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BMJ Open Multicentre randomised controlled trial to investigate the usefulness of continuous pneumatic regulation of tracheal cuff pressure for reducing ventilator-associated pneumonia in mechanically ventilated severe trauma patients: the AGATE study protocol

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ABSTRACT

Introduction Severe trauma represents the leading cause of mortality worldwide. While 80% of deaths occur within the first 24 hours after trauma, 20% occur later and are mainly due to healthcare-associated infections, including ventilator-associated pneumonia (VAP). Preventing underinflation of the tracheal cuff is recommended to reduce microaspiration, which plays a major role in the pathogenesis of VAP. Automatic devices facilitate the regulation of tracheal cuff pressure, and their implementation has the potential to reduce VAP. The objective of this work is to determine whether continuous regulation of tracheal cuff pressure using a pneumatic device reduces the incidence of VAP compared with intermittent control in severe trauma patients.

Methods and analysis This multicentre randomised controlled and open-label trial will include patients suffering from severe trauma who are admitted within the first 24 hours, who require invasive mechanical ventilation to longer than 48 hours. Their tracheal cuff pressure will be monitored either once every 8 hours (control group) or continuously using a pneumatic device (intervention group). The primary end point is the proportion of patients that develop VAP in the intensive care unit (ICU) at day 28. The secondary end points include the proportion of patients that develop VAP in the ICU, early (≤ 7 days) or late (> 7 days) VAP, time until the first VAP diagnosis, the number of ventilator-free days and antibiotic-free days, the length of stay in the ICU, the proportion of patients with ventilator-associated events and that die during their ICU stay.

Ethics and dissemination This protocol has been approved by the ethics committee of Poitiers University Hospital, and will be carried out according to the principles of the Declaration of Helsinki and the Good

Strengths and limitations of this study

- This study will be conducted as a multicentre randomised controlled and open-label trial adequately powered to determine whether continuous regulation of tracheal cuff pressure using a pneumatic device reduces the incidence of ventilator-associated pneumonia.
- This will be the first large study on that topic with the potential of changing international recommendations on ventilation-associated pneumonia prevention.
- Study's benefits include reduced duration of mechanical ventilation and stay in the intensive care unit, improved patient prognosis and reduction in antibiotics use.
- Limitations due to the lack of masking related to the nature of the intervention are limited by a masked end point assessment.

Clinical Practice guidelines. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration Clinical Trials NCT02534974

INTRODUCTION

Background and rationale

Severe trauma represents the leading cause of mortality worldwide, and is the third highest cause of death in France behind cardiovascular disease and cancer. About 46 deaths following trauma occur per 100 000 inhabitants per year in France, representing

close to 8% of all deaths.^{1 2} While 80% of deaths occur within the first 24 hours of trauma, directly related to the trauma itself, 20% of deaths occur later and are mainly due to healthcare-associated infections (HAI).³⁻⁶ More than 50% of patients that present with severe trauma will develop at least one HAI during their stay. Neurological disorders, recourse to mechanical ventilation and early post-traumatic immune suppression may explain the elevated incidence of HAI, particularly ventilator-associated pneumonia (VAP), which mainly occur in the first week following trauma.⁷⁻⁹

VAP represents the predominant HAI in severe trauma patients with a mean incidence of 35%, which may even exceed 60% in some series, followed by catheter infections and bacteraemia.³⁻⁶ HAI account for heightened morbidity and mortality, longer stays in the intensive care unit (ICU) and increased treatment costs. In France, the additional cost is estimated at €800 million per year.¹ These infections also require high use of antibiotics, and VAP alone makes up more than half of the antibiotic treatments prescribed in the ICU.⁷ Given the selection pressure they induce, these antibiotic therapies favour the appearance of bacterial resistance.

VAP pathophysiology

The presence of a foreign material (tracheal tube or stomach tube) facilitates colonisation of the upper airways and digestive tract by endogenous and exogenous microorganisms. Tracheal contamination originates through bacterial aspiration, resulting from the passage of secretions from around the cuff of the tracheal tube accumulating above the tracheal cuff.¹⁰ More rarely, VAP can arise from contaminated stagnant water in the ventilator circuit, use of colonised aerosols or a contaminated contiguous site (almost exclusively the pleural cavity).¹¹

Prevention measures for VAP

Enhanced knowledge of the pathophysiology of VAP has led to the development of effective preventive strategies. The VAP prevention measures recommended by the 2008 French consensus conference on nosocomial infection prevention¹² state that the orotracheal route should be used for tracheal intubation instead of the nasal route,^{7 11 13} and the tracheal cuff pressure should be maintained between 25 and 30 cm H₂O.^{14 15} They also recommend using a sedation-analgesia algorithm that facilitates early weaning off ventilation, avoidance of unplanned extubation,¹⁶ prioritising the use of non-invasive ventilation by following the recognised indications,^{16 17} placing the patient in a semi-recumbent position between 30° and 45°,^{18 19} regularly decontaminating the nasal and oropharyngeal cavity through suitable mouth care^{20 21} and starting enteral nutrition as early as possible.²² When combined with systemic antibiotic therapy, selective digestive decontamination may be recommended, but its implementation requires specification of its modalities (choice, dosing, duration of selective

digestive decontamination and antibiotic therapy) and the targeted population.

Maintaining a sufficient level of pressure in the tracheal tube cuff is of critical importance. When the pressure is too low, the patient risks inhaling the accumulated subglottic secretions from the oropharynx, which is known to play a major role in VAP incidence.^{14 15} Alternatively, if the pressure is too high there is a risk of ischaemia of the tracheal mucosa and, at removal, of tracheal oedema and later tracheal stenosis. Therefore, regular monitoring of tracheal cuff pressure is recommended, but the optimal monitoring frequency has yet to be clearly determined. Underinflation and/or overinflation of the tracheal cuff often occurs in ventilated patients under intermittent manual control of tracheal cuff pressure using a manometer, which is a well-known source of morbidity and mortality.²³ Recently published data favour use of automatic devices that are able to continuously regulate the tracheal cuff pressure.²⁴⁻³¹ Even though several learned societies do not recommend their implementation for the purpose of VAP prevention in ventilated patients, recent findings in the literature tend to favour their use.^{24 25 27 29 32} However, these studies have several limitations, as all were monocentre studies that included a relatively small number of participants, which rarely included severe trauma patients even though they are at greatest risk for VAP, and these studies did not systematically apply other recommended VAP preventive measures, with a contestable choice for the main study end point.

Two methods of continuous regulation of tracheal cuff pressure are available: pneumatic and electronic. Published studies favour the first³³ due to better reactivity with fewer periods of insufficient or excessive tracheal cuff pressure, and consequently, reduced risk of microbe inhalation and tracheal injuries, in addition to the low acquisition cost, ease of use and no electricity supply required.

Objectives

The objective of this study is to determine whether continuous regulation of tracheal cuff pressure using a mechanical pneumatic regulation device (Nosten, Leved, Paris) is superior to intermittent control of tracheal cuff pressure for reducing the incidence of VAP in severe trauma patients, who will receive all other recommended methods of VAP prevention. At an individual level, the benefits are expected to include a shorter duration of mechanical ventilation and stay in the ICU, as well as improved patient outcomes. At a collective level, in addition to reduced cost of hospital stay, the number of days on antibiotics should also decline, along with the selective pressure perpetuating the emergence of multidrug-resistant bacteria.

Study design

The AGATE trial is a multicentre randomised controlled and open-label clinical trial with two parallel groups, with the primary end point being the proportion of

Box 1 Inclusion and exclusion criteria**Inclusion criteria**

1. Patients aged at least 18 years
2. Suffering from a severe trauma as defined by an Injury Severity Score >15
3. With their tracheal intubated via the oral route for <15 hours
4. Requiring mechanical ventilation for an expected length \geq 48 hours.
5. Participating in a social security scheme or benefiting from such a scheme by means of a third party

Exclusion criteria

1. Patient likely to die in the 48 hours following admission
2. Having their trachea intubated via the nasal route
3. Patient intubated through a tracheal tube with subglottic secretion drainage
4. Having their trachea intubated 24 hours or more after trauma
5. Being ventilated with tracheotomy
6. Refusing to participate in the research
7. Having contraindication to the head-up position
8. Participating in another research protocol pertaining to an anti-infective treatment or to a measure decreasing risk of infection
9. Benefiting from reinforced protection or persons deprived of freedom subsequent to a legal or administrative decision, majors under legal protection

patients that develop VAP in the ICU at day 28. Randomisation will be carried out through a secure web-based randomisation system, stratified by the centre and severity of patient unconsciousness at the time of inclusion (Glasgow Coma Scale lower and higher or equal to 8).

METHODS AND ANALYSIS**Participants**

Patients will be considered candidates for inclusion in the study if they meet all of the inclusion criteria and none of the exclusion criteria (box 1). Patients suffering from severe trauma admitted within the first 24 hours, who require invasive mechanical ventilation expected to last longer than 48 hours, should be included in the study. For all cases, patient inclusion will take place as soon as possible after ICU admission, during the 24 hours following trauma and/or over the 15 hours following oral intubation of the trachea. Pregnant or lactating women can be included in the study because the material used does not present any specific risk of teratogenicity.

Interventions

All of the patients included in the study will be randomised in one of the two treatment groups, which are based on the method used to monitor tracheal cuff pressure and benefit from daily monitoring throughout their hospital stay in the ICU. The following criteria will be applied to all patients and controlled throughout the duration of the study.

- ▶ Monitoring of tracheal cuff pressure of the tracheal tube either once every 8 hours in the control group or continuously in the intervention group through the

use of a pneumatic device (Nosten), with the objective of maintaining pressure between 25 and 30 cm H₂O.

- ▶ Implementation of identical sedation and weaning protocols for all centres.
- ▶ Implementation of a lung protective ventilation strategy³⁴ by maintaining a tidal volume of 6–8 mL/kg of ideal body weight, positive end-expiratory pressure >3 cm H₂O and respiratory rate set to achieve normocapnia or optional moderate hypocapnia.
- ▶ According to the protocol observed in the unit, extubation should be considered as soon as: (1) the patient's Glasgow Coma Scale is >10; (2) the patient is coughing spontaneously or secondary to bronchial aspiration and (3) the level of pressure support is <10 cm H₂O, or spontaneous ventilation on a T-piece with F_IO₂ lower than 40% is tolerated by the patient for at least 30 min.
- ▶ No systematic changes to the respirator circuits.
- ▶ Preferential use of heat and humidity exchange filters to be changed only when soiled.
- ▶ Systematic application of bed inclination of at least 30° to be monitored every 4 hours.
- ▶ Hand washing (hydroalcoholic friction) prior to any treatment and following isolation measures.
- ▶ Mouth care every 4–8 hours according to the protocol observed in the unit.
- ▶ Tracheal aspiration carried out using sterile equipment, only to be performed when required.
- ▶ Preferential oral insertion of feeding tubes.
- ▶ Starting enteral feeding as soon as possible.
- ▶ Systematic application of a glucose monitoring protocol in which the patient's blood sugar level is measured every 4 hours, the objective being to maintain the glucose level between 4 and 8 mmol/L.
- ▶ Prophylactic antibiotic treatment limited to 48 hours for fractures operated within the first 6 hours.
- ▶ Curative antibiotic therapy reserved for infections for which the bacterial origin is documented, or probable, and in cases where other anti-infectious measures are insufficient, in accordance with the 2008 recommendations of the official French health authority on the proper use of antibiotics.³⁵ An adequate dosage regimen and method of antibiotic administration is provided to ensure an optimal concentration at the site of infection. Recourse to serum assay is useful whenever possible to avoid underdosing, which is a common cause of failure, as well as to avoid overdosing, which leads to iatrogenic pathologies. Narrow-spectrum antibiotics are preferred. In cases of severe infection, antibiotic treatment should be started as soon as possible following diagnostics and microbiological sampling, and started no later than the first hour in cases of septic shock. The duration of VAP treatment should be limited to 1 week, except in cases with non-fermenting Gram-negative bacterial infections for which antibiotic therapy should continue for 2 weeks to reduce the risk of recurrence. Antibiotic associations are strictly limited to precisely defined

Box 2 American Thoracic Society definition for VAP

VAP diagnosis is based on an association, 48 hours after the start of mechanical ventilation, of at least:

Two clinical signs among the following:

- ▶ Fever $\geq 38.0^{\circ}\text{C}$ or hypothermia $\leq 36.0^{\circ}\text{C}$
- ▶ Purulent endotracheal aspirations
- ▶ Hyperleucocytosis ($\geq 12\,000/\text{mL}$) or leucopenia ($\leq 4000/\text{mL}$)

One radiological sign such as:

- ▶ A new radiographic condensation
- ▶ Modification of a previously existing radiographic condensation

And a positive bacterial analysis of the respiratory tract with cultures of at least:

- ▶ 10^3 CFU/mL for a brush by fibroscopy or blind protected distal sampling
- ▶ 10^4 CFU/mL for bronchoalveolar lavage
- ▶ 10^6 CFU/mL for tracheal aspirates

CFU, colony-forming unit; VAP, ventilator-associated pneumonia.

situations: the need to broaden the antibacterial spectrum; severe and microbiologically undocumented infections; *Pseudomonas aeruginosa* infections and bacteria and antibiotic combinations associated with a high risk of resistance emergence. These include group 3 Enterobacteriaceae (eg, *Enterobacter*, *Serratia*, *Citrobacter freundii*, *Providencia* and *Morganella*) and third-generation cephalosporins; *Staphylococcus aureus* and fluoroquinolones, rifampicin, fusidic acid or fosfomycin and Enterobacteriaceae resistant to nalidixic acid and fluoroquinolones. Antibiotic therapy should be re-evaluated between 24 and 72 hours.

- ▶ Prevention of ulcer disease by anti- H_2 and proton pump inhibitors, in accordance with the protocol observed in the centre.

Study outcomes**Primary end point**

- ▶ Proportion of patients that develop VAP at day 28 in the ICU according to the American Thoracic Society (ATS) definition (box 2).⁷

Secondary end points

- ▶ Proportion of patients that develop VAP in the ICU according to the ATS definition.⁷
- ▶ Proportion of patients that develop bacteraemic VAP in the ICU according to the ATS definition. Bacteraemic VAP is defined as at least one positive blood culture that is not related to any other source of infection, and at least one positive respiratory sample culture obtained within 48 hours of each other. In addition, at least one of the microorganisms isolated in the respiratory sample needs to also be isolated in the blood cultures, whereas all isolates identified in the blood cultures (except for skin contaminants) should also grow in the simultaneously obtained respiratory sample in order to meet the complete definition of bacteraemic pneumonia.

- ▶ Proportion of patients that develop early (≤ 7 days) or late (> 7 days) VAP in the ICU according to the ATS definition.⁷
- ▶ Time until the first diagnosis of VAP according to the ATS definition.⁷
- ▶ Proportion of patients that develop ventilator-associated events (VAE) according to the Centers for Disease Control and Prevention (CDC) definition (table 1).³⁶
- ▶ Number of ventilator-free days.
- ▶ Number of antibiotic-free days.
- ▶ Length of stay in the ICU.
- ▶ Proportion of patients that die during their ICU stay.
- ▶ Proportion of patients that require corticosteroids or bronchodilators within 48 hours of tracheal extubation.

Attempted detection of VAP signs will be performed on a daily basis while the patient is being mechanically ventilated, in accordance with the definition established by the ATS in 2005 (box 2).⁷ A thoracic X-ray aimed at detecting VAP is to be carried out within a few hours whenever at least two of the following clinical signs of VAP are observed in the same clinical examination: fever $\geq 38.0^{\circ}\text{C}$ or hypothermia $\leq 36.0^{\circ}\text{C}$, purulent endotracheal secretions or either hyperleucocytosis ($\geq 12\,000/\text{mL}$) or leucopenia ($\leq 4000/\text{mL}$).

Whenever the patient meets the clinical and radiological criteria on the same day, VAP is suspected and the modified clinical pulmonary infection score will be calculated, as presented in table 2. Bacterial analysis of the respiratory tract will be carried out especially if the calculated score is > 6 . The type of sampling (bronchoalveolar lavage, blind distal sampling or tracheal aspirates) is left to the discretion of the attending physician, and depends on the procedures of the unit.

When a patient is suspected to have developed VAP, two assessors masked to the group assignment will review the case-report form and classify the case according to the accepted definition.

Participant timeline

The patients will be monitored from randomisation through to their discharge from the ICU without exceeding 60 days following inclusion. Evaluation of the assessment criteria will be carried out depending on the duration of patient stay in the ICU.

- ▶ Evaluation will be carried out on discharge from the ICU for patients with an ICU stay of < 28 days.
- ▶ Evaluations will be carried out on day 28 and on discharge from the ICU for patients with an ICU stay of ≥ 28 but < 60 days.
- ▶ Evaluations will be carried out on days 28 and 60 for patients with an ICU stay of ≥ 60 days.

Any patient who leaves the ICU will be considered to have exited the study. Any readmission into the ICU (even within 60 days following the trauma) will not be taken into account. Any event that occurs after the first

Table 1 The Centers for Diseases Control's modified definitions for ventilator-associated events³⁶

New respiratory deterioration	Ventilator-associated condition (VAC)	≥2 calendar days of stable or decreasing daily minimum positive end-expiratory pressure or daily minimum fraction of inspired oxygen, followed by a rise in daily minimum positive end-expiratory pressure of ≥3cm of water or a rise in the daily minimum percentage of inspired oxygen by >20 points sustained for ≥2 calendar days
New respiratory deterioration with evidence of infection	Infection-related ventilator-associated complication (IVAC)	VAC AND a temperature of 38°C or a leucocyte count of ≤4000 or ≥12 000 per cubic millimetre AND one or more new antibiotics continued for at least 4 days within two calendar days before or after onset of a VAC, excluding the first 2 days of mechanical ventilation
New respiratory deterioration with possible evidence of pulmonary infection	Possible ventilator-associated pneumonia	IVAC AND one of the following criteria: Criterion 1: positive culture of one of the following specimens, meeting quantitative or semi-quantitative thresholds as outlined in protocol, without requirement for purulent respiratory secretions: ▶ Endotracheal aspirate ≥10 ⁵ CFU/mL or corresponding semi-quantitative result ▶ Bronchoalveolar lavage, ≥10 ⁴ CFU/mL or corresponding semi-quantitative result ▶ Lung tissue, ≥10 ⁴ CFU/mL or corresponding semi-quantitative result ▶ Protected specimen brush, ≥10 ³ CFU/mL or corresponding semi-quantitative result Criterion 2: purulent respiratory secretions (defined as secretions from the lungs, bronchi or trachea that contain >25 neutrophils and <10 squamous epithelial cells per low power field (lpf, x100)) plus organism identified from one of the following specimens (to include qualitative culture, or quantitative/semi-quantitative culture without sufficient growth to meet criterion #1): ▶ Sputum ▶ Endotracheal aspirate ▶ Bronchoalveolar lavage ▶ Lung tissue ▶ Protected specimen brush
		<p>▶ Criterion 3: one of the following positive tests:</p> <ul style="list-style-type: none"> ▶ Organism identified from pleural fluid (where specimen was obtained during thoracentesis or initial placement of chest tube ▶ and NOT from an indwelling chest tube) ▶ Lung histopathology, defined as: 1) abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli; 2) evidence of lung parenchyma invasion by fungi (hyphae, pseudohyphae or yeast forms); 3) evidence of infection with the viral pathogens listed below based on results of immunohistochemical assays, cytology or microscopy performed on lung tissue ▶ Diagnostic test for <i>Legionella</i> species ▶ Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

Table 2 The modified clinical pulmonary infection score for ventilator-associated pneumonia⁷ ARDS, acute respiratory distress syndrome.

Temperature (°C)	
≥36.5 and ≤38.4	0
≥38.5 and ≤38.9	1
≥39.0 or ≤36.0	2
Leucocytes (g/L)	
≥4 and ≤11	0
<4 or >11	1
Tracheal secretion quantity	
Low	0
Moderate	1
Abundant	2
Tracheal secretion aspect	
Purulent	+1
PaO ₂ /FiO ₂	
>240 or ARDS	0
≤240 and absence of ARDS	2
Frontal chest radiograph	
No infiltrate	0
Diffuse and/or heterogeneous infiltrates	1
Localised infiltrate	2

ICU discharge will not be considered in the assessment criteria.

Any patient can exit the study if he or she wishes, without having to provide justification. The quality of their care will not be altered, and the outcome will not be taken into account in the final analysis.

Sample size calculation

The number of participants (n=220 in each group) is based on an estimation of VAP incidence of 20% of patients in the control group and a reduced VAP incidence (halved) in the intervention group, with a study power of 80% and p value of 5% in bilateral situation. The VAP incidence in the control group was chosen on the basis of an unpublished analysis of the database of AtlanRéa, a French research network devoted to studies on trauma patients.^{37 38}

Given the recruitment potential of the centres approached to participate in the study, together with the constraints associated with the protocol, the expected inclusion duration has been set at 33 months.

Recruitment

Patients admitted into the ICUs of 15 French University Hospitals will be screened and enrolled within 24 hours of trauma. Patient enrolment will be decided by the attending physicians.

Assignment of interventions and masking protocol

A computer-generated numbered list was provided by a statistician not involved in either screening patients or the assessment of outcomes. Randomisation will be carried out using a secure web-based randomisation system with stratification by centre and severity of unconsciousness at the time of inclusion (Glasgow Coma Scale <8 or ≥8), to account for differences in patient treatment between centres and the heightened VAP risk in patients with a Glasgow Coma Scale <8. Patients will be randomly assigned (1:1) into one of the two treatment groups, based on the method used to monitor tracheal cuff pressure. Masking of the participants and ICU staff will not be feasible due to the nature of the device, which is placed closed to the patient's face. However, the microbiologists that test the pulmonary and blood samples, the outcome assessors (NM and OM) and the statisticians will be masked to the group assignment.

Data collection, confidentiality, storage and archiving of study documents

Independent clinical research assistants are available at each participating hospital to help with running the study and data collection. Study documents will be de-identified and stored for 15 years, as per the protocol for non-clinical trial notification (CTN) interventional studies. Data will be electronically stored on double password-protected computers. Hard copies of data (clinical research files) will be stored in a locked, secure office. All personnel involved in data analysis will be masked. Only the principal investigators and the statisticians will have access to the final data set.

Statistical methods

Analyses will be performed following the intention-to-treat principle (all randomised patients except those that withdrew consent). Statistical analyses will take into account the stratified randomisation (centre and Glasgow Coma Scale <8 or ≥8), as recommended in the 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines and other studies reported in the literature.^{39 40}

The categorical variables will be reported as numbers and percentages, while continuous variables will be summarised using means (±SD) or medians (IQR) for normally and non-normally distributed data, along with their respective 95% CIs.

Analyses of the primary end point and secondary end points related to VAP incidence will use logistic regression models adjusted for stratification factors and covariates significantly imbalanced between groups.

The cumulative event curves (time until first VAP diagnosis) will be estimated using the Kaplan-Meier procedure.

The number of ventilator-free days (VFD) is the number of days for which the patient is successfully weaned from mechanical ventilation until the end point at day 28 (or day 60). This is defined as follows: VFD=0 for patients who died within 28 (or 60) days or required mechanical

ventilation for 28 (or 60) or more days; VFDs=(28 (or 60)–x) for patients who were successfully weaned off mechanical ventilation within 28 (or 60) days, where x is the number of days on mechanical ventilation.

The number of antibiotic-free days (AFD) is the number of days that the living patient did not receive antibiotics over 28 (or 60) days. Any prophylactic or curative antibiotic therapy related to the trauma will not be considered.

The VFD and AFD will be assessed in the same manner, and will be compared between groups using regression models that allow adjustment for stratification factors. The other categorical secondary end points will be compared between groups using logistic regression models. Statistical analyses will all be conducted using SAS V.9.3 software.

Missing data will be described as the number and corresponding percentage for each group. The presence of any imbalance in the proportion of missing data between treatment groups will be evaluated using logistic regression models. To assess the robustness of the results in the case of missing data, sensitivity analyses will be performed with imputation of missing data (worst value such as failure, death, etc) and multiple imputation.

Monitoring

Clinical research associates will ensure that patient inclusion, data collection, registry and rapport are in line with the protocol, and that the study is conducted in accordance with the Good Clinical Practice guidelines. Furthermore, he or she will verify the following variables: patient initials, date of birth, sex, signed consent form, eligibility criteria, date of randomisation, treatment assignment, adverse events and study end points.

ETHICS AND DISSEMINATION

Research ethics approval

The clinical trial will be carried out in line with the principles of the Declaration of Helsinki and according to the Clinical Trials Directive 2001/20/EC of the European Parliament on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practices in the conduct of clinical trials on medicinal products for human use. Ethical aspects of this research project have been approved by the ethics committee of Poitiers University Hospital (France). The ethics committee of Poitiers approval cover all participant sites. The trial will be monitored by the research monitoring officer of Poitiers University Hospital.

Consent

Prior consent of the subject will not be possible; therefore, consent of the subject's legally acceptable representative will be requested. A consent form specifically designed for the subject's legally acceptable representative will be provided with documented approval or favourable opinion of the institutional review board in order to

protect the rights, safety and well-being of the subject and to ensure compliance with any applicable regulatory requirements. Non-objection to participation in the study by the patient's relatives will be solicited, according to the requirements of the ethics committee.

Confidentiality

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be rendered anonymous. Only initials and inclusion number will be registered.

Dissemination policy

The results of the study will be released to the participating physicians, referring physicians and medical community no later than 1 year after the completion of the trial, through presentation at scientific conferences and publication in peer-reviewed journals

DISCUSSION

To the best of our knowledge, this is the first large-scale study to evaluate the usefulness of continuous pneumatic regulation of tracheal cuff pressure in a population of severe trauma patients, who will also benefit from other recommended VAP preventive measures. At an individual level, the benefits are expected to include reduced duration of mechanical ventilation and stay in the ICU, as well as improved patient prognosis. At a collective level, a lower cost of hospital stay is expected, in addition to fewer days on antibiotics, associated with a reduction in the selective pressure perpetuating multidrug-resistant bacteria.

In order to keep management practices as standardised as possible, we decided to limit the number of investigating centres to 15 university hospital centres (CHU), all of which are recognised in the field of trauma care and treat more than 50 severe trauma patients per year. These centres belong to three networks that share the common objective of promoting multicentre clinical research, consisting of AtlanRéa (Grand Ouest surgical intensive care network), AzuRéa (Grand Sud intensive care network) and TraumaBase (APHP trauma intensive care network). These 15 centres also share the same standards of care.

Previous studies that have evaluated devices aimed to continuously regulate tracheal cuff pressure have reported that these devices are efficient in controlling cuff pressure,⁴¹ and are well-tolerated by patients.³³ In this setting, the choice of a pneumatic device instead of an electronic device presents several advantages³³: better reactivity with fewer periods of insufficient or excessive pressure into the tracheal cuff, and consequently, reduced risk of microinhalations and tracheal lesions; no need for an electricity supply; low acquisition cost and ease of use. Finally, the encouraging preliminary results previously reported using this device also significantly contributed to our choice.²⁷

In the present study, no additional risk will be incurred by the study participants in terms of the usual therapy received during their hospital stay. Patients will be cared for as usual by their attending physicians. No supplementary examination will be imposed by the protocol. As the patient will be unable to hear the given information, information regarding the study will be delivered to his or her close relatives or friends. In accordance with the directives of the French national commission for data protection and liberties, the patient will be afforded the possibility of objecting to the use of data gathered in his or her name.

Study limitations

The incidence of VAP is the primary end point of this trial; however, VAP diagnosis may be difficult to perform in the ICU. Several criteria have been proposed,^{7 36 42–44} but their reported performances are poor.⁴⁵ In this trial, VAP incidence will be determined according to the 2005 ATS criteria.⁷ This choice could be challenged; however, these criteria have been commonly used for VAP diagnosis in the literature. We will also record VAE according to the CDC criteria,³⁶ and compare the ATS and CDC definitions for VAP as a secondary objective. The halving of VAP rate could seem ambitious for a single intervention. However, such a finding was reported in two previous studies assessing the clinical impact of continuous control device of cuff pressure.^{46 47}

Because, mouth care and stress ulcer prophylaxis are based on local written protocols, they may act as potential confounding variables. However, this will be controlled by the stratification of the randomisation at the centre level and adjustment of statistical analyses in cases of differences between groups.

Finally, masking is not feasible due to the nature of the intervention. However, the end points will be assessed by two assessors masked to the group assignment in order to minimise bias.

In conclusion, this trial is the first multicentre randomised controlled open-label study adequately powered to test the hypothesis that a continuous pneumatic regulation of tracheal cuff pressure prevents VAP in mechanically ventilated severe trauma patients.

Participating centres

University Hospital of Poitiers (Professor Olivier Mimoz), University Hospital of Angers (Professor Sigismond Lasocki), University Hospital of Beaujon (Professor Catherine Paugam), University Hospital of Bicêtre (Professor Jacques Durteau), University Hospital of Clermont-Ferrand (Professor Jean-Michel Constantin), University Hospital of Grenoble (Professor Jean-François Payen), University Hospital of Marseille (Professor Marc Leone), University Hospital of Nantes (Professor Karim Asehoun), University Hospital of Nice (Professor Carole Ichai), University Hospital of Nîmes (Professor Jean-Yves Lefrant), University Hospital of Rouen (Professor Benoit Veber), University Hospital of Strasbourg (Professor Julien Pottecher), University Hospital of Besançon

(Professor Sébastien Pili-Floury), University Hospital of Dijon (Professor Belaid Bouhemad), University Hospital of Nancy (Professor Gérard Audibert); all in France.

Trial status

The trial is currently in progress, and the inclusion process started in July 2015. At the time of manuscript submission, 229 patients had been included. The first patient was included 2 days after registration of the study on ClinicalTrials.gov. We estimate that the last patient will be recruited in January 2018.

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Contributors OM conceived the study, coordinated its design and drafted the manuscript. NM and OM wrote the manuscript. DFr, JG, KA, CP, SL, CI, JYL, ML, CDF, JP, DFa, BV, JMC and SS read and were involved in critical appraisal and revision of the manuscript. DFr provided statistical expertise. All authors approved the final manuscript prior to submission.

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