PReVENT – Protective Ventilation in Patients without ARDS at Start of Ventilation: study update and detailed statistical analysis plan

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ABSTRACT

BACKGROUND: It is uncertain whether lung–protective mechanical ventilation using low tidal volumes should be used in invasively ventilated critically ill patients without the acute respiratory distress syndrome (ARDS).

PReVENT was a national multicenter parallel randomized controlled pragmatic two–arm trial comparing two tidal volume strategies in intensive care unit (ICU) patients without ARDS at onset of ventilation. To prevent outcome reporting bias, selective reporting and data–driven results we here present a study protocol update and the pre–specified detailed statistical analysis plan.

METHODS/DESIGN: PReVENT was a clinical trial in invasively mechanically ventilated ICU patients without ARDS with an anticipated duration of ventilation of longer than 24 hours, performed in the ICUs of 6 hospitals in The Netherlands. Patients were randomly assigned to a strategy targeting low tidal volumes (4 to 6 ml/kg predicted body weight [PBW]) or high tidal volumes (8 to 10 ml/kg PBW).

The primary outcome was the number of ventilator–free days and alive at day 28. Secondary endpoints included ICU and hospital length of stay (LOS), ICU–, hospital–, 28– and 90–day mortality, and the incidence of pulmonary complications, including new ARDS, pneumonia, atelectasis and pneumothorax.

DISCUSSION: Enrollment of patients was complete on August 22, 2017. The 90-day follow–up for the last included patient is on the end of November, 2017. The database will be cleaned and locked thereafter, which is expected on December 30, 2017.

TRIAL REGISTRATION: The trial is registered at www.clinicaltrials.gov under reference number NCT02153294 on 23 May 2014.

KEYWORDS: Mechanical ventilation, ventilator–induced lung injury, tidal volume, respiratory rate, protective ventilation, intensive care unit, critical care, non–injured lungs

INTRODUCTION

PReVENT ('PRotective VENTilation in patients without ARDS at start of ventilation trial') is a clinical trial comparing two tidal volume strategies in intensive care unit (ICU) patients without ARDS at onset of ventilation [1]. The primary objective of this trial is to determine whether protective ventilation with low tidal volumes increases the number of ventilator–free days and alive at day 28 of patients without ARDS at onset of invasive ventilation compared to a conventional strategy of ventilation with high tidal volumes. Enrollment of patients in PReVENT was complete on August 22, 2017; follow–up will be complete on the end of November, 2017. Data collection is expected to be complete one month later. Thereafter the database will be cleaned and finally closed.

To prevent outcome reporting bias and data–driven analysis results, the International Conference on Harmonization of Good Clinical Practice (ICH–GCP) recommends that clinical trials should be analyzed according to a pre–specified detailed statistical analysis plan [2]. The present study update and statistical analysis plan are drafted without knowledge of the randomization codes and of outcome data.

METHODS

Design

This is a national multicenter parallel randomized controlled pragmatic two–arm trial comparing invasive ventilation targeting low tidal volumes (4 to 6 ml/kg predicted body weight [PBW]) or high tidal volumes (8 to 10 ml/kg PBW) in ICU patients without ARDS at start of invasive ventilation. The trial was conducted in ICUs of 6 hospitals in The Netherlands. The trial protocol was previously published [1], was registered in ClinicalTrials.gov (NCT02153294) and was approved by the Institutional Review Board of the Academic Medical Center, Amsterdam, The Netherlands, under reference number 2014_075#B2014424.

Eligibility of the patients

Consecutive patients admitted to one of the participating ICUs who needed invasive ventilation were screened for eligibility. Patients were included under a strategy of deferred consent if they fulfilled the inclusion and exclusion criteria, because randomization was to be performed within 1 hour of start of invasive ventilation in the ICU. Informed consent was asked from a legal representative in all cases within 24 hours. When after randomization consent was rejected or not obtained within this time window, the patient was excluded.

Inclusion and exclusion criteria

ICU patients receiving invasive mechanical ventilated were eligible for participation if they were expected not to be extubated within the next 24 hours. Patients who were receiving in–hospital invasive ventilation shortly before the present ICU admission, for instance in the emergency room or operation room, were also eligible as long as duration of ventilation before admission to the ICU did not exceed 12 hours and needed to be included within 1 hour after ICU

admission. Reasons for exclusion were age < 18 years, previous randomization in PReVENT or participating in another interventional trial, patients with a clinical diagnosis of ARDS according to the Berlin definition [3], patients being pregnant, having increased and uncontrollable intracranial pressure (≥ 18 mmHg), patients suffering from GOLD classification III or IV chronic obstructive pulmonary disease (COPD), with status asthmaticus or premorbid restrictive pulmonary disease (evidence of chronic interstitial infiltration on previous chest radiographs), new proven pulmonary thrombo–embolism or previous pneumectomy or lobectomy.

Randomization

Eligible patients were randomly allocated in a 1:1 ratio to the low or high tidal volume strategy. Randomization was performed using a dedicated, password protected, SSL–encrypted website with ALEA® software (TenALEA consortium, Amsterdam, The Netherlands) using random block sizes and stratified per center and per intubation location (intubated in the ICU, or before ICU admittance in the emergency room or operation room).

The ventilation strategies

In both arms the size of tidal volumes was titrated on the predicted body weight (PBW), which is calculated according to a previously used formula [4]:

50 + 0.91 x (centimeters of height – 152.4) *for male*; and

45.5 + 0.91 x (centimeters of height – 152.4) *for females*

Patients randomized to the low tidal volume strategy started with a tidal volume of 6 ml/kg PBW in the volume–controlled ventilation mode (Table 1). The tidal volume size was then decreased in steps of 1 ml/kg PBW per hour, to a minimum of 4 ml/kg PBW if possible. In case a patient suffered from severe dyspnea (identified by increased respiratory rate > 35 breaths per minute accompanied by

increasing levels of discomfort with or without need for more sedation), severe asynchrony, or unacceptable acidosis, tidal volumes could be increased. When pressure support ventilation was used, the lowest level (5 cm H_2O) of pressure support determined the lowest possible tidal volume size. Thus, if the tidal volume exceeded 6 ml/kg PBW at 5 cm H_2O, this was to be accepted. Additional use of sedation and/or muscle relaxants, with the purpose to facilitate the use of lower tidal volumes, was not allowed. In patients in whom respiratory acidosis did not respond to an increase in the respiratory rate, removal of the heat and moisture exchanger and decreasing instrumental dead space, to limit dead space ventilation, could be considered.

Patients randomized to the high tidal volume strategy started with a tidal volume of 10 ml/kg PBW in the volume–controlled ventilation mode (Table 2). If the plateau pressure or maximum airway pressure exceeded 25 cm H_2O, respectively during volume–controlled and pressure support ventilation, tidal volume was decreased in steps of 1 ml/kg PBW to 8 ml/kg PBW. Additional use of sedation and/or muscle relaxants, with the purpose to allow higher tidal volumes, was also not allowed in this arm of the trial.

Outcomes

The primary outcome is the number of ventilator–free days and alive at day 28, defined as the number of days from day 1 to day 28 when the patient is alive and breathes without invasive assistance of the mechanical ventilator for at least 24 consecutive hours. To calculate this endpoint all relevant data are to be taken into account and collected, including all additional periods of ventilation during the first 28 days.

Secondary outcomes included ICU– and hospital length of stay, ICU–, hospital–, 28– and 90–day mortality, development of new ARDS, ventilator–associated pneumonia (VAP), atelectasis or pneumothorax.

Study organization

The steering committee was composed of the principal investigator, the coordinating investigator, local investigators in the participating ICUs, and six (inter–) national experts in ventilatory support in critically ill patients, who all contribute to the design and revisions of the original study protocol. The coordinating investigator was responsible for administrative management and communication with the local investigators and provided assistance to the participating clinical sites in trial management, record keeping and data management. The coordinating investigator helped in setting up local training in the participating ICUs to ensure the study was conducted according to the ICH–GCP guidelines, to guaranty integrity of data collection and to ensure timely completion of the case report forms. Local investigators provided structural and scientific leadership. They guaranteed the integrity of data collection and ensure timely completion of the case report forms.

Data collection

Data collection was performed using electronic case report forms in the Oracle Clinical application (Oracle Corporation, CA, USA) via the Internet at the Clinical Research Unit system of the Academic Medical Center. The system had the following functions: patient registration, data input, data cleaning, and data export for statistical analysis. Local investigators entered data directly into the system. Instructions for using the system were available to investigators at all times. Electronic files were archived in the Academic Medical Center–based server in a

secure and controlled environment to maintain confidentiality. Electronic documents were controlled with password protection according to best practices.

Data management

The objective of the clinical data management plan was to provide high–quality data by adopting standardized procedures to minimize the number of errors and missing data, and consequently, to generate an accurate database for analysis. An independent monitor was installed to perform study monitoring. Remote monitoring was performed to signal early aberrant patterns, issues with consistency, credibility and other anomalies. On–site monitoring comprised controlling presence and completeness of the research dossier and the informed consent forms, and source data checks were performed in the files of 25 % of the patients. All ICUs were visited regularly.

Data monitoring board and safety analyses

An independent Data and Safety Monitoring Board (DSMB) was established that included five independent individuals (Prof. Herman Wrigge (chair) [Germany], Prof. Antonio Artigas Raventós [Spain], Prof. Thomas Bein [Germany], Prof. Ognjen Gajic [USA] and Dr. Diederik Gommers [The Netherlands]). The responsibilities of the DSMB were to ensure safety of patients in the trial by protecting them from avoidable harm. Second, the DSMB provided the Steering Committee with advice about conduct of the study and integrity of the data to protect the validity and scientific credibility of the trial. The DSMB met by conference calls. A statistician performed safety analyses and safety reports which were sent to the DSMB after recruitment of the first 150 patients and in the year after.

Based on the provided information the DSMB had no concerns over safety. The DSMB recommended continuation of the trial after all DSMB meetings.

Cleaning and locking of the database

The database will be locked as soon as all data are entered and all discrepant or missing data are resolved – or if all efforts are employed and we consider that the remaining issues cannot be fixed. At this step, the data will be reviewed before database locking. After that, the study database will be locked and exported for statistical analysis. At this stage, permission for access to the database will be removed for all investigators, and the database will be archived.

Missing data

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, that is, excluding patients with missing data. However, if more than 1% of missing data were found for the primary outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be carried out.

Sample size

The trial was designed to last until 952 patients are enrolled. This number of patients was expected to be sufficient to detect an increase of 1 ventilator–free days in the treatment group considering a common standard deviation in ventilator–free days of 5.0 [5], a type I error of 5%, 80% of power, similar allocation of subjects to each group and corrected for dropouts.

Predefined statistical analysis plan

There were no major adjustments from the preliminary analysis plan, as reported previously in this journal [1]. In accordance, all statistical analyses will be conducted according to the intention–to–treat principle, considering all patients in

the treatment groups to which they were randomly assigned, except for cases lost to follow-up due to withdraw of consent.

Continuous distribution of the data will be assessed by visual inspection of histograms and D'Agostino–Pearson's normality tests. For the experimental and control arms, the baseline characteristics will be expressed as counts and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR) whenever appropriate as indicated in the eTables, which we intend to include in the main results paper.

Hypothesis tests will be two–sided with a significance level of 5%. We will not adjust *P*–values for multiple comparisons. Analyses will be performed using the R (R Core Team, 2016, Vienna, Austria) program.

Trial profile: Patient flows will be presented in a CONSORT flowchart (Figure 1).

Baseline comparisons: Patient's baseline characteristics will be presented by study arm (eTable 1).

Adherence to study interventions and ventilatory variables: Ventilatory variables and other interventions will be reported from post–randomization to day 7 (or extubation) and compared between the two groups, as shown in eTable 2 and 3. Tidal volume size in mL/kg PBW over the first seven days will be analyzed using a mixed model with repeated measures and plotted in an interaction plot.

Primary outcome: The effects of the intervention on ventilator–free days at day 28 will be estimated with a Student's *t*–test and reported as the mean difference between the two groups. The two–sided α–level for the primary outcome is 0.05 (eTable 4). The ventilator–free days between the two groups will be compared according to an interaction plot. Kaplan–Meier curves will be used to report time

to liberation of mechanical ventilation. Curves will be compared with the log–rank tests.

Secondary outcomes: The number and percentages of deaths in the ICU, hospital, within 28 days and 90 days will be reported. Survival within 28 and 90 days will be assessed using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models without adjustment for covariates. The proportional hazard assumptions will be tested and alternative parametric survival models will be used if the proportionality assumption is not sustained [6]. The effect of the intervention on ICU and hospital mortality will be assessed with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.

The effects of the intervention on length of hospitalization and ICU stay will be estimated with generalized 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 [7]. The effect of the intervention on the other secondary outcomes described in eTable 4 will be assessed with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.

Per–protocol analysis: In creating a per–protocol population we will exclude patients who had one or more major protocol violations. Patients assigned to the low tidal volume strategy will be excluded for the per–protocol analysis if receiving tidal volume > 6 ml/kg PBW for the first 2 days while ventilation was not executed according to the boundaries that were imposed by the study protocol, like

reducing tidal volume size or the level of pressure support in the absence of severe dyspnea, severe asynchrony, or unacceptable acidosis. Patients assigned to the high tidal volume strategy will be excluded for the per–protocol analysis if receiving tidal volume < 8 ml/kg PBW for the first 2 days while ventilation was not executed according to the boundaries that were imposed by the study protocol, like increasing tidal volume size or the level of pressure support while the plateau pressure or maximum airway pressure did not exceed 25 cm H_2O.

Subgroup analyses: Treatment effects on ventilator–free days at day 28 will be analyzed according to the following subgroups: 1) ventilation because of pneumonia *versus* ventilation for other reasons; 2) sepsis *versus* non–sepsis; 3) $PaO_2/FiO_2 \leq 200$ *versus* $PaO_2/FiO_2 > 200$; 4) Lung Injury Prediction Score (LIPS) ≥ 4 *versus* LIPS < 4; 5) clinical admission *versus* surgical admission; 6) Simplified Acute Physiology Score (SAPS) II ≥ 50 *versus* SAPS II < 50; 7) mechanical ventilation before randomization > 6 hours *versus* ≤ 6 hours; 8) start of invasive ventilation in the ICU *versus* start of ventilation before ICU admission; and 9) high versus a low respiratory rate (based on the median of the first 2 days of ventilation). The effects on subgroups will be evaluated according to the interaction effects between each subgroup and the study arms by generalized linear models considering zero–inflated distributions and presented in a forest plot.

Other exploratory analyses: All are pre-specified post-hoc exploratory analyses. As a sensitivity analysis, the effect of the intervention on the primary outcome will be re-estimated using generalized linear models considering zero-inflated distributions and with adjustment for the following covariates at baseline:

age, LIPS, SAPS II score and PaO_2/FiO_2. Also, in a second analysis a generalized linear mixed model considering zero-inflated distributions and with stratification variables (center and intubation location) as random effects will be tested.

Due to progressing insights into the potential harm of mechanical ventilation since we started this trial, which is caused by the concept of mechanical power [8], we will perform a mediation analysis to assess if mechanical power mediates the eventual effects of the randomly assigned treatment on ventilator-free days. As we did not collect all variables that are needed for this calculation directly into the database, i.e., we did not collect the driving pressure and the flow, we will calculate these from the variables that are available. Driving pressure will be calculated using the PEEP and plateau pressure level, when present. The flow will be calculated using the respiratory rate, inspiration to expiration ratio and the tidal volume in milliliters.

CONCLUSION

According to best research practice, we reported here the pre–specified detailed statistical analysis plan prior to locking the database and starting analyses. This document guarantees against reporting bias, selective reporting and data–driven results, as such enhancing the utility of the reported results.

FIGURE LEGENDS

Figure 1 – Flow of the patients in the PReVENT trial

LIST OF ABBREVIATIONS

ARDS: acute respiratory distress syndrome

CONSORT: Consolidated Standards of Reporting Trials

COPD: chronic obstructive pulmonary disease

DSMB: Data and Safety Monitoring Board

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ICH-GCP: International Conference on Harmonisation - Good Clinical Practice

ICU: intensive care unit

IQR: interquartile range

LIPS: lung injury prediction score

LOS: length of stay

PBW: predicted body weight

PReVENT: PRotective VENTilation in patients without ARDS

SAP: statistical analysis plan

SAPS: Simplified Acute Physiology Score

SD: standard deviation

VAP: ventilator-associated pneumonia

DECLARATIONS

Ethics approval and consent to participate: The Institutional Review Board of the Academic Medical Center, Amsterdam, The Netherlands, approved the study for all centers (reference number 2014_075#B2014424).

Consent for publication: Not applicable.

Availability of data and material: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

FDS, ASN, PP, MGA, and MJS, designed the study, the statistical analysis plan and approved the initially submitted version of this manuscript. All authors read and approved the final manuscript.

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MODIFICATIONS FROM THE ORIGINAL ANALYSIS PLAN

ANALYSIS	ORIGINAL PLAN (*Trials* 2015;16:226)	UPDATE IN THE SAP* (Closed in November 24, 2017)	IN THE PAPER	MODIFICATIONS *POST-HOC***
Primary outcome	Cox proportional hazards model	Student's *t*–test and reported as the mean difference	Student's *t*–test and reported as the mean difference	None
Secondary outcomes	ICU length of stay Hospital length of stay ICU mortality Hospital mortality 90-day mortality Development of ARDS Development of VAP Development of Atelectasis Presence of Pneumothorax Cumulative use and duration of sedatives Cumulative use and duration of NMBA ICU-acquired weakness Delirium	ICU length of stay Hospital length of stay ICU mortality Hospital mortality 28-day mortality 90-day mortality Development of ARDS Development of VAP Development of Atelectasis Development of Pneumothorax	ICU length of stay Hospital length of stay ICU mortality Hospital mortality 28-day mortality 90-day mortality Development of ARDS Development of VAP Development of Atelectasis Development of Pneumothorax Extra-pulmonary infection Extra-pulmonary sepsis Delirium Need of tracheostomy	Extra-pulmonary infection Extra-pulmonary sepsis Need of tracheostomy
Additional analyses	Not planned	GLM with adjustment for covariates GLMM with stratifications variables as random-effect	GLMM with stratifications variables as random-effect	Not reporting the GLM with adjustment for covariates
Subgroup analyses	Pneumonia or not Sepsis or not	Pneumonia or not Sepsis or not PaO_2 / FiO_2 ratio LIPS Clinical or not SAPS Ventilation before randomization Location of start of ventilation	Pneumonia or not Sepsis or not PaO_2 / FiO_2 ratio LIPS Clinical or not SAPS Ventilation before randomization	None

		Respiratory rate	Location of start of ventilation Respiratory rate	
Statistical approach for subgroup analyses	Not described	Interaction effects between each subgroup and the study arms by GLM considering zero–inflated distributions	Interaction effects between each subgroup and the study arms by GLM considering Gaussian distributions	Change the zero-inflated distribution to Gaussian distribution (according to the CLT)
Per protocol analyses	Described	Described according to protocol violations	Not described	None
Mock tables	Not included	Included	Slightly different from the mock tables reported in the SAP	None
Other	Nothing	Mediation analyses	None	None

ICU: intensive care unit; ARDS: acute respiratory distress syndrome; VAP: ventilator-associated pneumonia; NMBA: neuromuscular blocking agent; GLM: generalized linear models; GLMM: generalized linear mixed-effect model; LIPS: Lung Injury Prediction Score; SAPS: Simplified Acute Physiology Score; CLT: central limit theorem

* Database locking in December 30, 2017

** Not considered neither in the original plan nor in the updated SAP