Original Articles

Low tidal volume ventilation during anaesthesia for major surgery: protocol and statistical analysis plan

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Mechanical ventilation is a mandatory intervention in patients undergoing general anaesthesia for major surgery. However, it has many potentially detrimental effects, the most dangerous being ventilator-induced lung injury (VILI). VILI can result from cyclic overstretching of aerated alveoli induced by the use of high tidal volume (volutrauma), from repeated opening and closing of peripheral airways induced by the use of insufficient levels of positive end-expiratory pressure (PEEP) (barotrauma) and from the direct use of high airway pressures (barotrauma).1,2

For several years, a high tidal volume strategy using tidal volumes higher than 10 mL/kg of predicted body weight (PBW) has been advocated for intraoperative ventilation.3 The potential advantages of this strategy include reduced incidence of atelectasis, owing to the maintenance of a high pressure in the airways, and a consequent reduction in risk of perioperative hypoxaemia.3 However, the potential benefits of a low tidal volume strategy first became apparent in studies of critically ill patients with acute respiratory distress syndrome, in whom the use of low tidal volume is strongly associated with better clinical outcomes.4 In addition, recent studies suggest that the use of high tidal volumes can initiate lung injury even in healthy lungs, especially during major surgery with its associated inflammatory response, making the lungs more prone to VILI.5

A recent multicentre clinical trial in France showed that, in a high risk population, a bundle of care composed of low tidal volume, moderate levels of PEEP and recruitment manoeuvres reduced the incidence of major complications in patients undergoing abdominal surgery compared with the use of high tidal volume and no PEEP.6 Nevertheless, this study compared a bundle of interventions and it is impossible to isolate which component was beneficial. A recent multicentre clinical trial sought to address this issue and compared the effect of a low PEEP strategy (< 2 cmH2O) with a high PEEP strategy (12 cmH2O) in patients undergoing major abdominal surgery and receiving low tidal volume ventilation.7 In this study, the use of high levels of PEEP was not associated with better outcomes, suggesting

ABSTRACT

Background: Mechanical ventilation is mandatory in patients undergoing general anaesthesia for major surgery. Tidal volumes higher than 10 mL/kg of predicted body weight have been advocated for intraoperative ventilation, but recent evidence suggests that low tidal volumes may benefit surgical patients. To date, the impact of low tidal volume compared with conventional tidal volume during surgery has only been assessed in clinical trials that also combine different levels of positive end-expiratory pressure (PEEP) in each arm. We aimed to assess the impact of low tidal volume compared with conventional tidal volume during general anaesthesia for surgery on the incidence of postoperative respiratory complications in adult patients receiving moderate levels of PEEP.

Study design and methods: Single-centre, two-arm, randomised clinical trial. In total, 1240 adult patients older than 40 years scheduled for at least 2 hours of surgery under general anaesthesia and routinely monitored with an arterial line were included. Patients were ventilated intraoperatively with a moderate level of PEEP (5 cmH2O) and randomly assigned to tidal volume of 6 mL/kg predicted body weight (low tidal volume) or 10 mL/kg predicted body weight (conventional tidal volume in Australia).

Main outcome measure: The primary outcome is the occurrence of postoperative respiratory complications, recorded as a composite endpoint of adverse respiratory events during the first 7 postoperative days.

Results and conclusions: This is the first well powered study comparing the effect of low tidal volume ventilation versus high tidal volume ventilation during surgery on the incidence of postoperative respiratory complications in adult patients receiving moderate levels of PEEP.

Trial registration: Australian New Zealand Clinical Trials Registry (ACTRN12614000790640).
that tidal volume may be more important in preventing complications. Indeed, an individual patient meta-analysis including data from 21 studies supported this notion.

Our group recently reported that, in Australia, the use of high tidal volume (about 10 mL/kg PBW) is common, the average tidal volume during major abdominal surgery is about 10 mL/kg of PBW, and the standard level of PEEP used in the intraoperative period is 5 cmH$_2$O. These findings suggest that in this setting a high tidal volume strategy in combination with moderate levels of PEEP is likely the most common strategy for intraoperative ventilation in Australia. The findings also suggest that the control groups of previous randomised controlled trials of a low tidal volume strategy for intraoperative ventilation do not reflect the practice of intraoperative mechanical ventilation in Australia. To date, no suitably powered randomised clinical trial has assessed the isolated impact of tidal volume in surgical patients in the setting of a fixed moderate level of PEEP.

This article outlines the protocol and statistical analysis plan for a prospective randomised controlled trial comparing the effect of low tidal volume ventilation using 6 mL/kg PBW with conventional ventilation using 10 mL/kg PBW (as currently practised in Australia) on the incidence of postoperative respiratory complications in adult patients undergoing major surgery and receiving 5 cmH$_2$O of PEEP. Recruitment for the trial has now been completed but data analysis has not yet been undertaken. This trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000790640).

**Study design**

The study is a single-centre, randomised superiority trial of low tidal volume ventilation compared with conventional ventilation. The study setting is a tertiary teaching hospital affiliated with the University of Melbourne. The protocol was approved by the Austin Health Human Research Ethics Committee, and informed consent was collected by local investigators for all patients before inclusion in the trial. No interim analyses were planned.

**Study population**

**Inclusion criteria**

Patients included needed satisfy all the following criteria:
- age ≥ 40 years;
- expected duration of ventilation for surgery ≥ 2 hours;
- need of an arterial line for routine monitoring during the surgery.

**Exclusion criteria**

Patients were excluded from the study if any of the criteria listed below applied:
- pregnancy;
- thoracic surgery;
- cardiac surgery;
- intracranial neurosurgery; or
- previous enrolment in the trial.

**Rationale for the inclusion and exclusion criteria**

Older patients and longer expected duration of surgery are well known major risk factors for the development of postoperative respiratory complications, so we aimed to enrol an “enriched” population where the rate of the primary outcome would be expected to be higher. In addition, the use of an arterial line during surgery also denotes a higher risk procedure, and permits sampling of arterial blood gases for evaluation of Pa$_2$.

The exclusion criteria relate to situations where: (i) ventilation practice differs markedly (one-lung ventilation in thoracic surgery and no ventilation during cardiopulmonary bypass in cardiac surgery); (ii) the use of low tidal volume and consequent hypercapnia can induce harm (intracranial surgery); and (iii) the outcome and management is expected to be different from usual (pregnancy and use of nitrous oxide).

**Randomisation and masking**

A randomisation list was computed-generated by an independent investigator. Randomisation was conducted using sealed, sequentially numbered and opaque envelopes placed in the operating room and without any stratification factor. Patients who satisfied all inclusion criteria and had no exclusion criteria were randomly assigned in a 1:1 ratio to either low tidal volume ventilation or conventional ventilation, using a permuted block method with random block sizes of 2, 4 or 6. Owing to the nature of the intervention, blinding was not possible.

**Intervention**

General management considerations — such as inspired fraction of oxygen (Fi$_O_2$), respiratory rate, general anaesthesia technique, fluid management, use of vasoactive drugs, analgesia plan, use of prophylactic antibiotics and use of antiemetic agents — were at the discretion of the treating anaesthesiologist. They were also in accordance with existing protocols for patients undergoing major surgery and equal for both groups. PBW was calculated as 50 + 0.91 × (height [cm] − 152.4) for men and
45.5 + 0.91 × (height [cm] – 152.4) for women. Patients were randomised to one of two interventions: low tidal volume ventilation or conventional ventilation.

**Low tidal volume ventilation**

Immediately after randomisation, patients assigned to the low tidal volume group were ventilated with volume-
controlled ventilation, a tidal volume of 6 mL/kg PBW and PEEP of 5 cmH₂O. This combination of allocated tidal volume target and PEEP was maintained for the whole duration of the surgical procedure.

Conventional ventilation
Immediately after randomisation, patients assigned to the conventional ventilation group were ventilated with volume-controlled ventilation, a tidal volume of 10 mL/kg PBW and PEEP of 5 cmH₂O. This combination of allocated tidal volume target and PEEP was maintained for the whole duration of the surgical procedure.

Data collection
A purpose-built case report form was used for data collection. All data were collected by trained research staff at the study site, directly from the clinical chart source data. Information recorded in the case report form was required to accurately reflect the participant’s medical and hospital notes. The study timelines, procedures and assessments are shown in Table 1. After the data collection was completed, the database was locked so that only the principal investigator and the statistician responsible for the analyses have access to it.

Study outcomes

Primary outcome
The primary outcome is the incidence of a composite outcome of postoperative respiratory complications, defined as positive if any component developed during the first 7 postoperative days. The following complications will be considered:

- pneumonia (defined as need of antibiotics for a suspected respiratory infection and one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever and/or white blood cell count $> 12 \times 10^9$/$\mu$L) in the absence of another clinical focus;
- bronchospasm (defined as newly detected expiratory wheeze on clinical examination treated with bronchodilators recorded in the patient medical record);
- atelectasis (defined as lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent non-atelectatic lung);
- pulmonary congestion (defined as clinical signs of congestion, including dyspnoea, oedema, rales and jugular venous distension, with or without chest x-ray showing increase in vascular markings and diffuse alveolar interstitial infiltrates);
- respiratory failure (defined as a postoperative PaO₂ $< 60$ mmHg on room air, a PaO₂/FiO₂ ratio $< 300$ mmHg or arterial oxyhaemoglobin saturation measured with pulse oximetry $< 90\%$ and requiring oxygen therapy);
- pleural effusion (defined as chest radiograph showing blunting of the costophrenic angle, loss of 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 hemithorax with preserved vascular shadows);
- pneumothorax (defined as air in the pleural space with no vascular bed surrounding the visceral pleura);
- requirement for mechanical ventilation (defined as unplanned need of non-invasive or invasive ventilation).

All components of the primary outcome that rely on the assessment of chest x-rays or computed tomography will be adjudicated by a consultant radiologist blinded to the treatment allocation.

Secondary outcomes
The secondary outcomes (according to the definition in Table S1, online Appendix, available at cicm.org.au/Resources/Publications/Journal) include:

- incidence of postoperative respiratory complications during hospital stay;
- incidence of pulmonary embolism;
- incidence of acute respiratory distress syndrome;
- incidence of systemic inflammatory response syndrome;
- incidence of sepsis;
- incidence of acute kidney injury;
- incidence of wound infection (superficial and deep);
- rate of intraoperative need of vasopressor;
- incidence of unplanned intensive care unit (ICU) admission;
- rate of need for medical emergency team call;
- ICU length of stay;
- hospital length of stay; and
- incidence of in-hospital mortality.

Sample size calculation
The sample size for this study was calculated based on the incidence of postoperative respiratory complications of 10.8% observed in a previous study by our group [unpublished data]. A study population of 1240 patients will provide 80% power at a two-sided significance level of 0.05 to detect an absolute reduction in primary outcome of 3.4% allowing a dropout rate of 3%.

Statistical analyses
All statistical analyses will be conducted on an intention-to-treat basis, with patient data analysed according to
their assigned treatment arms, unless otherwise indicated (Figure 1). No or minimal losses to follow-up for the primary and secondary outcomes are anticipated. Complete case analysis will be carried out for all the outcomes. However, if more than 5% of missing data are found for the primary outcome, a sensitivity analysis using multiple imputations and estimating equation methods will be carried out. Hypothesis tests will be two sided with a significance level of 0.05. The P values will not be adjusted for multiple comparisons. Analyses will be performed using the R program (R Core Team, Vienna, Austria).

Baseline characteristics

A description of the baseline characteristics of the trial participants will be presented by treatment group (online Appendix, Table S2). Discrete variables will be summarised as number (percentage). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Continuous variables will be summarised by either means and standard deviations or medians and interquartile ranges, according to the observed distribution of the variable.

Intraoperative characteristics

Intraoperative characteristics including ventilation practice will be reported according to Table S3, Table S4, Table S5 and Table S6 in the online Appendix. Absolute differences between the groups with the respective 95% confidence intervals will be calculated as mean differences from an independent t test for continuous variables and
risk differences derived from a generalised linear model considering a binomial distribution with an identity link.

Proposed additional figures
A graph showing incidence of a composite of respiratory complications according to pre-specified subgroups may be included in the published analysis. In addition, a forest plot showing the results of the sensitivity analysis for the primary outcome individual component analysis, count analysis, common effect test and average relative effect test may also be created for publication as supplementary material.

Primary outcome
The effects of the intervention on incidence of postoperative respiratory complications will be reported as numbers and percentages, and estimated with risk ratios and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with \( \chi^2 \) tests for hypothesis testing (online Appendix, Table S7). In addition, a generalised linear model with binomial distribution and with an identity-link function will be used to derive risk difference with 95% confidence intervals.

Secondary outcomes
The effects of the intervention on binary secondary outcomes will be reported as numbers and percentages and estimated with risk ratios and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with \( \chi^2 \) tests for hypothesis testing (online Appendix, Table S7). In addition, a generalised linear model with binomial distribution and with an identity-link function will be used to derive risk difference with 95% confidence intervals. The effects of the intervention on length of ICU and hospital stay will be estimated with generalised linear models considering distributions that will fit a possible heavy right-tailed distribution without zero (such as truncated Poisson, gamma distribution or inverse Gaussian), choosing the best fit according to model's deviance.

Subgroup analyses
The effects of the intervention on pre-specified subgroups will be assessed using generalised linear models considering a binomial distribution with an interaction between each subgroup and the study arm as fixed effect. All such subgroup analyses will be exploratory, and we acknowledge the potentially reduced power of such tests to find evidence of significant interactions. These results will be reported as a forest plot. The specific subgroups that will be considered are:
- body mass index > 35 kg/m\(^2\) versus body mass index \(\leq 35\) kg/m\(^2\); and
- higher versus lower risk of respiratory complications.

Sensitivity analyses
As a sensitivity analysis, the effect of the intervention on primary outcome will be re-estimated using a generalised linear model with binomial distribution with additional adjustment for age, sex, baseline \(\text{SpO}_2\), body mass index and ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) score, plus any variables with substantial imbalance across treatment arms at baseline.

Since the primary outcome of the present study is a composite one, the choice of the statistical method is an important part of design because various methods provide different power, depending on the situation. In addition to the standard analysis described above, the following analyses will be performed to test the robustness of the trial findings:
- Count analysis: the number of positive component events (ie, counts) across the composite will be assessed. The groups will be compared on the count using a Wilcoxon rank sum test, and the odds ratio with the 95% confidence interval will be assessed with a proportional odds logistic regression model.
- Individual component analysis: the effect of the intervention in each component will be analysed using a generalised linear model using a Bonferroni correction for multiple comparisons. The 99.37% Bonferroni-corrected confidence intervals will be reported (1 – 0.05 \(\div\) 8 = 0.9937).
- Common effect test: a multivariate (ie, multiple outcomes per subject) generalised estimating equations (GEE) model will be used to estimate a common effect odds ratio across the components.
- Average relative effect test: the average relative effect test will be assessed by averaging the component-specific treatment effect from the distinct effects model, and testing whether the average is equal to zero. In the GEE distinct effect model, a distinct treatment effect is estimated for each component.
- Heterogeneity of treatment effect: heterogeneity of treatment effect across components will be assessed by a treatment-by-component interaction test in the distinct effects GEE model.

Consenting and ethical compliance
All patients gave consent before being included in the study. Two situations could have resulted in cessation of trial treatment:
- abdominal versus non-abdominal surgery;
- open versus laparoscopic surgery;
ORIGINAL ARTICLES

- patient or legal surrogate could decline consent to continue trial treatments; or
- patient or legal surrogate could withdraw consent to continue in the trial.

In both cases, trial-specific treatments would be interrupted, and the patient would continue therapy as prescribed by the treating anaesthesiologist. In such situations, consent for data collection would be sought, and if declined, the patient's data would be removed from the database and not analysed, apart from data related to randomisation and consent.

Data safety monitoring board
No monitoring by an independent monitoring board will be done.

Addendum
This trial was registered with Australian and New Zealand College of Anaesthetists (ANZCA) on 24 July 2014. During the planning of the statistical analysis plan, the trial steering committee made the following recommendations for modification of the trial protocol:
1. inclusion of pleural effusion and pneumothorax as components of the primary composite outcome;
2. modification of the timeframe for primary outcomes from duration of hospital stay to 7 postoperative days;
3. exclusion of pulmonary embolus from the primary composite outcome and its inclusion as a secondary outcome only; and
4. correction of secondary outcomes that were incomplete on the initial registration to include the list below (these outcomes were listed on our original datasheet that was designed before the study commenced):
   - incidence of each individual component of the primary composite outcome during hospital stay;
   - incidence of postoperative respiratory complications during hospital stay;
   - incidence of pulmonary embolism at 7 postoperative days and during hospital stay;
   - incidence of acute respiratory distress syndrome;
   - incidence of systemic inflammatory response syndrome;
   - incidence of sepsis;
   - incidence of acute kidney injury;
   - incidence of wound infection (superficial and deep);
   - rate of intraoperative need of vasopressor;
   - incidence of unplanned ICU admission;
   - rate of need for medical emergency team call;
   - ICU length of stay;
   - hospital length of stay; and
   - incidence of inhospital mortality.

Radiological outcomes were added after technology that enabled natural language processing of radiology reports became available, which allowed a feasible method of identifying these outcomes. The above modifications also resulted after further review of previous publications, which allowed our protocol to be further aligned with previous comparable studies.

As a result, a modification of the ANZCA trial registration protocol was submitted on 10 August 2019. This was done to align the trial registration with this protocol and statistical analysis plan. All changes were made before any knowledge of the frequency of these outcomes and before any data analysis had been undertaken. No statistical analysis will commence until after acceptance for publication of this protocol.

Summary
The present study is a single-centre randomised clinical trial that was designed to recruit a total of 1240 patients and compare a low tidal volume ventilation (6 mL/kg of PBW) with a conventional ventilation (10 mL/kg PBW). It includes adult patients who underwent general anaesthesia for major surgery that was expected to last at least 2 hours and who received PEEP of 5 cmH₂O. The study was funded by ANZCA.

Competing interests
None declared.

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ORIGINAL ARTICLES

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