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Protective mechanical ventilation during open surgery on the abdomen with general anaesthesia

Submission date
29/10/2010

Recruitment status
No longer recruiting

Registration date
06/12/2010

Overall study status
Completed

Last Edited
21/07/2015

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
When abdominal surgery is carried out with general anesthesia (i.e., the patient is given a drug to make them unconscious), a machine called a ventilator must be used to assist or replace spontaneous breathing (mechanical ventilation). Mechanical ventilation may cause partial collapse of the lungs, a medical condition termed 'atelectasis'. Atelectasis can cause problems after surgery, sometimes leading to severe illness. Measures to prevent atelectasis were found to be beneficial in studies of mechanically ventilated Intensive Care Unit patients. It is uncertain whether such preventive measures also benefit patients undergoing surgery. This study compares two ventilation strategies. One generally used strategy uses low airway pressures; the other less frequently used strategy uses higher airway pressures. The strategy using lower pressures may lead to collapse of parts of the lung; the strategy using higher pressures may prevent partial lung collapse, but at the same time may cause low blood pressure, requiring infusion of more fluids and/or agents to maintain adequate blood pressures during surgery. We do not know which of these two ventilation strategies is the best. However, we think the strategy using higher pressures can protect against atelectasis and therefore protect against lung problems after surgery.

Who can participate?
Patients over 18 years of age who will be mechanically ventilated because of planned general anesthesia for abdominal surgery. Patients with an increased risk of lung problems after surgery are selected for this study.

What does the study involve?
Participants will be randomly allocated to be mechanically ventilated according to one of the two ventilation strategies (i.e., lower or higher airway pressure) throughout the surgical procedure.

What are the possible benefits and risks of participating?
You will not experience any discomfort because you will be under general anesthesia during mechanical ventilation. You will be closely monitored during and after surgery for up to 5 days.

We cannot promise the study will help you, but the information we get from this study may benefit future patients.

Where is the study run from?
Academic Medical Center, Amsterdam. This is an international trial in which up to 40 centers worldwide will participate.

When is the study starting and how long is it expected to run for?
The study started recruiting patients in February 2011 and is expected to run until June 2013.

Who is funding the study?
European Society of Anesthesiology.

Who is the main contact?
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Study website
https://sites.google.com/site/provhilo/

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01441791

Secondary identifying numbers
NTR2517

Study information

Scientific Title
Protective ventilation during general anaesthesia for open abdominal surgery: a randomised controlled trial

Acronym
PROVHILO

Study objectives
Post-operative respiratory failure, in particular after abdominal surgery and general anaesthesia, adds to morbidity and mortality of surgical patients. Lung protective mechanical ventilation, with the use of positive end-expiratory pressure (PEEP) and recruitment manoeuvres, has the potential to prevent lung injury in patients with injured lungs. It is the question whether PEEP and recruitment also protects the lungs in patients without previous lung injury.

Please note, the Steering Committee decided to add an amendment to the trial protocol as of 10 /07/2011. In this amendment the adjusted criteria for chest Xray and standard laboratory investigations are explained and stated, because of the costs related to performing 2x chest X-ray and 4x laboratory tests. The changes can be foud in the interventions section below.

On 21/05/2013 the following changes were made to the trial record:
1. The overall trial end date was changed from 01/12/2013 to 30/04/2013.
2. France and Sweden were removed from the countries of recruitment, and Belgium, Chile, Croatia, UK and USA were added to the countries of recruitment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical commission of the AMC, Amsterdam. Amendent approved on 10/07/2011.

Study design
Multinational prospective double-blind randomised controlled two-arm trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Patient information can be found at: https://docs.google.com/viewer?a=v&pid=sites&srcid=ZGVmYXVsdGRvbWFpbnxwcm92aGlsb3xneDo2YThiNWMzOGExYWQyYmFh

Health condition(s) or problem(s) studied
Ventilator acquired lung injury (VILI)

Interventions

1. The conventional group will be ventilated with low PEEP (max 2 cm H2O), without recruitment
2. The interventional group will be ventilated with higher PEEP (12 cm H2O), with intra-operative recruitment manoeuvres; directly after induction of anaesthesia, after any disconnection from the mechanical ventilator and directly before extubation.

The recruitment manoeuvre will be performed as follows:
1. Set peak inspiratory pressure limit at 45 cm H20
2. Set tidal volume at 8 ml/kg IBW and respiratory rate at 6 - 8 breaths/min, while PEEP at 12 cm H20. In case an anaesthesia ventilator does not allow a rate of 8/min or lower, then the lowest possible respiration rate allowed by the machine should be used
3. Set inspiratory to expiratory ratio (I:E) at 1:2
4. Increase tidal volume in steps of 4 ml/kg IBW until plateau pressure is 30 - 35 cm H20
5. Allow 3 breaths with the plateau pressure of 30 - 35 cm H20
6. Set respiratory rate, I:E, inspiratory pause and tidal volume back at values preceding recruitment, while maintaining the PEEP at 12 cm H20

Added 25/10/2011 in accordance with protocol change from 10/07/2011:

Chest radiography (CXR):
1. CXRs (pre-operative and on post-operative day 1) will not be standard.
However, a CXR can be taken at the lowest clinical threshold. In the occurrence of one of the following criteria obtaining a CXR should seriously be considered:

Pre-operative
1.1 SpO2 < 96% (in supine position in room air)
1.2 Increased dyspnea within last 2 months
1.3 Upper or lower respiratory tract infection in last 30 days
1.4 COPD with inhalation therapy or glucocorticosteroid treatment
1.5 Presence of clinical signs of congestion (e.g., dyspnea, edema, rales and/or jugular venous distension)

Post-operative
1.6 SpO2 < 96% (in supine position in room air)
1.7 PaO2 < 60 mmHg
1.8 Suspected pulmonary infection (new or changed sputum or fever > 38.3 oC or WBC > 12 x 109/ml or started antibiotics, without any other focus of infection)
1.9 Presence of clinical signs of congestion (e.g., dyspnea, edema, rales and/or jugular venous distension)

Criteria for obtaining a CXR on day 2 to 5 remain unchanged; CXRs on those days should be obtained on clinical judgment by attending physicians. If a CXR is obtained, radiological signs should be used for scoring post-operative pulmonary complications of that day

2. Timing pre-operative CXR:
CXR obtained within 6 months before surgery is acceptable, provided there has been no clinical change in pulmonary condition of the patient
3. Timing of post-operative CXR:
CXRs obtained until 24 hours after surgery are accepted as day 1 post-operative CXR
4. If a CXR is obtained, the radiology report should be translated into English, Italian or German.

Standard laboratory tests:
1. Standard laboratory tests on day 3 and day 5 are not necessary. However, it has our preference to collect them if possible. If laboratory tests are ordered by the attending physician, they can be used for scoring extra-pulmonary complications.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Post-operative pulmonary complications composed of:
1. Mild respiratory failure (PaO2 less than 60 mmHg or SpO2 less than 90% in room air but responding to supplemental oxygen (excluding hypoventilation)
2. Severe respiratory failure (need for non-invasive or invasive mechanical ventilation or a PaO2 less than 60 mmHg or SpO2 less than 90% despite supplemental oxygen (excluding hypoventilation)
3. ALI/ARDS (by the consensus criteria - only in case of non-invasive or invasive mechanical ventilation)
4. Suspected pulmonary infection (in case patient receives antibiotics and meets at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest X-ray when clinically indicated, timpanic temperature greater than 38.3°C, WBC count greater than 12,000/mm3)
5. Pulmonary infiltrate (chest X-ray demonstrating monolateral or bilateral infiltrate)
6. Pleural effusion (chest X-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemi-thorax with preserved vascular shadows)
7. Atelectasis (suggested by lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent nonatelectatic lung)
8. Pneumothorax (defined as air in the pleural space with no vascular bed surrounding the visceral pleura)
9. Bronchospasm (defined as newly detected expiratory wheezing treated with bronchodilators)
10. Aspiration pneumonitis (defined as respiratory failure after the inhalation of regurgitated gastric contents)
11. Cardiopulmonary oedema (defined as clinical signs of congestion, including dyspnoea, oedema, rales and jugular venous distention, with the chest X-ray demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates)

These outcomes will primarily be presented as a total percentage of post-operative pulmonary complications.

Primary and secondary endpoints are assessed on day 1, 3 and 5 after surgery, and at the last day before discharge or on day 90, if patient is still admitted to the hospital at that time. Clinical data and the presence of pulmonary and extra-pulmonary post-operative complications will be scored; the day of development of any complication will be indicated.

Secondary outcome measures

1. Intra-operative complications (desaturation, barotrauma, hypotension during recruitment, need for vasopressors)
2. Need for ICU admission (if not as part of routine) or ICU readmission
3. Hospital-free days at day 90
4. Post-operative wound healing (devided in superficial, deep and organ/space)
5. Systemic levels of markers of pulmonary inflammation, markers of acute lung injury and markers of distal organ injury
6. Post-operative non-pulmonary organ function, defined as follows:
6.1. Systemic inflammatory response syndrome (SIRS); presence of two or more of the following findings:
6.1.1. Body temperature less than 36°C or greater than 38°C
6.1.2. Heart rate greater than 90 beats per minute
6.1.3. Respiratory rate greater than 20 breaths per minute or, on blood gas, a PaCO2 less than 32 mmHg (4.3 kPa)
6.1.4. White blood cell (WBC) count less than 4,000 cells/mm3 or greater than 12,000 cells/mm3 or greater than 10% band forms
6.2. Sepsis (SIRS in response to a confirmed infectious process; infection can be suspected or proven by culture, stain, or polymerase chain reaction [PCR]), or a clinical syndrome pathognomonic for infection. Specific evidence for infection includes WBCs in normally sterile fluid (such as urine or cerebrospinal fluid [CSF]), evidence of a perforated viscus (free air on abdominal x-ray or computed tomography [CT] scan, signs of acute peritonitis), abnormal chest x-ray (CXR) consistent with pneumonia (with focal opacification), or petechiae, purpura, or purpura fulminans
6.3. Severe sepsis (sepsis with organ dysfunction, hypoperfusion, or hypotension)
6.4. Septic shock: sepsis with refractory arterial hypotension or hypoperfusion abnormalities in spite of adequate fluid resuscitation; signs of systemic hypoperfusion may be either end-organ dysfunction or serum lactate greater than 4 mmol/dL. Other signs include oliguria and altered mental status. Patients are defined as having septic shock if they have sepsis plus hypotension after aggressive fluid resuscitation, typically upwards of 6 litres or 40 ml/kg of crystalloid.
6.5. Extra-pulmonary infection (wound infection or any other infection)
6.6. Coma (Glasgow Coma Score less than 8 in the absence of therapeutic coma or sedation)
6.7. Acute myocardial infarction (detection of rise and/or fall of cardiac markers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with: symptoms of ischaemia, ECG changes indicative of new ischaemia, development of pathological Q-waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or sudden unexpected cardiac death, involving cardiac arrest with symptoms suggestive of cardiac ischaemia (but death occurring before the appearance of cardiac markers in blood)
6.8. Acute renal failure: renal failure documented as follows -
6.8.1. Risk: increased creatinine x 1.5 or glomerular filtration rate (GFR) decrease greater than 25% or urine output (UO) less than 0.5 ml/kg/h x 6 hr
6.8.2. Injury: increased creatinine x 2 or GFR decrease greater than 50% or UO less than 0.5 ml/kg /h x 12 hr
6.8.3. Failure: increase creatinine x 3 or GFR decrease greater than 75% or UO less than 0.3 ml/kg /h x 24 hr or anuria x 12 hrs
6.8.4. Loss: persistent ARF = complete loss of kidney function greater than 4 weeks
6.9. Disseminated intravascular coagulation (DIC) score, documented as follows:
6.9.1. Platelet count less than 50 (2 points), less than 100 (1 point), or = 100 (0 points)
6.9.2. D-dimer greater than 4 µg/ml (2 points), greater than 0.39 µg/ml (1 point) or = 0.39 µg/ml (0 points)
6.9.3. Prothrombin time greater than 20.5 seconds (2 points), greater than 17.5 seconds (1 point) or = 17.5 seconds (0 points)

6.9.4. If = 5 points: overt DIC
6.10. Gastro-intestinal failure: gastro-intestinal bleeding or gastro-intestinal failure (GIF) score documented as follows: 0 = normal gastrointestinal function; 1 = enteral feeding with under 50% of calculated needs or no feeding 3 days after abdominal surgery; 2 = food intolerance (FI) or intra-abdominal hypertension (IAH); 3 = FI and IAH; and 4 = abdominal compartment syndrome (ACS)
6.11. Hepatic failure (serum bilirubin level greater than 2 mg/dL with elevation of the transaminase and lactic dehydrogenase levels above twice normal values)

Primary and secondary endpoints are assessed on day 1, 3 and 5 after surgery, and at the last day before discharge or on day 90, if patient is still admitted to the hospital at that time. Clinical data and the presence of pulmonary and extra-pulmonary post-operative complications will be scored; the day of development of any complication will be indicated.

Overall study start date
01/12/2010

Completion date
30/04/2013

Eligibility

Key inclusion criteria
1. Planned elective abdominal surgery
2. General anaesthesia with intravenous medication
3. High or intermediate risk for post-operative pulmonary complications
4. Aged greater than or equal to 18 years, either sex

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
900 patients recruited by 21/01/2013

Key exclusion criteria
1. Aged less than 18 years
2. Body mass index greater than 40 kg/m^2
3. Laparoscopic surgery
4. Previous lung surgery (any)
5. Persistent haemodynamic instability, intractable shock (considered haemodynamic unsuitable for the study by the patient's managing physician)

6. History of previous severe chronic obstructive pulmonary disease (COPD) (non-invasive ventilation and/or oxygen therapy at home, repeated systemic corticosteroid therapy for acute exacerbations of COPD)
7. Recent immunosuppressive medication (patients receiving chemotherapy or radiation therapy within the last 2 months)
8. Severe cardiac disease (New York Heart Association class III or IV, or acute coronary syndrome, or persistent ventricular tachyarrhythmia's)
9. Mechanical ventilation greater than than 30 minutes (e.g., in cases of general anaesthesia because of surgery) within last 30 days
10. Pregnancy (excluded by laboratory analysis)
11. Acute lung injury or acute respiratory distress syndrome expected to require prolonged post-operative mechanical ventilation
12. Neuromuscular disease (any)
13. Consented for another interventional study or refusal to participate in the study

Date of first enrolment
01/02/2011

Date of final enrolment
30/04/2013

Locations

Countries of recruitment
Austria

Belgium

Chile

Croatia

Germany

Italy

Netherlands

Spain

United Kingdom

United States of America

Study participating centre
Academic Medical Center, University of Amsterdam
Amsterdam
Netherlands
1105 AZ

Sponsor information

Organisation
Academic Medical Centre (AMC) (Netherlands)

Sponsor details
Meibergdreef 9
Amsterdam
Netherlands
1105 AZ

Sponsor type
Hospital/treatment centre

Website
http://www.amc.nl/

ROR
https://ror.org/03t4gr691

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Academisch Medisch Centrum

Alternative Name(s)
Academic Medical Center, AMC

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Netherlands

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	06/05/2011		Yes	No
Results article	results	09/08/2014		Yes	No