several pathophysiologic effects, including decreased lung compliance, impairment of oxygenation and increased pulmonary vascular resistance[3]. Atelectasis is a major cause of intra- and post- operative hypoxemia while it also predisposes to postoperative lung infections.

The consequences of atelectasis persist into the postoperative period and can influence patient recovery[3]; over the last years there is growing evidence that an intraoperative lung-protective mechanical ventilation strategy, using low Tidal Volumes (Vts), with or without high levels of Positive End-Expiratory Pressure (PEEP) and Recruitment Maneuvers (RMs), prevents Post-operative Pulmonary Complications (PPCs)[3,4].

Laparoscopic Surgery in Adults and Children

In the recent years, advances in laparoscopic technique and refinement in the equipment have led to a significant increase in the use of Laparoscopy in Children, offering its benefits to young patients. In comparison to conventional open technique, Laparoscopy is related with reduced surgical trauma, less postoperative pain, reduced perioperative morbidity, earlier postoperative mobilization, shorter hospital stays and better cosmetic results[5].

Nevertheless, from the anesthetic point of view, Laparoscopic Surgery exposes the patient to additional physiological modifications and thus potential risks. Laparoscopic Surgery involves the intraperitoneal insufflation of carbon dioxide (CO_2) to permit adequate visualization and manipulation of the abdominal viscera. The pneumoperitoneum, except the CO_2 absorption, involves an increase in the Intraabdominal Pressure (IAP), which, among other, can have significant cardiovascular, respiratory and neurological effects. A thorough understanding of the pathophysiological changes mentioned above is crucial for optimal anesthetic care[6–8].

CO_2 Absorption effects

During intraperitoneal insufflation, CO_2 diffuses to the body and its diffusion leads to increased $PaCO_2$ (tension of carbon dioxide in arterial blood) values in the intra- and post-operative period[9]. Hypercapnia constitutes a strong stimulus for Minute Ventilation (MinV) to increase, by as much as 60%, to normalize the End-tidal CO_2 ($EtCO_2$) while it activates the sympathetic nervous system leading to an increase in blood pressure, heart rate, myocardial contractility, and arrhythmias. It also sensitizes the myocardium to catecholamines, particularly when volatile anesthetic agents are used[10].

Hemodynamics during Laparoscopy

Main hemodynamic changes include alterations in arterial blood pressure (i.e., hypotension and hypertension) and arrhythmias. The extent of the cardiovascular changes associated with creation of pneumoperitoneum depends on the level of IAP, volume of CO_2 absorbed, patient's intravascular volume, ventilatory technique, surgical conditions and anesthetic agents used. However, the most important determinants of cardiovascular function during laparoscopy are the IAP and patient position[8].

Pulmonary Function during Laparoscopy

Changes in pulmonary function during laparoscopy include reduction in lung volumes, increase in peak airway pressures, and decrease in pulmonary compliance, secondary to increased IAP and patient positioning[11].

Creation of pneumoperitoneum at an IAP of 15 mm Hg reduces respiratory system compliance and increases peak inspiratory and mean airway pressures. Elevated IAP reduces diaphragmatic excursion and shifts the diaphragm cranially, resulting in early closure of smaller airways leading to intraoperative atelectasis with a decrease in functional residual capacity. On one hand, upward displacement of the diaphragm leads to preferential ventilation of nondependent parts of the lung, which results in ventilation-perfusion (V/Q) mismatch with a higher degree of intrapulmonary shunting, whereas on the other, it leads to endobronchial intubation. These pulmonary pathophysiological changes lead to hypercapnia and hypoxemia, in case of non-effective ventilation, and to pulmonary vasoconstriction[8,10]

Blood gas changes and respiratory mechanics are affected by the duration of pneumoperitoneum and patient positioning. The deterioration in respiratory function is reduced when the patient is in the reverse Trendelenburg position and worse when the patient is in the Trendelenburg position[11].

Ventilation strategy during Laparoscopy

The above physiological modifications during Laparoscopy, have been already extensively studied both for adults[12] and for children[7,13–15].

Regarding adult patients, the reasonable idea of using during Laparoscopy a Ventilatory Strategy closer to Protective Ventilation Strategies (with low Vt, PEEP and RM) has been already studied with positive results[16–19].

On the contrary, while RM has been extensively studied in the context of Pediatric Intensive Care Units (PICUs) with positive results as well[20–25], there is a paucity in literature about performing RM during Laparoscopic Surgery in Children.

Study Objectives

In this study, overall, we will test the hypothesis that the application of RM after deflation of pneumoperitoneum during Abdominal Laparoscopy in Children improves Lung Dynamic Compliance (Com_{dyn}) and Perioperative Oxygenation. In this study, we aim to suggest that the Recruitment Maneuver could reverse Lung Atelectasis which is a major cause for respiratory complications intra- and post-operatively.

Investigational Plan

Study population and Control Group

This will be a Prospective, Randomized, Double-blind, Controlled Clinical Trial. After approval of the Institutional Ethics Committee (Papageorgiou General Hospital of Thessaloniki, Scientific and Ethic Committee), this trial will be conducted at Papageorgiou General Hospital, starting from XXXX XXXX. After having obtained written informed consent for the participation in the study (see below: Ethics), 30 children (the number originates from the power analysis – see below) with American Society of Anesthesiology Classification scores (ASA) 1 – 2 will be scheduled for Abdominal Laparoscopic Surgery. The Control Group will be managed with a more conventional anesthetic practice (no recruitment, moderate levels of PEEP). This will be a non-treatment concurrent control trial.

Inclusion Criteria

Children aged between 1-14 years who are scheduled for elective Abdominal Laparoscopy will be eligible for this study.

Exclusion Criteria

Exclusion criteria will be parental or patient refusal, Body Mass Index (BMI) > 40, history of prematurity (birth at post-conceptual age < 37 weeks) or history of congenital lung disorder, clinically recognized airway disease, obstructive or restrictive lung disease, pulmonary hypertension, congenital or acquired heart disease, history of intrathoracic instrumentation, history of severe brain injury and intracranial hypertension.

In addition, all patients who, from the induction of anesthesia until the deflation of pneumoperitoneum, will present any cardiovascular or respiratory major complication (i.e. massive blood loss, arrhythmia, laryngospasm, bronchospasm) will be excluded from the study. In addition, patients will be excluded in case laparoscopy will be converted to open operation due to surgical reasons.

Removal of Patients from Therapy

Hemodynamic instability during the RM will be the main cause for removing patients from therapy, defined as persistent Hypotension (SBP <70 mm Hg in those 1–4 years, <80 mm Hg in those 5–12 years, and <90mm Hg in those >12 years). Hypoxemia (oxygen saturation <92%), bradycardia (heart rate <80 bpm in those <2 years, <60 bpm in those > 2 years) or arrhythmias will also impose the removal of RM and application of therapeutic measurements in case the symptoms insist.

Randomization

In order to perform Randomization, the investigators will use web-software-generated blocks (available at: http://www.randomization.com/). Patients will be randomized to one of the two Ventilation Management Groups (RM or Control group) with 15 patients per group. Each patient assigned to participate in the study will have a sequentially numbered (from 1 to 30) sealed envelope containing Randomization Code (A or B). The Principal Investigator will be the only person who will be aware of the correspondence between Codes and study Groups. The envelopes will be concealed until deflation of pneumoperitoneum, just prior to application of RM (or not). All operations will be performed by the same team of surgeons and by the same anesthesiologists (PI and Second Investigator). In Appendix 1, there is an example of performed permuted blocks randomization with 30 patients, created by this web-software.

Interventions & Treatments

Anesthetic Management (prior to manipulation)

Patients of each group will have the same standardized anesthetic management.

Preoperative assessment

Preoperative assessment will be conducted to all eligible patients by the Principal Investigator (PI) according to local routine practice, few days or the day before the operation. During the preoperative evaluation, PI will obtain written informed consent (see below: Ethics).

Premedication

Patients will be premedicated 30-60 minutes before the procedure with midazolam 0,5 mg/kg po (maximum dose: 15mg).

Monitoring and Induction

ASA Standard noninvasive monitors will be applied before the induction of anesthesia. Induction will take place with inhalational technique with sevoflurane. When patients will reach stage 3 of anesthesia, an intravenous catheter will be inserted. Tracheal intubation, with a cuffed Endotracheal Tube (ETT) appropriate for each patient's size, will be performed after the iv administration of fentanyl 1 mcg/kg, lidocaine 1 mg/kg, rocuronium 0,6 mg/kg and adequate low doses of propofol, if necessary. The ETT cuff pressure will be measured with a Portex low pressure scale manometer and will be maintained at 20-25 cm H_2O. After the

induction, an arterial catheter will be placed in the radial artery for invasive blood pressure monitoring and blood gas measurements.

Maintenance of anesthesia

Maintenance of anesthesia will be performed using sevoflurane (MAC: 1,2-1,4) and a mixture of oxygen and air (FiO_2 0.4). Fentanyl and/or remifentanil will be used for intraoperative analgesia as appropriate.
Ringer's Lactate solution will be used for routine intraoperative fluid management.
Maintenance doses of rocuronium will be guided by Monitoring of Neuromuscular Function of the Ulnar nerve with a Peripheral Nerve Stimulator, to maintain Post-Tetanic Count 1-2.
Subsequent care will be at the discretion of the anesthetic team and will not be part of the study.

Ventilation Strategy

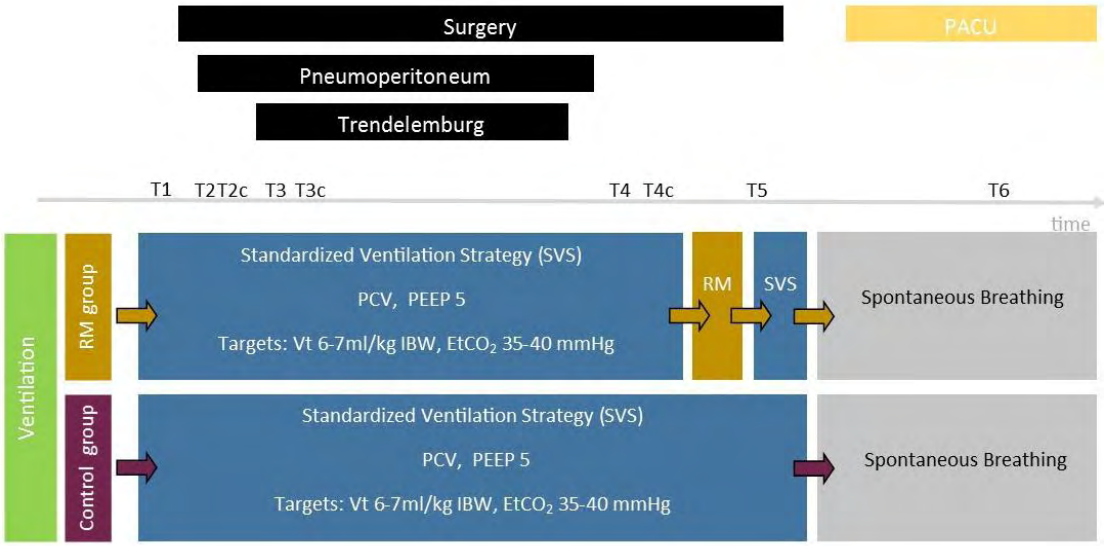
Baseline Ventilation Strategy

Pulmonary ventilation in all patients will be supported with Dräger Primus Anesthesia workstation (SW 4.5n) Ventilator.
Baseline ventilatory parameters include Pressure-Controlled Ventilation (PCV), Positive End-Expiratory Pressure (PEEP) of 5 cm H_2O, and Peak Inspiratory Pressure (PIP) of 10-15 cm H_2O. These parameters will be titrated to achieve a Vt of 6-7 mL/kg Ideal Body Weight (IBW) and a Respiratory Rate (RR) of 12-20 breaths/min and then finally adjusted to achieve an End-tidal CO_2 ($EtCO_2$) of 35-40 mmHg and a target SPO_2 of ≥ 97 %.
Ventilatory parameters will be manually recorded from the Anesthesia workstation monitor screen.
Ventilatory adjustments will be performed during each period, increasing PIP by 2 cm H_2O until a VT of 6-7 mL/kg IBW or within 10% of baseline Vt will be obtained, with a maximum PIP of 25 cm H_2O and $EtCO_2$ of 35-40 mmHg. Respiratory rate will be increased by 2 breaths/min after adjusting Vt to maintain an $EtCO_2$ of 35-40 mmHg. Operating room table angle will be measured with a Johnson Magnetic Angle Locator.

Recruitment Maneuver (Time and Method of RM)

After deflation of pneumoperitoneum, patients in Control group will continue to be ventilated with the same ventilation settings while RM will be performed to patients in RM group.
Since the locally available Anesthesia Workstation does not permit CPAP > 20 cm H_2O[26], RM will be performed by setting Manual / Spontaneous Ventilation Mode and by setting Adjustable Pressure Limitation (APL) Valve to 30 cm H_2O for 30 seconds (Fresh Gas Flow: 5 lt/min, FiO_2 0,4), measured by operating room digital clock, while monitoring the patient for signs of adverse effects, such as hemodynamic instability.

Ventilation Management Flowchart



Anesthetic Management (post-manipulation)

Ventilation Strategy (post-manipulation)

The patients of the RM group, after the RM, will be ventilated with the Standardized Ventilation strategy described above. The patients of the Control group will be ventilated with the same strategy throughout the surgical procedure.

Reversal of the residual blockade, Extubation and Post-Anesthesia Care

At the end of the procedure, residual neuromuscular blockade will be reversed with adequate doses of suggamadex. Tracheal extubation will be performed and the patient will be transported to the Post-Anesthesia Care Unit (PACU) according to the local practice. Patients will be discharged according to standard PACU discharge criteria.

Measurements

Primary endpoint

The improvement of Com_{dyn} will be the primary endpoint of the study. Com_{dyn} will be measured automatically by the Dräger Primus Anesthesia workstation (SW 4.5n). Com_{dyn} is determined from Pplateau and Expiratory Tidal Volume and is equal to the measured Total Compliance [Vt / (Pplateau – PEEP)] minus the System and Hose Compliance determined in the Self-Test of the workstation. Weight-corrected Com_{dyn} will be calculated by dividing Com_{dyn} by the weight of patient in kilograms (Com_{dyn}-wc = Com_{dyn} /weight). Time points of measurements are defined below.

Secondary measurements

Secondary Mechanical Ventilation measurements will be PIP, Expired Vt, RR, MV, $EtCO_2$. Hemodynamic measurements will include Arterial Blood Pressure (Systolic, Diastolic, Mean), and Heart Rate. Blood gas data Measurements will be pH, PO_2, PCO_2, SPO_2 and PO_2/FiO_2.

Time points of measurements

After a stabilization period of 1-2 minutes of Mechanical Ventilation (stabilization defined as a stable Vt for at least 4 consecutive breaths), the above parameters (except Blood gas measurements – see Appendix 6) will be measured at the following time points:

T1	Baseline	After tracheal intubation and ventilation stabilization, with the patient in the supine position and before surgical incision
T2	Pneumoperitoneum	After insufflating CO_2 to the defined IAP
T2c	Correction	After adjusting PIP to return Vt to 6-7 ml/kg IBW or within 10% of baseline
T3	Trendelemburg	After Trendelemburg positioning
T3c	Correction	After Trendelemburg positioning and after adjusting PIP to return Vt to 6-7 ml/kg IBW or within 10% of baseline
T4	Deflation	After completing the laparoscopic procedure with the patient returned to the supine position with the abdomen deflated
T4c	Correction	Post-deflation correction, after returning PIP to baseline
T5	After RM / Before Reversal of Neuromuscular Blockade	3 minutes after RM in the RM group and before the reversal of neuromuscular blockade and Extubation in both groups
T6	Post-operative	30 min after the admission in PACU

Follow up measurements

There will be a postoperative follow up for all patients participating in our study, concerning, among other, signs and symptoms of respiratory failure. Respiratory failure practically means the need for invasive or non-invasive ventilation after extubation. In such case, we should define the pulmonary pathophysiology involved, i.e. pneumonia, atelectasis, pulmonary embolism, pneumothorax, acute lung injury (ALI), asthma, non-cardiogenic pulmonary edema and severe hypercapnia. The routine postoperative oxygen will be applied for 30 minutes postoperatively and will also be noted.

End of Treatment

The treatment (RM) will start 3 minutes after the Pneumoperitoneum deflation and will last for 30 seconds.

End of Study

The patients will be monitored throughout the operation and in the postoperative period too, in PACU and in Pediatric Clinic (see also the measurements section - primary endpoint, secondary measurements and follow up). Patients will be followed up during their hospital stay, the length of which will be recorded. Possible adverse events during the hospital stay will also be recorded.

Efficacy and Safety Issues

The efficacy of the RM to improve Com_{dyn} and gas exchange is the main issue of this study. The investigators regard that Com_{dyn} will be statistically significantly improved in the RM group compared to Control group. In this study, we consider clinically significant a 20% increase in the weight corrected mean Com_{dyn} in the RM group.

This improvement in lung compliance maybe would not be clinically significant, as our study population consists of healthy children (children with ASA I-II classification). Nevertheless, the possibility of underlying comorbidities should always be taken into account and anesthesia in addition to these comorbidities could negatively influence cardiovascular and pulmonary function, and thus patients' outcome. This is the reason that ventilation strategy adopted in this study has a protective-lung ventilation strategy orientation, with lower Vt and higher PEEP than usual in clinical practice the past years.

The investigators regard that there would be statistical significant difference within RM group, as well. Com_{dyn} is expected to be significantly improved in post-RM measurements in comparison to baseline Com_{dyn}, for the patients of RM group. A 20% increase in Com_{dyn} would be clinically significant too.

Secondarily, the investigators regard that RM will improve post-RM intra- and post-operative PO_2 and ratio PO_2/FiO_2. For the population of this study (children ASA I-II), this improvement may also not have a clinically significant impact.

Although recruitment procedures are generally well tolerated with few adverse effects, there are several potential complications that could occur[28].

Because of the transient increase in intrathoracic pressure and consequent reduction in venous return, cardiac output may be impaired, producing hypotension – a complication that appears to be more common in patients with poor chest wall compliance and limited oxygenation response from recruitment[29]. Generally, hypotension during the maneuver suggests relative volume depletion[28]. In this study, RM will be performed with a parallel beat-to-beat hemodynamic monitoring (Invasive Arterial Blood Pressure Monitoring). Patients with severe hemodynamic instability (hypotension or arrhythmias) will be removed from the study, as already mentioned. In these patients, the removal of RM is expected to improve arterial blood pressure – in case hypotension persists, vasoconstrictors (ephedrine, norepinephrine) will be administered in adequate for each patient doses.

A decrease in cerebral perfusion pressure has been noted as a RM complication, which may contraindicate this procedure in head injured patients[30]. In this study, patients with history of severe brain injury and intracranial hypertension meet the exclusion criteria and will be excluded.

Barotrauma, including pneumothorax and pneumomediastinum, has been also described but the exact risk remains unclear[28]. Nevertheless, when RM is performed with the duration and the pressure levels adopted in this study (Sustained Inflation with CPAP 30 mm H_2O for 30

seconds) is thought to be a safe clinical maneuver without such major complications to children[20–25]

Adverse Events

In addition to RM complications (see above), any perioperative adverse event will be recorded, such as laryngospasm, bronchospasm, pneumothorax, subcutaneous emphysema, hypotension, bradycardia, desaturation (SPO_2 < 92%) or hypercapnia ($PaCO_2$ > 45 mmHg).

Patient Records

For each patient we will have 4 data files

1. Demographic, intra- and post-operative patient data (Appendix 3)
2. Mechanical Ventilation data (Appendix 4)
3. Hemodynamic data (Appendix 5)
4. Blood Gas data (Appendix 6)

Blinding Procedure

This will be a Double-blind clinical study. Patients will not be aware of ventilation strategy during the operation. The only un-blind person will be the Principal Investigator (PI). After the RM (or not), at T4 point time (see below), a Second Investigator (SI) will come into the operating room and will record measurements from monitor. The same person will also perform blood gas analyses on the specified time points and postoperative records in PACU. The measurements will be recorded in special files for each separate patient with patient id number and then will be entered in a SPSS data file (SPSS version 22) and will be analyzed. Analysis will be performed by the two investigators separately (the PI will be un-blind) and results should be matched.

Statistical Methods

Sample size determination

Power Analysis will be conducted for determination of the Sample Size of this study, in order to estimate a Sample Size that is required so that the study would have adequate power to detect clinically meaningful differences between the two groups, especially concerning Lung Compliance (which is the primary outcome of the study).

For this analysis, we used G*Power Software[27] (version 3.1.9.2), which is freely available at http://www.gpower.hhu.de/en.html from the Heinrich-Heine-Universität of Dusseldorf.

Our Power Analysis is based on a published study in literature, from Manner et al[15]. Assuming that Clinically meaningful difference between the two groups is 20% of the mean value and SD of the observed Lung Compliance is 15% of the mean value[15], therefore Size effect = 0.2 /

0.15 = 1.33, with two-sided testing, with alpha = 0.05 and power = 0.9 (therefore, b = 1 – power = 0.1). Under these assumptions, G*Power calculated that we will need minimum 13 patients in each group (totally, 26 subjects) for this study to have adequate power.
Assuming a 15% drop-out rate of the initial number of subjects enrolled to this trial, total number of **30** patients will have to be randomized
Alternatively, using the adequate mathematic formula (see Appendix 2) and the results from the Manner et al[15] study, we confirm a minimum Sample Size of 26 patients.

Statistical Analysis

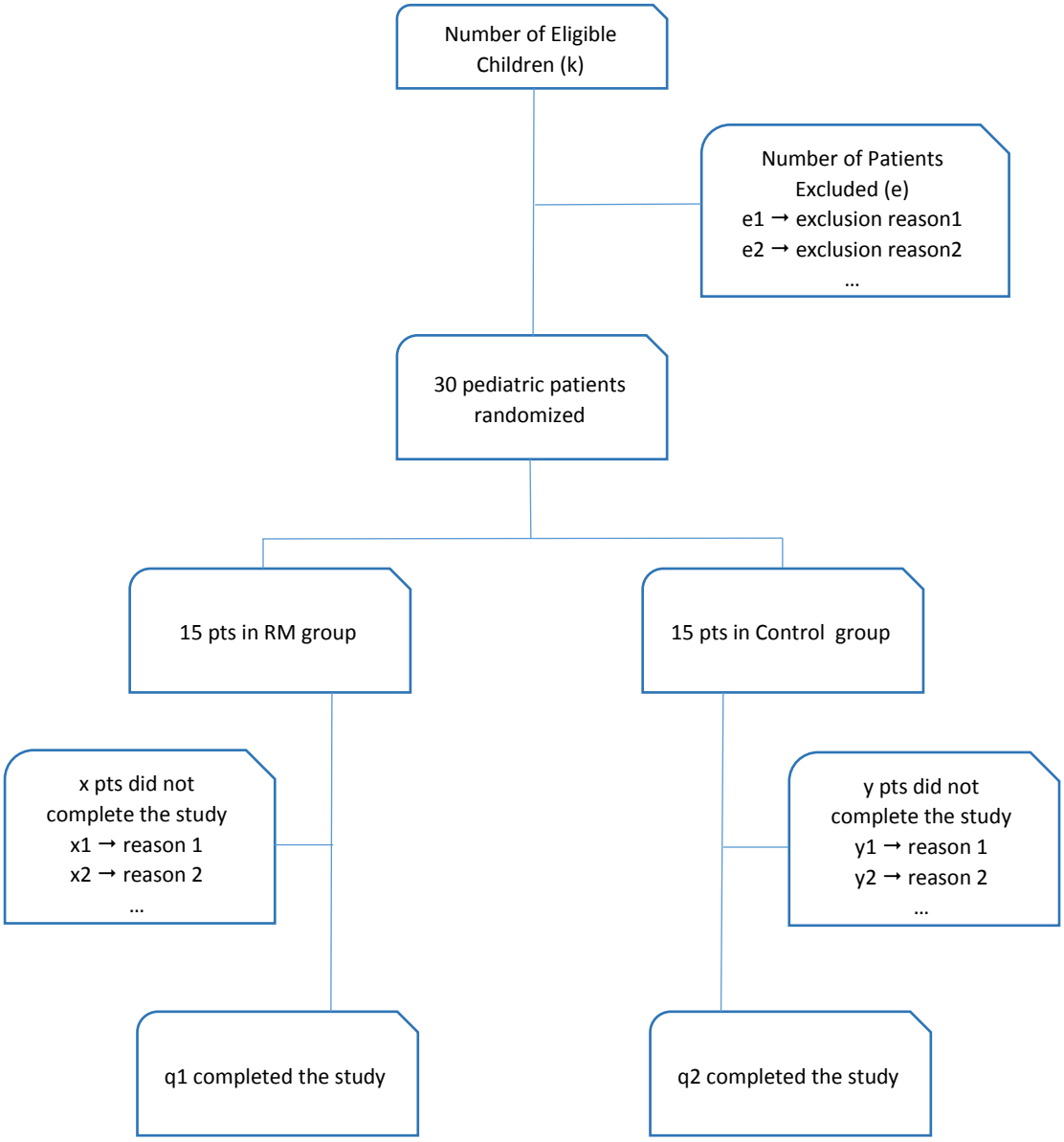
Investigators will assess data for normality (using Kolmogorov Smirnoff and Shapiro Wilks test). Ventilatory and hemodynamic data and intraoperative and postoperative variables (all continuous variables) will be presented as mean values (+/- SD). Data will be compared between and within groups using Mixed Analysis of Variance (Mixed Anova - General Linear Model) if are normally distributed or with Kruskal Wallis test in case that we do not have normally distributed data. Bonferroni correction will be used for multiple comparisons correction. In order to check and supplement our Mixed Analysis of Variance we will also use two-sample t-test to compare the two groups at each time point (for ventilatory and hemodynamic variables). Patient and procedural characteristics will be compared between groups using independent-sample t-test for continuous variables and chi-square test for categorical variables. Two tailed P-values < 0.05 will be considered statistically significant. For data analysis, the investigators will use SPSS statistical software (version 22).

Data Presentation Plan

Flow chart

Supposing the number of eligible children is *k* and the number of excluded children before randomization is *e*, with possible reasons for exclusion (e1, e2, e3), trial flow chart is shaped as below.

Finally, 30 patients will be randomized in two groups.



If the great majority of the patients will complete the study, we will use a Per Protocol analysis. If many of the randomized patients will not complete the study, we will use an Intention to Treat analysis of data (ITT). According to ITT analysis of data, we will use all the data of all the randomized patients regardless of whether they completed the trial or not. For the missing values we will use the Last Observation Carried Forward (LOCF) approach.

Patient demographics should be similar between the two groups (Table 1). If not, differences will be mentioned and this will be a major limitation of our study.
Intraoperative characteristics (anesthesia duration, pneumoperitoneum duration, IAP, blood loss, administration of crystalloids and / or blood products and intraoperative use of vasoconstrictors should be similar between the two groups (Table 1).
The length of hospital stay and the possible differences between the two groups should be mentioned (Table 1). The number of patients that will develop postoperative pulmonary complications (mainly pneumonia, diagnosed with clinical evaluation and chest radiogram) and possible differences between the two groups should also be recorded.
Pneumothorax and pneumomediastinum would be serious complications, which could have a strong relationship with the RM manipulation, and should be also recorded (see adverse event section above)

Table 1. Patient demographics presented as mean (SD) or n = number of patients. Intra- post-operative events presented as mean (SD)

	RM group (n = 15)	Control group (n =15)
Patient Demographics		
Age (years) [mean (SD))		
ASA (n) [mean (SD))		
Weight (grams)		
Height (m)		
BMI (kg/m2)		
Sex (male / female)		
Intraoperative characteristics		
Duration of Anesthesia (min)		
Duration of Pneumoperitoneum (min)		
IAP (mmHg)		
Crystalloids (ml)		
Blood (units)		
Need for Vasoconstrictor drugs (n)		
Postoperative characteristics		
Length of Hospital stay (days)		
Pulmonary Complications (n)		
Pneumothorax (n)		
Pneumomediastinum (n)		
Pneumonia (n)		
Other (n)		

Study committees

Executive Committee (EC)

The EC will consist of members of the academic leadership of the study and 1 member from the sponsor. The EC will ultimately be responsible for the conduct of the study including addressing any Data Monitoring Committee recommendations and overseeing publication of the results.

Steering Committee

A Steering Committee will be formed consisting of members who are lead investigators. The Steering Committee will advise and assist the EC with regard to the scientific and operational aspects of the study.

Independent Data Monitoring Committee (DMC)

This study will be conducted under the auspices of an independent Data Monitoring Committee (DMC), which will monitor the progress of the study and ensure that the safety of subjects enrolled in the study is not compromised. The DMC will have a chairperson and include at least 2 anesthesiologists, a pediatric surgeon as well as a statistician. This committee will review accumulating data on a regular basis and may request to review partially unblinded or unblinded accumulating data. The DMC will make recommendations to the Executive Committee and Sponsor regarding the continuing safety of subjects currently enrolled and yet to be enrolled in the trial. At all times during the course of the study, the DMC may request access to unblinded data if needed.

Ethical Considerations

This study will be conducted in compliance with the protocol, the ethical principles set forth in the Declaration of Helsinki, the ICH Guideline E6 for GCP and applicable regulatory requirement(s). Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting research studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Institutional Review Board / Independent Ethics Committee

The protocol and any amendments, the Investigator's Brochure, the subject informed consent and any information on compensation for study-related injuries or payment to subjects, will receive IRB / IEC approval prior to initiation of the study. During the study the investigator will send to the IRB any reports of adverse events that are serious, unlisted, and associated with the investigational technique and any new information that may adversely affect the safety of the subjects or the conduct of the study.
Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their task.

Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the parents or patient's legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The ICF will be obtained by PI during the preoperative evaluation.

Consent must represent the minor's presumed will and may be revoked at any time.

Patients will be informed about the trial to the extent compatible with their understanding and, if capable, patients should sign and personally date informed consent form.

In addition, the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from this clinical trial at any time will be considered by the investigators.

Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor, subjects should be identified by a unique subject identifier as designated by the Sponsor. Sponsor personnel whose responsibilities require access to personal data should agree to keep the identity of study subjects confidential.

Discussion

Protective Lung Ventilation Strategy, a strategy characterized by low Vts, high PEEP and the use of RMs, has been developed in ICU context as a ventilation strategy for ARDS adult patients and is now the current standard of care for MV in critically ill patients. Over the last years, the use of such ventilatory strategies in the perioperative period has mobilized interesting research studies, especially for adult population[4], with positive results in preventing Post-operative Pulmonary Complications[31,32].

Previous studies

In regard to RM in Adults Laparoscopy, in several studies it has been demonstrated that RM is effective in improving lung compliance and lung mechanics[16–18,29]. Nevertheless, children should not be considered as small adults and the generalization of such conclusions could not be sufficiently justified.

In the context of Pediatric Intensive Care Units (PICUs), studies have been developed to estimate the benefits of RMs.

In an observational prospective study, Duff et al. performed Sustained Inflation (SI) (30–40 cm H_2O for 15–20 seconds) on ventilated patients in the PICU with hypoxemia. During the RM there was no blood pressure, heart rate or oxygen saturation changes, and a significant FiO_2 reduction was seen in the 6 hours following the procedure. They concluded that RMs (as SI) are safe in ventilated PICU patients and are associated with a significant reduction in oxygen requirements for the 6 h after the RM[20].

In ARDS children, Gaudencio et al. using progressive PEEP levels and 15 cm H_2O controlled pressure until obtaining less than 5% collapse in the tomography, found improved PaO_2/FiO_2 ratio[21].

However, clinical trials in children in ICU have still shown controversial findings[21]. In addition to the observed beneficial effects, RM in critically ill pediatric patients may also have untoward effects such as inflammatory cytokines release[21]

Two studies performed in children with not known lung disease undergoing general anesthesia for either computed tomography or magnetic resonance imaging showed a decrease in atelectasis as measured by thoracic computed tomography or magnetic resonance imaging with intermittent RMs[22,33,34]

Finally, in the context of perioperative period, Marcus et al. demonstrated that a RM improves Com_{dyn} in anaesthetized young children; laparoscopic surgery, however, was included in exclusion criteria [35]. Scohy et al. concluded that a RM with relative high PEEP significantly improves compliance, oxygenation, ($PaCO_2$ – $PETCO_2$) difference and EELV in pediatric patients undergoing cardiac surgery for congenital heart disease, with the RM being performed post-operatively, in PICU.

To our knowledge, this study will be the first where RM will be performed intra-operatively in pediatric patients under laparoscopy.

Limitations of the study

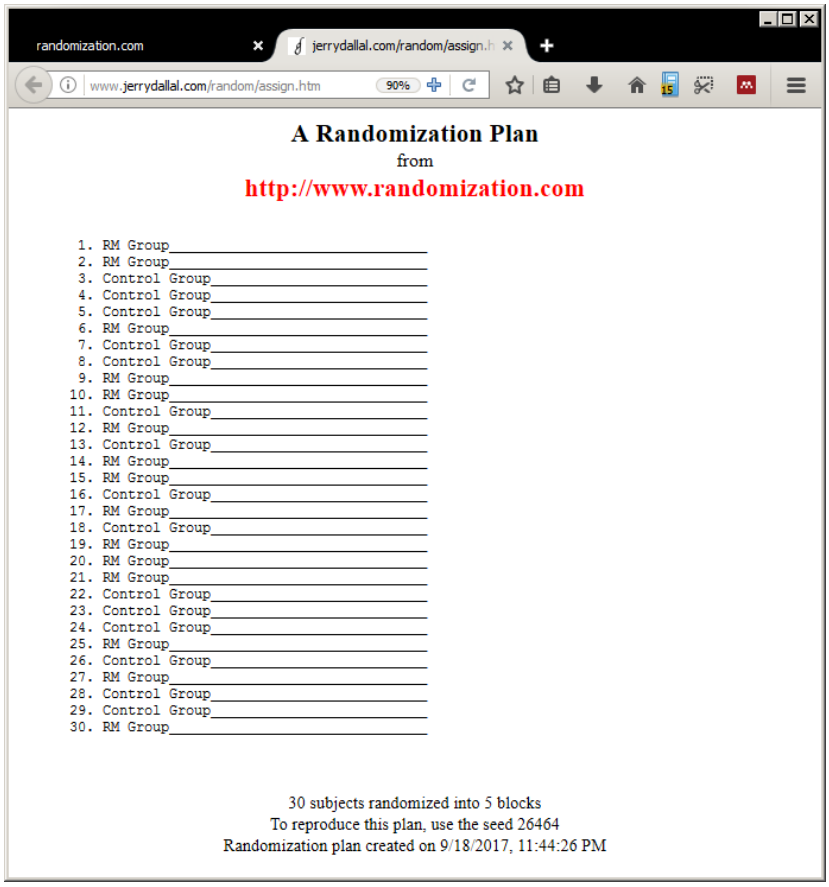
This study is aimed to demonstrate a restoration in Com_{dyn} and gas exchange by the RM. It will not be powered to describe overall pulmonary outcomes, such as postoperative atelectasis or lung infection.

Lung mechanics include a variety of properties approaching lung function in a spherical way; this study, however, is limited to Com_{dyn} – as an easily accessible parameter in everyday clinical practice.

Our study population will be healthy and heterogeneous in terms of age and therefore size. Although Com_{dyn} will be adjusted by weight, Com_{dyn} may be affected by other factors related to age, such as compliance of the chest wall and resistance of the airways. In addition, both the ventilator used and the measurement technique used to obtain Com_{dyn} could also affect our results.

Appendix 1 - Permuted Blocks Randomization

30 subjects randomized into 5 blocks



Appendix 2 - Sample Size Estimation

Using Power Analysis for Comparison of Means for Two Independent Groups [Clinical Trial Methodology. Lecture 2016, Elias Zintzaras]

The formula to calculate the sample size is

$$N = \frac{4\sigma^2(z_{crit} + z_{pwr})^2}{D^2},$$

where N is the total sample size (the sum of the sizes of both comparison groups), σ is the assumed SD of each group (assumed to be equal for both groups), the Z_{crit} value is that given for the desired significance criterion, the Z_{pwr} value is that given for the desired statistical power, and D is the minimum expected difference between the two means[36]

Appendix 3 - Demographic intra- & post-operative patient's data

Patient ID	
Age (years)	
ASA (n)	
Weight (grams)	
Height (m)	
BMI (kg/m2)	
Sex (male / female)	
Type of Surgery	
Duration of Anesthesia (min)	
Duration of Pneumoperitoneum (min)	
IAP (mmHg)	
Crystalloids (ml)	
Blood (units)	
Need for Vasoconstrictor drugs (n)	
Length of Hospital stay (days)	
Pulmonary Complications (n)	

Appendix 4 - Mechanical Ventilation patient's data

Patient ID:	Time Point							
	T1	T2	T2c	T3	T3c	T4	T4c	T5
Com_{dyn} (ml/cm H_2O)								
Com_{dyn}-wc (ml/cm H_2O*kg)								
PIP (cm H_2O)								
Vt (ml)								
RR (breaths/min)								
MinV (ml)								
$EtCO_2$ (mmHg)								

Appendix 5 - Hemodynamic patient's data

Patient ID:	Time Point								
	T1	T2	T2c	T3	T3c	T4	T4c	T5	T6
SBP									
DBP									
MAP									
HR									

Appendix 6 - Patient's Blood Gas Data

Patient ID:	Time Point								
	T1	T2	T2c	T3	T3c	T4	T4c	T5	T6
pH		-	-	-	-	-			
PO_2		-	-	-	-	-			
PCO_2		-	-	-	-	-			
PO_2 / FiO_2		-	-	-	-	-			
SpO_2									

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