BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: the randomised STYLETO study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036718
Article Type:	Protocol
Date Submitted by the Author:	30-Dec-2019
Complete List of Authors:	Jaber, S.; Montpellier Univ Hosp, Anesthesia and Critical Care ROLLE, Amélie Jung, Boris Chanques , Gerald; University of Montpellier Saint Eloi Hospital, Montpellier, France Bertet, Helena Galeazzi, David Chauveton, Claire MOLINARI, Nicolas; Université Montpellier I/ INSERM, Biostats DE JONG, Audrey
Keywords:	Adult intensive & critical care < ANAESTHETICS, INTENSIVE & CRITICAL CARE, RESPIRATORY MEDICINE (see Thoracic Medicine)

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Study protocol

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: the randomised STYLETO study protocol

Samir Jaber,[1,2] Amélie Rollé,[1,3] Boris Jung,[2,4] Gérald Chanques,[1,2] Helena Bertet,[5] David Galeazzi,[5] Claire Chauveton,[6] Nicolas Molinari,[5] Audrey De Jong[1,2]

[1] Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France

[2] PhyMed Exp, Université de Montpellier, INSERM U1046 Montpellier, France

[3] Intensive Care & Anesthesiology Department, University of Pointe à Pitre Hospital. Guadeloupe, France

[4]Departement of Medical Intensive Care, Lapeyronie Teaching Hospital, Montpellier University, 191, Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5

[5] IMAG, CNRS, Univ Montpellier, CHU Montpellier, Montpellier, France

[6] Clinical research department of Montpellier university hospital, Montpellier, France

Correspondence: Pr Samir JABER, Intensive Care Unit & Anaesthesiology Department, University of Montpellier Saint-Eloi Hospital. Montpellier, France; 80 avenue Augustin Fliche. 34295 Montpellier Cedex 5, France
Tel: 00. 33. 467. 337. 271; Fax: 00. 33. 467.337. 448; E-mail: s-jaber@chu-montpellier.fr

Abstract word counts: 300 (max 300)
Total word counts: 3930 (max 4000)
References, n=37
Table, n=1
Figures, n=2
Supplemental Figure, n=1 in Supplemental File 1

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Introduction: Tracheal intubation is one of the most daily practiced procedures performed in intensive care unit (ICU). It is associated with severe life-threatening complications, which can lead to intubation-related cardiac arrest. Using a preshaped endotracheal tube plus stylet may have potential advantages over endotracheal tube without stylet. The stylet is a rigid but malleable introducer which fits inside the endotracheal tube and allows for manipulation of the tube shape; to facilitate passage of the tube through the laryngeal inlet. However, some complications from stylets have been reported including mucosal bleeding, perforation of the trachea or oesophagus, and sore throat. The use of a stylet for first-attempt intubation has never been assessed in ICU and benefit remains to be established.

Methods and analysis: The endotracheal tube plus STYLET to increase first-attempt success during orotracheal intubation compared to endotracheal tube alone in ICU patients (STYLETO) trial is an investigator-initiated, multicenter, stratified, parallel-group unblinded trial with an electronic system–based randomization. Patients will be randomly assigned to undergo the initial intubation attempt with endotracheal tube alone (i.e, without stylet, control group) or endotracheal tube+stylet (experimental group). The primary outcome is the proportion of patients with successful first-attempt orotracheal intubation. The single, prespecified, secondary outcome is the incidence of complications related to intubation, in the hour following intubation. Other outcomes analysed will include safety, exploratory procedural and clinical outcomes.

Ethics and dissemination: The study project has been approved by the appropriate ethics committee. Informed consent is required. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences. If combined use of endotracheal tube plus stylet facilitates tracheal intubation of ICU patients compared to endotracheal tube alone, its use will become standard practice, thereby decreasing first-attempt intubation failure rates and, potentially, the frequency of intubation-related complications.

Registration details: ClinicalTrials.gov Identifier: NCT04079387.

Strengths and limitations of the study:

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes between endotracheal tube + stylet and endotracheal tube alone to facilitate tracheal intubation of critically ill adults.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- The broad inclusion criteria and the high number of participating ICUs will increase generalisability and the large size will provide the opportunity to examine subgroups of interest.
- All intubation performed around the clock (nights and week-end) will be included.
- The nature of the study intervention does not allow blinding.

Keywords: Acute respiratory failure, airway, complications, critical care, intensive care unit, intubation, stylet

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Patients admitted to Intensive Care Units (ICU) often require respiratory support. Tracheal intubation is one of the most frequent procedures performed in ICU.[2 3] Intubation is a challenging issue as it may be associated with life-threatening complications in up to one third of cases,[4 5] including cardiac arrest related to intubation in 2.7% of cases.[6] Difficult intubation, defined by more than two intubation attempts, is associated with life-threatening complications.[4 5 7-10] To prevent and limit the incidence of severe hypoxemia following intubation and its complications, several intubation algorithms have been developed,[7 8] and specific risk factors for difficult intubation in ICU have been identified, constituting the MACOCHA score (Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening < 3 cm, Coma, severe Hypoxemia (<80%) and non-Anaesthesiologist status).[5]

Devices aiming to facilitate tracheal intubation in ICU have been recently assessed. In 2018, a large multicentre study[2] reported first-attempt intubation success rates using direct laryngoscopy of 70% and videolaryngoscopy of 67%. In 2019, a multicentre randomized trial,[11] assessing whether positive-pressure ventilation with a bag-mask device (bag-mask ventilation) during tracheal intubation of critically ill adults prevents hypoxemia, reported a first-attempt success rate of 81%. Other authors reported an overall first-attempt intubation success rate of 74%.[5] The 20% to 40% first-attempt failure rates throughout studies highlight the opportunity to improve the safety and efficiency of this critical procedure. Using a preshaped endotracheal tube plus stylet may have potential advantages over endotracheal tube alone without stylet. The stylet is a rigid but malleable introducer which fits inside the endotracheal tube and allows for manipulation of the tube shape; usually into a hockey stick shape, to facilitate passage of the tube through the laryngeal inlet. The stylet can help to increase success of intubation in operating rooms.[12]

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

However, some complications from intubating stylets have been reported including mucosal bleeding, perforation of the trachea or oesophagus, and sore throat.[13 14] In 2018, one study has assessed the effect of adding a stylet in case of difficult intubation in prehospital setting.[10] However, in ICU, the systematic use of a stylet is still debated and recent recommendations[15 16] do not recommend to use or not to use such devices for first-attempt intubation.

The routine utilisation of a stylet for first-attempt intubation using direct laryngoscopy in ICU has never been assessed and benefit remains to be established.

We hypothesise that adding a stylet to the endotracheal tube will facilitate higher first-attempt intubation success compared to endotracheal tube alone (i.e. without stylet) in ICU patients needing mechanical ventilation.

Objectives

Primary objective. To determine whether endotracheal tube plus stylet increases first-attempt success during intubation procedure over endotracheal tube alone in ICU patients needing mechanical ventilation.

Secondary objectives. To compare in both groups, the incidence of complications related to intubation and other secondary outcomes.

The main hypothesis is that endotracheal tube plus stylet increases first-attempt success during intubation procedure over endotracheal tube alone in ICU patients needing mechanical ventilation.

Trial design

The endotracheal tube plus stylet to increase first-attempt success during endotracheal tube alone in ICU patients (STYLETO) trial is an investigator-initiated, multicenter, stratified, parallel-group unblinded trial with an electronic system–based randomization. Patients will be

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

randomly assigned to undergo the initial intubation attempt with endotracheal tube alone (i.e, without stylet, control group) or endotracheal tube+stylet (experimental group).

CONSORT diagram

Figure 1 shows the CONSORT diagram of the STYLETO trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The STYLETO study will take place in 35 ICUs, in France.

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU, adult (age ≥ 18 years), covered by public health insurance, with written informed consent from the patient or proxy (if present) before inclusion or once possible when patient has been included in a context of emergency and require mechanical ventilation through an endotracheal tube.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: intubation in case of cardio circulatory arrest, previous intubation during the same ICU stay with previous inclusion in the study, age <18 years, pregnant or breastfeeding woman, protected person, refusal of study participation or to pursue the study by the patient, absence of coverage by the French statutory healthcare insurance system.

Outcomes (Figure 2)

Primary outcome

Primary outcome variable is the proportion of patients with successful first-attempt endotracheal intubation, which is defined based on a normal-appearing waveform of the partial pressure of end-tidal exhaled carbon dioxide curve over 4 or more breathing cycles.[2]

Main secondary outcome

The single, prespecified, secondary outcome is the incidence of complications related to intubation[4 5] in the hour following intubation (severe: severe hypoxemia defined by lowest

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

saturation < 80 %, severe cardiovascular collapse, defined as systolic blood pressure less than 65 mm Hg recorded at least once or less than 90 mm Hg lasting 30 minutes despite 500–1,000 ml of fluid loading (crystalloids solutions) or requiring introduction or increasing doses by more than 30% of vasoactive support, cardiac arrest, death during intubation; moderate: difficult intubation, severe ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, agitation, pulmonary aspiration, dental injuries).

Main safety outcomes

The main safety outcomes will be the lowest peripheral oxygen saturation (SpO2), highest fraction of inspired oxygen (FiO2), and highest positive end-expiratory pressure (PEEP) in the time period of 6 to 24 hours post-intubation.[11] The complications that could be directly related to the Stylet use will also be recorded during the first intubation attempt: mucosal bleeding, laryngeal, tracheal, mediastinal or oesophageal injuries or others.[10 13]

Exploratory procedural and safety outcomes

A separate analysis of severe and moderate complications related to intubation[4 5] and of each of its components will be performed.

The other exploratory procedural and safety outcomes will be the incidence of lowest SpO2 less than 90% from induction to 2 minutes after intubation;[11] change in SpO2 from SpO2 at induction to lowest SpO2;[11] desaturation, defined as a change in SpO2 of more than 3% from induction to 2 minutes after intubation;[11] Cormack-Lehane grade of glottic view;[11] operator-assessed difficulty of intubation;[11] need for additional airway equipment or a second operator;[11] number of laryngoscopy attempts;[11] lowest SpO2, highest FiO2, and highest PEEP from 0-1 hours and 1-6 hours after intubation;[11] new infiltrate on chest imaging in the 48 hours after intubation;[11] new pneumothorax on chest imaging in the 24 hours after intubation,[11] new pneumomediastinum on chest imaging in the 24 hours after intubation.[11]

Exploratory clinical outcomes

The exploratory clinical outcomes will be: ICU length of stay, ICU-free days, invasive ventilator-free days, mortality rate on day 28, in hospital (until day 90) and day 90 mortality.[11] [17]

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Interventions

Patients eligible for inclusion will be randomly assigned to the experimental group (endotracheal tube plus stylet) or to the control group (endotracheal tube alone, Figure 2, supplemental Figure S1 in Supplemental File 1). First laryngoscopy for first-attempt will be performed with a standard Macintosh laryngoscope. The experimental group consists in intubating the trachea with an endotracheal tube + stylet with a “straight-to-cuff” shape and a bend angle of 25° to 35°.[18] The control group consists in intubating the trachea with an endotracheal tube alone (i.e, without stylet). The type of blade (plastic or metal, size 3 or 4) for standard laryngoscopy and the type of endotracheal tube will be left to the operator discretion according to standard recommendations.[19]

The availability of equipment for management of a difficult airway will be checked.[20] The difficulty of intubation will be assessed using the MACOCHA score.[5] The Montpellier intubation protocol[8 21] will be followed for each procedure. Pre-intubation period interventions consist in fluid loading in absence of cardiogenic edema, preoxygenation with noninvasive ventilation and high-flow nasal cannula oxygen for apneic oxygenation in the case of acute respiratory failure,[17 22 23] preparation of sedation by the nursing team and the presence of two operators. During the intubation period, recommended induction is rapid sequence induction using short acting, well tolerated hypnotics (etomidate or ketamine or propofol in case of hemodynamic stability), and a rapid onset muscle relaxant (succinylcholine or rocuronium in case of hyperkaliemia), with application of cricoid pressure (Sellick maneuver). Just after the intubation (post-intubation period), we recommend verification of the tube’s position by capnography (a technique which allows to confirm the endotracheal position of the tube and to verify the absence of esophageal placement), initiation of long-term sedation as soon as possible (to avoid agitation) and use of “protective” mechanical ventilation settings, with a recruitment maneuver following intubation after hemodynamic stabilization.[24 25] At any time, vasopressors are mandatory in the event of severe hemodynamic collapse.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

During the procedure, after preoxygenation, the patient will be ventilated in case of desaturation to less than 90 %. In case of inadequate ventilation and unsuccessful intubation, emergency non-invasive airway ventilation (supraglottic airway) will be used. In cases of intubation failure, the intubation algorithm of each unit will be followed.[7]

Participant timeline

The participant timeline is described in Table 1.

Sample size

The primary outcome is the first-attempt success during intubation procedure. For this study, 2 × 485 patients are needed to detect a 10% difference in the first-attempt success rate during intubation procedure (from 70% without stylet to 80% with stylet), at a two-sided α level of 0.05 and a statistical power of 95%.[4 26 27] To take into account withdrawn consent after randomisation, inclusions not meeting the inclusion criteria or improvement or death before intubation, 1040 patients will be included: 520 patients in each group.

Recruitment

Patients are expected to be included during a one and half-year inclusion period starting October 2019. Among the 35 participants centre, each one would include 4 to 10 patients per month during the 8 months-study period.

March 2019-September 2019: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

October 2019 to May 2020: Inclusion of patients.

September 2020: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Allocation and sequence generation

Randomization will be managed by the clinical research unit of Montpellier University Hospital with Capture System software (Ennov Clinical, randomization module). The randomization will be centralized and available online. It will be stratified on centre,[5 15] balanced with a 1:1 ratio and blocks of variable sizes.

Blinding

Given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. The methodologist will be blinded to the group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on electronic case report forms by trained local research coordinators or physicians. Patients will receive standard ICU monitoring consisting of electrocardiogram analysis, SpO2, and a noninvasive blood pressure cuff. Prior to tracheal intubation, the nurse will set the time intervals on the noninvasive blood pressure cuff monitoring and electronic medical record in the patient's room to run every minute until 15 minutes after successful intubation.

The following data will be collected and registered before intubation: demographic and epidemiologic data: age, sex, weight, height, date and hour of intubation, on-call procedure, severity scores (Simplified Acute Physiologic Score (SAPS) II at admission, Sequential Organ Failure Assessment (SOFA) score on the day of the procedure), type of admission, reason of ICU admission, indication of intubation, co morbidities. The following parameters will be recorded during the four hours before intubation: nature and number of operators, and their training, arterial pressure and lowest saturation, arterial blood gases with calculated arterial oxygen tension to FiO2 ratio (PaO2/FiO2) ratio if performed, delay between the time where the intubation is decided and its realization, presence of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

vasopressor drugs, prior noninvasive ventilation or high-flow nasal cannula oxygen use, existence of predictive criteria of difficult intubation evaluated by the MACOCHA score.[5]

During preoxygenation, the following data will be recorded: the length of preoxygenation, the vital parameters (SpO2 at the beginning and at the end of the preoxygenation, the type of preoxygenation).

During the intubation procedure, the following parameters will be collected : doses of hypnotic and neuromuscular blocker used, SpO2 at the beginning and at the end, lowest SpO2, lowest and highest arterial pressure and heart rate, total duration of the intubation procedure, number of operators, number of attempts, Cormack grade, traction force on the laryngoscope, Sellick maneuver, difficult intubation (more than 2 attempts), modified Intubation Difficulty Scale score[28] and occurrence of complications related to intubation. The compliance with the Montpellier intubation protocol[8] will be recorded.

After the intubation procedure (until one hour after): arterial blood gases with calculated PaO2/FiO2 ratio if performed at 5-min and 30-min and ventilatory settings will be recorded. Moderate and severe complications occurring will be collected.[11]

From postoperative day 1 to hospital discharge will be assessed: ventilatory settings (lowest SpO2, highest PEEP and highest FiO2 at 1 hour, 6 hours and 24 hours), chest X ray at 24 hours and 48 hours to identify pneumothorax or new pulmonary infiltrate, morbi-mortality by the length of mechanical ventilation, the length of stay in ICU and the mortality at day 28.

Statistical methods

Statistical analysis

The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or improve before intubation and were not intubated. All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.4; SAS Institute;

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Cary, NC, USA, and R, version 3.6.2). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges.

Primary Analysis

Unadjusted test of intervention effect. Uncorrected chi square test will be used for primary outcome analysis. Endotracheal tube plus stylet group will be compared to endotracheal tube alone.

Secondary Analyses

We will conduct the following pre-specified secondary analyses:

1. Secondary, Safety and Exploratory Outcomes.

We will perform unadjusted, intention-to-treat analyses comparing patients in the endotracheal tube plus stylet group to the endotracheal tube alone group with regard to each of the pre-specified secondary and exploratory outcomes.

Continuous outcomes will be compared with the Student t test or Mann-Whitney rank-sum test according to the conditions of application and categorical variables with the chi-square test or the Fisher exact test, according to the conditions of application. For repeated data, a mixed linear model will be used, including the subject as a random variable.

2. Per-Protocol Analysis.

We will perform a per-protocol analysis comparing patients in the endotracheal tube plus stylet group to the endotracheal tube alone group (regardless of group assignment).

3. Effect Modification (Subgroup Analyses). We will examine whether pre-specified baseline variables modify the effect of study group on the primary outcome. We will evaluate for effect

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

modification by fitting a logistic regression model for the primary outcome of first-attempt success. Independent variables will include study group assignment, the potential effect modifier variable of interest, and the interaction between the two (e.g., study group*SpO2 at induction). Significance will be determined by the P value for the interaction term, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analysed using cubic splines with 3-5 knots. If the presentation of data requires it, dichotomization of continuous variables for inclusion in a forest plot will be performed.

Pre-specified subgroups that may modify the effect of adding a stylet for tracheal intubation include:[11]

1. SpO2 at induction (continuous variable)[11]
2. Highest FiO2 received in the 6 hours prior to intubation (continuous variable)[11]
3. Receipt of non-invasive ventilation in the 6 hours prior to intubation (yes / no)[11]
4. Indication for intubation (acute respiratory failure, not acute respiratory failure)[11]
5. Neuromuscular blocking agent (depolarizing, non-depolarizing, none)[11]
6. SAPS II score at enrolment (continuous variable)[11]
7. Body mass index (continuous variable)[29 30]
8. Operator's prior number of tracheal intubations (continuous variable)[11]
9. Operator training (critical care medicine, anaesthesia)[11] and experience[2 5]
10. Obesity (yes / no)[31 32]
11. Difficult intubation (yes / no)[5]

4. Multivariable Modelling to Account for Confounding.

A logistic regression will be used for the analysis of the main criteria with odds ratio of first-attempt success calculation, before and after adjustment on confounding variables despite the randomization. Covariates will be defined as binary variables and continuous variables dichotomised according to their median tested in the model, and will be selected in a

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

backward selection procedure if p<0·15 in the univariate analysis and then presented as adjusted odds ratios with 95% confidence intervals.

A centre effect will be checked using a mixed effect logistic model, considering the centre both as a random and then a fixed variable. Interactions between variables and time will be tested.

Handling of Missing Data

Based on prior trials in similar settings, we anticipate less than 5% missing data for the primary outcome. For the primary analysis, missing data will not be imputed.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. For the exploratory outcomes, a False Discovery Rate method[33] will be used.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICUs will attend formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the technique of intubation used.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ETHICS AND DISSEMINATION

Research ethics approval

This research involving humans will be conducted in compliance with French 'Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (Loi Jardé), 'Loi N°78-17 du 6 janvier 1978 modifiée relative à l'Informatique, aux fichiers et aux Libertés')

This study will be conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation.

The study project has been approved by the ethics committee "Comité de Protection des Personnes Nord Ouest 3 19.04.26.65808 Cat 2 RECHMPL19_0216 / STYLETO 2019-A01180-57". The STYLETO study is conducted in accordance with the declaration of Helsinki and is registered on at http://www.clinicaltrials.gov (NCT04079387).

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki. If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of underlying disease. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial.

Patient and public involvement

The development of the research question and outcome measures was not informed by patients' priorities, experience, and preferences. Patients were not involved in the design, recruitment and conduct of the study. The burden of the intervention was not assessed by patients themselves. The results will be available for study participants on demand. No systematic disseminating of the results for study participants was planned.

Confidentiality

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

For Peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

To the best of our knowledge, the STYLETO trial is the first pragmatic randomised controlled trial powered to investigate if adding a stylet to the endotracheal tube increases first-attempt success during the intubation procedure in ICU.

Intubation in ICU is associated with severe complications,[4 5] the ultimate being the occurrence of intubation-related cardiac arrest.[6] Intubation-related cardiac arrest was found to be an independent risk factor for Day 28 mortality.[6] Optimizing intubation procedure is, therefore, of particular importance, to reduce morbi-mortality in ICU.[7] However, although many efforts have been made to improve the security of intubation procedure in ICU,[8] the devices used for intubating the trachea have been poorly studied. Use of a stylet allows to pre-shape the endotracheal tube, and could help to improve the ability to catheterize the trachea.[34]

The primary endpoint of the trial is the first-attempt success during intubation procedure. The first-attempt success rate in ICU is ranged between 60% and 80% depending on the setting, the population, the level of expertise of operators and the device used.[2 5 17] Increasing first-attempt success could decrease the apnea period length which can last several minutes, especially when the intubation is difficult. Increased length of apnea before successful intubation and ventilation is associated with increased occurrence of hypoxemia.[7] The ability to succeed first-attempt intubation is of critical importance to prevent the development of subsequent complications, which can lead to intubation-related cardiac arrest.[6] The first-attempt success rate is one of the most used main criteria when evaluating devices used for intubation procedure in emergency settings.[2 10] Moreover, since we collect and report on most complications related to intubation, either severe or moderate, it may still be possible to determine the effects of stylet on other complications associated with intubation. If combined use of endotracheal tube plus stylet facilitates tracheal intubation of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ICU patients compared to endotracheal tube alone, its use could become standard practice worldwide.

Strengths of the study are that all intubation performed around the clock (nights and week-end) will be included. The randomized design of the study, combined to a sufficient power (95%) with large sample size, will allow to conclude to the usefulness of a stylet. Moreover, as it is a pragmatic and multicentre study, the external validity of the study will be high. Limitations of the study are the non-blinded design, even if it will likely not influence the operator, given the vital character of the intubation procedure. We chose not to allow videolaryngoscopy for the first-attempt of intubation, to avoid confounding factors regarding the association between stylet use and first-attempt success.[2 35 36]

In conclusion, the STYLETO trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that adding a stylet to the endotracheal tube in comparison to the endotracheal tube alone allows to increase first-attempt success and decrease intubation-related complications during the intubation procedure of ICU patients requiring mechanical ventilation.

Trial status

The trial is started and actively enrolling since October 2019.

Abbreviations

ICU: Intensive Care Unit; MACOCHA score: Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening < 3 cm, Coma, severe Hypoxemia (<80%) and non-Anaesthesiologist status; SpO2: peripheral oxygen saturation; FiO2: fraction inspired in oxygen; PEEP: positive end expiratory pressure; PaO2/FiO2: Arterial oxygen tension to FiO2 ratio; SAPS: Simplified Acute Physiologic Score; SOFA: Sequential Organ Failure Assessment

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. Chan AW, Tetzlaff JM, Gotzsche PC*, et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
2. Lascarrou JB, Boisrame-Helms J, Bailly A*, et al.* Video Laryngoscopy vs Direct Laryngoscopy on Successful First-Pass Orotracheal Intubation Among ICU Patients: A Randomized Clinical Trial. *Jama* 2017;317(5):483-93.
3. Roux D, Reignier J, Thiery G*, et al.* Acquiring procedural skills in ICUs: a prospective multicenter study*. *Crit Care Med* 2014;42(4):886-95.
4. Jaber S, Amraoui J, Lefrant J-Y*, et al.* Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Crit Care Med* 2006;34(9):2355-61.
5. De Jong A, Molinari N, Terzi N*, et al.* Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187(8):832-9.
6. De Jong A, Rolle A, Molinari N*, et al.* Cardiac Arrest and Mortality Related to Intubation Procedure in Critically Ill Adult Patients: A Multicenter Cohort Study. *Crit Care Med* 2018;46(4):532-39.
7. De Jong A, Jung B, Jaber S. Intubation in the ICU: we could improve our practice. *Crit Care* 2014;18(2):209.
8. Jaber S, Jung B, Corne P*, et al.* An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive care medicine* 2010;36(2):248-55.
9. Martin LD, Mhyre JM, Shanks AM*, et al.* 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114(1):42-48.
10. Driver BE, Prekker ME, Klein LR*, et al.* Effect of Use of a Bougie vs Endotracheal Tube and Stylet on First-Attempt Intubation Success Among Patients With Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial. *Jama* 2018;319(21):2179-89.
11. Casey JD, Janz DR, Russell DW*, et al.* Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults. *N Engl J Med* 2019;380(9):811-21.
12. Apfelbaum JL, Hagberg CA, Caplan RA*, et al.* Practice Guidelines for Management of the Difficult Airway: An Updated Report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2013;118(2):251-70.
13. Kotoda M, Oguchi T, Mitsui K*, et al.* Removal methods of rigid stylets to minimise adverse force and tracheal tube movement: a mathematical and in-vitro analysis in manikins. *Anaesthesia* 2019;74(8):1041-46.
14. Jaber S, Quintard H, Cinotti R*, et al.* Risk factors and outcomes for airway failure versus non-airway failure in the intensive care unit: a multicenter observational study of 1514 extubation procedures. *Crit Care* 2018;22(1):236.
15. Quintard H, l'Her E, Pottecher J*, et al.* Intubation and extubation of the ICU patient. *Anaesthesia, critical care & pain medicine* 2017;36(5):327-41.
16. Higgs A, McGrath BA, Goddard C*, et al.* Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth* 2018;120(2):323-52.
17. Jaber S, Monnin M, Girard M*, et al.* Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. *Intensive Care Med* 2016;42(12):1877-87.
18. Levitan RM, Pisaturo JT, Kinkle WC*, et al.* Stylet bend angles and tracheal tube passage using a straight-to-cuff shape. *Acad Emerg Med* 2006;13(12):1255-8.
19. Langeron O, Bourgain JL, Francon D*, et al.* Difficult intubation and extubation in adult anaesthesia. *Anaesthesia, critical care & pain medicine* 2018;37(6):639-51.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

20. Jaber S, Bellani G, Blanch L*, et al.* The intensive care medicine research agenda for airways, invasive and noninvasive mechanical ventilation. *Intensive Care Medicine* 2017;43(9):1352-65.
21. De Jong A, Citerio G, Jaber S. Focus on ventilation and airway management in the ICU. *Intensive Care Med* 2017;43(12):1912-15.
22. Baillard C, Prat G, Jung B*, et al.* Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial. *Br J Anaesth* 2018;120(2):361-67.
23. Baillard C, Fosse JP, Sebbane M*, et al.* Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006;174(2):171-7.
24. Pensier J, de Jong A, Hajjej Z*, et al.* Effect of lung recruitment maneuver on oxygenation, physiological parameters and mortality in acute respiratory distress syndrome patients: a systematic review and meta-analysis. *Intensive Care Med* 2019;45(12):1691-702.
25. Constantin JM, Futier E, Cherprenet AL*, et al.* A recruitment maneuver increases oxygenation after intubation of hypoxemic intensive care unit patients: a randomized controlled study. *Crit Care* 2010;14(2):R76.
26. Baillard C, Fosse J-P, Sebbane M*, et al.* Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006;174(2):171-77.
27. De Jong A, Clavieras N, Conseil M*, et al.* Implementation of a combo videolaryngoscope for intubation in critically ill patients: a before-after comparative study. *Intensive care medicine* 2013;39(12):2144-52.
28. Adnet F, Borron SW, Racine SX*, et al.* The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997;87(6):1290-97.
29. Schetz M, De Jong A, Deane AM*, et al.* Obesity in the critically ill: a narrative review. *Intensive Care Med* 2019;45(6):757-69.
30. De Jong A, Verzilli D, Jaber S. ARDS in Obese Patients: Specificities and Management. *Crit Care* 2019;23(1):74.
31. De Jong A, Chanques G, Jaber S. Mechanical ventilation in obese ICU patients: from intubation to extubation. *Crit Care* 2017;21(1):63.
32. De Jong A, Molinari N, Pouzeratte Y*, et al.* Difficult intubation in obese patients: incidence, risk factors, and complications in the operating theatre and in intensive care units. *Br J Anaesth* 2015;114(2):297-306.
33. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)* 1995;57(1):289-300.
34. Gombar S, Ahuja V. Malleable stylet in difficult intubation: a modified technique. *Br J Anaesth* 2014;113(2):298-9.
35. Jaber S, De Jong A, Pelosi P*, et al.* Videolaryngoscopy in critically ill patients. *Crit Care* 2019;23(1):221.
36. De Jong A, Molinari N, Conseil M*, et al.* Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. *Intensive care medicine* 2014;40(5):629-39.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Author statement

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ. NM and ADJ wrote the statistical analysis plan and estimated the sample size. All authors (ADJ, BJ, GC, NM, SJ) revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Data statement

Technical appendix, statistical code, and dataset available on demand.

Conflicts of interests

Dr. Jaber reports receiving consulting fees from Drager, Fisher & Paykel and Xenios. No potential conflict of interest relevant to this article was reported for other authors.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Participant timeline

	Inclusion	Intubation + 5 min + 60 min	48 hours after intubation	Discharge from ICU	Day 28	Day 90
Informed consent	X					
Eligibility: check inclusion and exclusion criteria	X					
Randomisation	X					
Filling of case report forms	X	X	X	X	X	X
Outcomes		X	X		X	X

ICU, Intensive care unit

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure legend

Figure 1: Consort diagram of the STYLETO trial

ICU: Intensive Care Unit.

Figure 2

Study design of the STYLETO trial

ICU: Intensive Care Unit.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

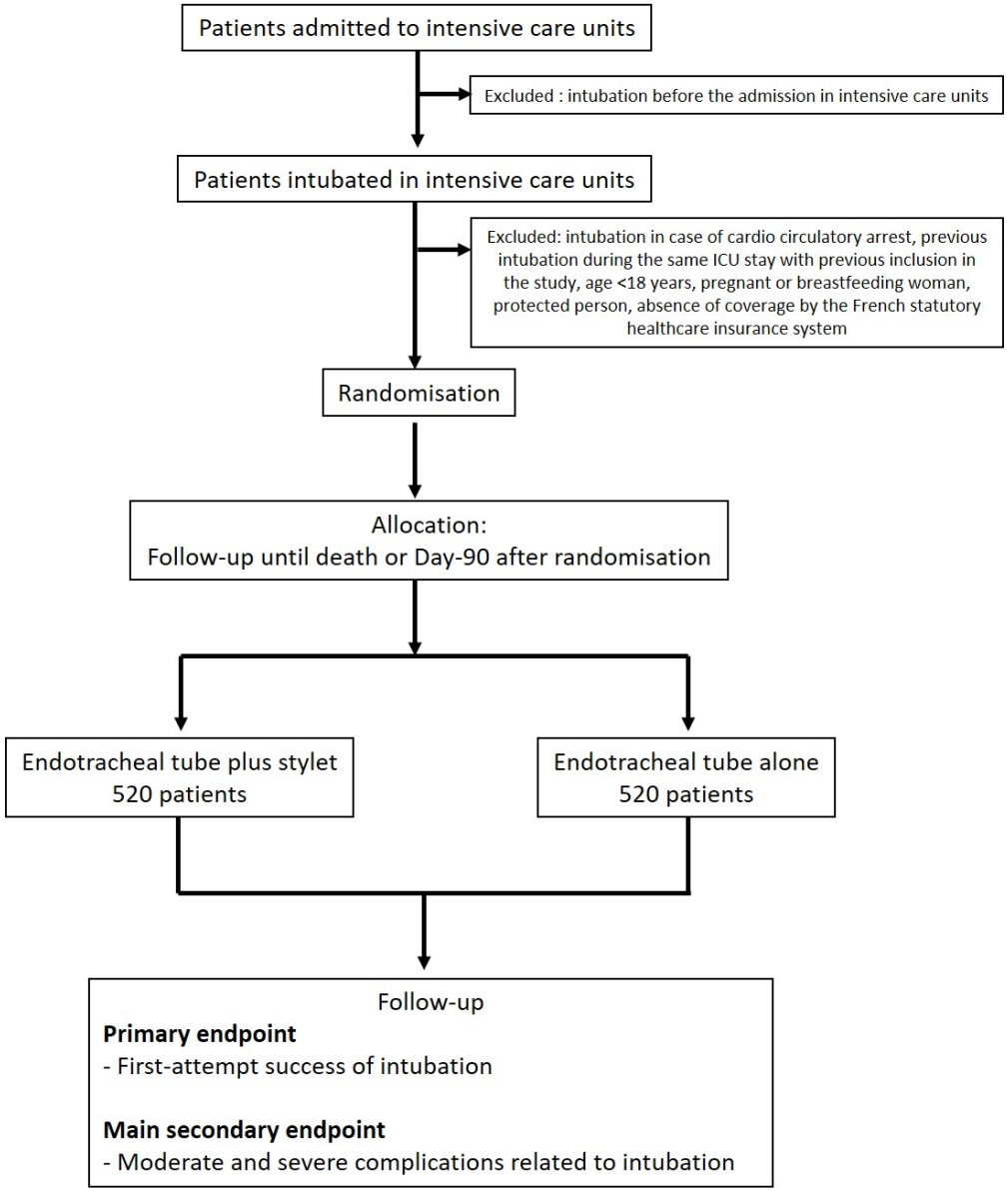


Figure 1

185x220mm (150 x 150 DPI)

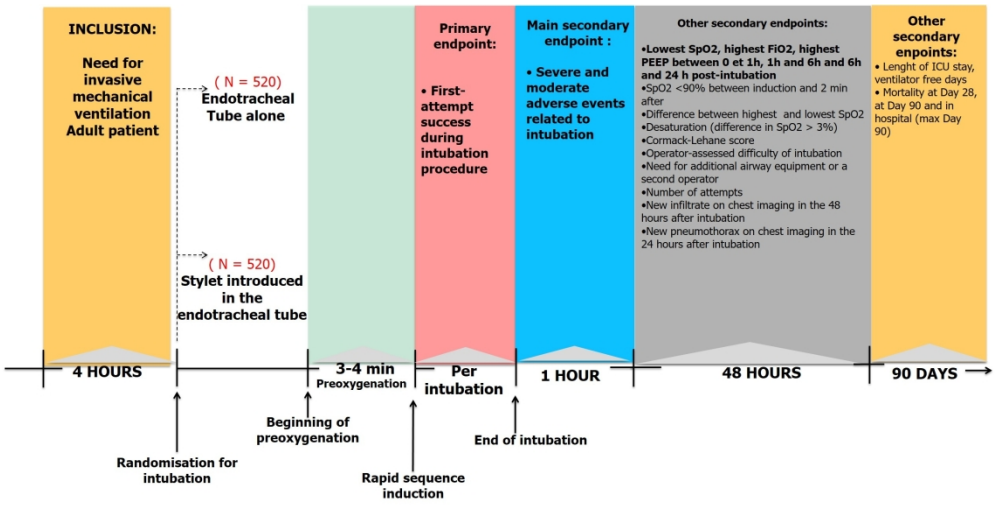
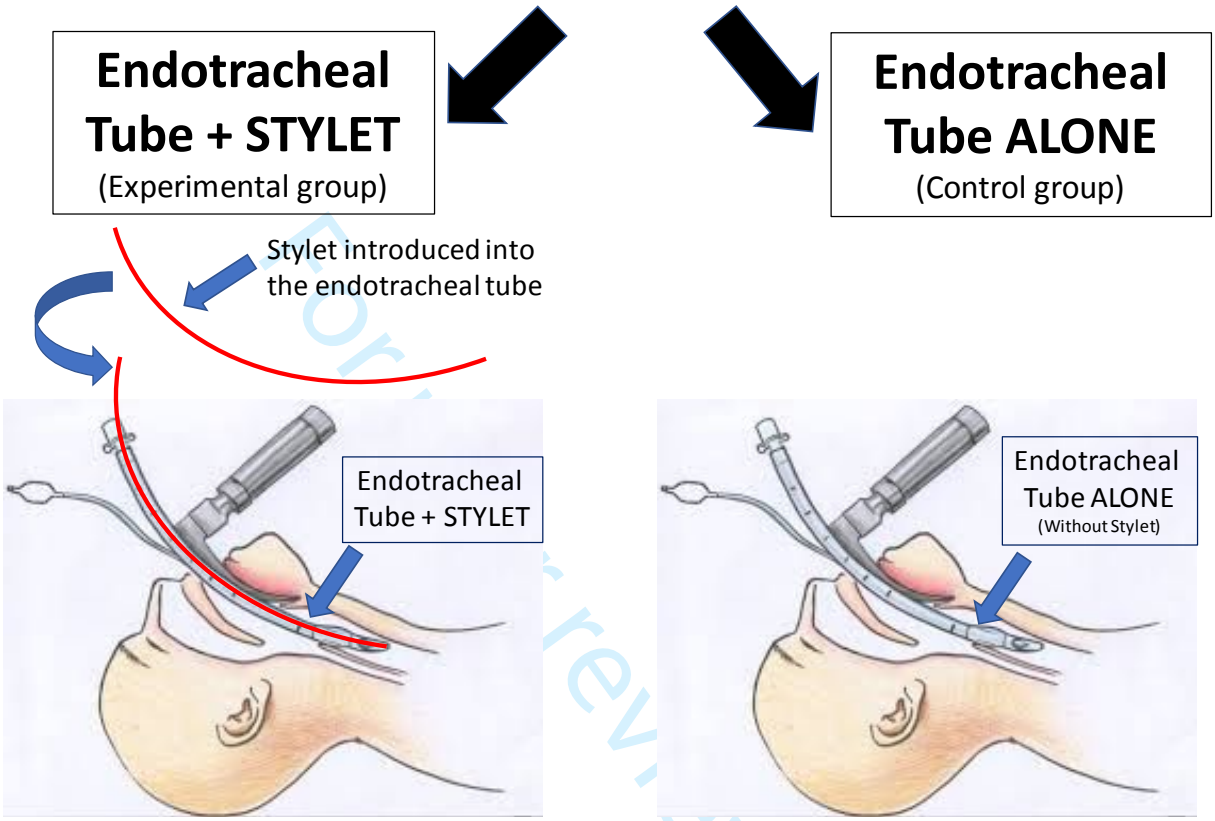


Figure 2

433x219mm (150 x 150 DPI)

Supplemental Figure S1

Description of the endotracheal intubation procedure according the group of randomisation with (Experimental group) and without the Stylet in red color (Control group).



For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: The multicenter randomised STYLETO study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036718.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Apr-2020
Complete List of Authors:	Jaber, S.; Universite de Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France; Inserm U1046, PhyMed Exp, Université de Montpellier, INSERM U1046 Montpellier, France ROLLE, Amélie; Université des Antilles Bibliothèque Hospitalo-universitaire de Guadeloupe, Intensive Care & Anesthesiology Department, University of Pointe à Pitre Hospital. Guadeloupe, France Jung, Boris; Université de Montpellier, Departement of Medical Intensive Care, Lapeyronie Teaching Hospital, Montpellier University, 191, Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5; Inserm U1046, PhyMed Exp, Université de Montpellier, INSERM U1046 Montpellier, France Chanques , Gerald; Universite de Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France; Inserm U1046, PhyMed Exp, Université de Montpellier, INSERM U1046 Montpellier, France Bertet, Helena; Universite de Montpellier, IMAG, CNRS, Univ Montpellier, CHU Montpellier, Montpellier, France Galeazzi, David; Universite de Montpellier, IMAG, CNRS, Univ Montpellier, CHU Montpellier, Montpellier, France Chauveton, Claire; Universite de Montpellier, Clinical research department of Montpellier university hospital, Montpellier, MOLINARI, Nicolas; Universite de Montpellier, IMAG, CNRS, Univ Montpellier, CHU Montpellier, Montpellier, France DE JONG, Audrey; Universite de Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France; Inserm U1046, PhyMed Exp, Université de Montpellier, INSERM U1046 Montpellier, France
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Anaesthesia

Keywords:	Adult intensive & critical care < ANAESTHETICS, INTENSIVE & CRITICAL CARE, RESPIRATORY MEDICINE (see Thoracic Medicine)

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Study protocol

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: The multicenter randomised STYLETO study protocol

Samir Jaber,[1,2] Amélie Rollé,[1,3] Boris Jung,[2,4] Gérald Chanques,[1,2] Helena Bertet,[5] David Galeazzi,[5] Claire Chauveton,[6] Nicolas Molinari,[5] Audrey De Jong[1,2]

[1] Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France

[2] PhyMed Exp, Université de Montpellier, INSERM U1046 Montpellier, France

[3] Intensive Care & Anesthesiology Department, University of Pointe à Pitre Hospital. Guadeloupe, France

[4]Departement of Medical Intensive Care, Lapeyronie Teaching Hospital, Montpellier University, 191, Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5

[5] IMAG, CNRS, Univ Montpellier, CHU Montpellier, Montpellier, France

[6] Clinical research department of Montpellier university hospital, Montpellier, France

Correspondence: Pr Samir JABER, Intensive Care Unit & Anaesthesiology Department, University of Montpellier Saint-Eloi Hospital. Montpellier, France; 80 avenue Augustin Fliche. 34295 Montpellier Cedex 5, France
Tel: 00. 33. 467. 337. 271; Fax: 00. 33. 467.337. 448; E-mail: s-jaber@chu-montpellier.fr

Abstract word counts: 300 (max 300)
Total word counts: 3930 (max 4000)
References, n=39
Table, n=1
Figures, n=2
Supplemental Figure, n=1 in Supplemental File 1
Supplemental File 2: Patient consent form

For peer review only

Abstract

Introduction:Tracheal intubation is one of the most daily practiced procedures performed in intensive care unit(ICU). It is associated with severe life-threatening complications, which can lead to intubation-related cardiac arrest. Using a preshaped endotracheal tube plus stylet may have potential advantages over endotracheal tube without stylet. The stylet is a rigid but malleable introducer which fits inside the endotracheal tube and allows for manipulation of the tube shape; to facilitate passage of the tube through the laryngeal inlet. However, some complications from stylets have been reported including mucosal bleeding, perforation of the trachea or oesophagus, and sore throat. The use of a stylet for first-attempt intubation has never been assessed in ICU and benefit remains to be established.

Methods and analysis: The endotracheal tube plus STYLET to increase first-attempt success during orotracheal intubation compared to endotracheal tube alone in ICU patients (STYLETO) trial is an investigator-initiated, multicenter, stratified, parallel-group unblinded trial with an electronic system–based randomization. Patients will be randomly assigned to undergo the initial intubation attempt with endotracheal tube alone (i.e,without stylet, control-group) or endotracheal tube+stylet (experimental-group). The primary outcome is the proportion of patients with successful first-attempt orotracheal intubation. The single, prespecified, secondary outcome is the incidence of complications related to intubation, in the hour following intubation. Other outcomes analysed will include safety, exploratory procedural and clinical outcomes.

Ethics and dissemination: The study project has been approved by the appropriate ethics committee "Comité-de-Protection-des-Personnes Nord-Ouest3-19.04.26.65808 Cat2 RECHMPL19_0216/STYLETO2019-A01180-57". Informed consent is required. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences. If combined use of endotracheal tube plus stylet facilitates tracheal intubation of ICU patients compared to endotracheal tube alone, its use will become standard practice, thereby decreasing first-attempt intubation failure rates and, potentially, the frequency of intubation-related complications.

Registration details: ClinicalTrials.gov Identifier: NCT04079387.

Strengths and limitations of the study:

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes between endotracheal tube + stylet and endotracheal tube alone to facilitate tracheal intubation of critically ill adults.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- The broad inclusion criteria and the high number of participating ICUs will increase generalisability and the large size will provide the opportunity to examine subgroups of interest.
- All intubation performed around the clock (nights and week-end) will be included.
- The nature of the study intervention does not allow blinding.

Keywords: Acute respiratory failure, airway, complications, critical care, intensive care unit, intubation, stylet

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Patients admitted to Intensive Care Units (ICU) often require respiratory support. Tracheal intubation is one of the most frequent procedures performed in ICU.[2 3] It may be associated with life-threatening complications in up to one half of cases,[4 5] the ultimate complication being cardiac arrest related to intubation in 2.7% of cases.[6] Difficult intubation, defined by more than two intubation attempts, is associated with life-threatening complications.[4 5 7-10] To prevent and limit the incidence of complications related to intubation, intubation algorithms have been developed,[7 8] and risk factors for difficult intubation in ICU have been identified that constitute the MACOCHA score (Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening < 3 cm, Coma, severe Hypoxemia (<80%) and non-Anaesthesiologist status).[5]

Devices aiming to facilitate tracheal intubation in ICU have been recently assessed. In 2018, a large multicentre study[2] reported first-attempt intubation success rates using direct laryngoscopy of 70% and videolaryngoscopy of 67%. In 2019, a multicentre randomized trial,[11] assessing whether positive-pressure ventilation with a bag-mask device (bag-mask ventilation) during tracheal intubation of critically ill adults prevents hypoxemia, reported a first-attempt success rate of 81%. Other authors reported an overall first-attempt intubation success rate of 74%.[5] The 20% to 40% first-attempt failure rates throughout studies highlight the opportunity to improve the safety and efficiency of this critical procedure. Using a preshaped endotracheal tube plus stylet may have potential advantages over endotracheal tube alone without stylet. The stylet is a rigid but malleable introducer which fits inside the endotracheal tube and allows for manipulation of the tube shape; usually into a hockey stick shape, to facilitate passage of the tube through the laryngeal inlet. The stylet also provides additional rigidity to the tube which may aid in tube passage. The stylet can help to increase success of intubation in operating rooms, although the available literature is poor.[12]

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

However, some complications from intubating stylets have been reported including mucosal bleeding, perforation of the trachea or oesophagus, and sore throat.[13 14] In 2018, one study has compared the use of a bougie to the use of the endotracheal tube plus stylet in the emergency department.[10] However, in ICU, the systematic use of a stylet is still debated and recent recommendations[15 16] do not recommend to use or not to use such devices for first-attempt intubation.

The routine utilisation of a stylet for first-attempt intubation using direct laryngoscopy in ICU has never been assessed and benefit remains to be established.

We hypothesise that adding a stylet to the endotracheal tube will facilitate higher first-attempt intubation success compared to endotracheal tube alone (i.e. without stylet) in ICU patients needing mechanical ventilation.

Objectives

Primary objective. To determine whether endotracheal tube plus stylet increases first-attempt success during intubation procedure over endotracheal tube alone in ICU patients needing mechanical ventilation.

Secondary objectives. To compare in both groups, the incidence of complications related to intubation and other secondary outcomes.

The main hypothesis is that endotracheal tube plus stylet increases first-attempt success during intubation procedure over endotracheal tube alone in ICU patients needing mechanical ventilation.

Trial design

The endotracheal tube plus stylet to increase first-attempt success during endotracheal tube alone in ICU patients (STYLETO) trial is an investigator-initiated, multicenter, stratified, parallel-group unblinded trial with an electronic system–based randomization. Patients will be

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

randomly assigned to undergo the initial intubation attempt with endotracheal tube alone (i.e, without stylet, control group) or endotracheal tube+stylet (experimental group).

CONSORT diagram

Figure 1 shows the CONSORT diagram of the STYLETO trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The STYLETO study will take place in 35 ICUs, in France.

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU, adult (age ≥ 18 years), covered by public health insurance, with written informed consent from the patient or proxy (if present) before inclusion or once possible when patient has been included in a context of emergency and require mechanical ventilation through an endotracheal tube.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: intubation in case of cardio circulatory arrest, previous intubation during the same ICU stay with previous inclusion in the study, age <18 years, pregnant or breastfeeding woman, protected person, refusal of study participation or to pursue the study by the patient, absence of coverage by the French statutory healthcare insurance system.

Outcomes

Primary outcome

Primary outcome variable is the proportion of patients with successful first-attempt endotracheal intubation, which is defined based on a normal-appearing waveform of the partial pressure of end-tidal exhaled carbon dioxide curve over 4 or more breathing cycles.[2] In case of absence of end-tidal exhaled carbon dioxide (dysfunction or cardiac arrest during intubation), the first-attempt success was defined using pulmonary auscultation: Auscultation for bilateral breath sounds and absence of stomach inflation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The criterion “first-attempt intubation success” was chosen because directly related to the potential benefits of using a stylet and associated with complications related to intubation.[17]

Main secondary outcome

The single, prespecified, secondary outcome is the incidence of complications related to intubation[4 5] in the hour following intubation (severe: severe hypoxemia defined by lowest saturation < 80 %, severe cardiovascular collapse, defined as systolic blood pressure less than 65 mm Hg recorded at least once or less than 90 mm Hg lasting 30 minutes despite 500–1,000 ml of fluid loading (crystalloids solutions) or requiring introduction or increasing doses by more than 30% of vasoactive support, cardiac arrest, death during intubation; moderate: difficult intubation, severe ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, agitation, pulmonary aspiration, dental injuries).

Main safety outcomes

The main safety outcomes will be the lowest peripheral oxygen saturation (SpO2), highest fraction of inspired oxygen (FiO2), and highest positive end-expiratory pressure (PEEP) in the time period of 6 to 24 hours post-intubation.[11] The complications that could be directly related to the Stylet use will also be recorded during the first intubation attempt: mucosal bleeding, laryngeal, tracheal, mediastinal or oesophageal injuries or others.[10 13]

Exploratory procedural and safety outcomes

A separate analysis of severe and moderate complications related to intubation[4 5] and of each of its components will be performed.

The other exploratory procedural and safety outcomes will be the incidence of lowest SpO2 less than 90% from induction to 2 minutes after intubation;[11] change in SpO2 from SpO2 at induction to lowest SpO2;[11] desaturation, defined as a change in SpO2 of more than 3% from induction to 2 minutes after intubation;[11] Cormack-Lehane grade of glottic view;[11] operator-assessed difficulty of intubation;[11] need for additional airway equipment or a second operator;[11] number of laryngoscopy attempts;[11] lowest SpO2, highest FiO2, and highest PEEP from 0-1 hours and 1-6 hours after intubation;[11] new infiltrate on chest imaging in the 48 hours after intubation;[11] new pneumothorax on chest imaging in the 24 hours after

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

intubation,[11] new pneumomediastinum on chest imaging in the 24 hours after intubation.[11] New infiltrate, pneumothorax, or pneumomediastinum on chest imaging will be determined by the referent local ICU investigator

Exploratory clinical outcomes

The exploratory clinical outcomes will be: ICU length of stay, ICU-free days, invasive ventilator-free days, mortality rate on day 28, in hospital (until day 90) and day 90 mortality.[11 18]

Interventions

Patients eligible for inclusion will be randomly assigned to the experimental group (endotracheal tube plus stylet) or to the control group (endotracheal tube alone, Figure 2, supplemental Figure S1 in Supplemental File 1). First laryngoscopy for first-attempt will be performed with a standard Macintosh laryngoscope. The experimental group consists in intubating the trachea with an endotracheal tube + stylet with a “straight-to-cuff” shape and a bend angle of 25° to 35°.[19] The control group consists in intubating the trachea with an endotracheal tube alone (i.e, without stylet). The type of blade (plastic or metal, size 3 or 4) for standard laryngoscopy and the type of endotracheal tube will be left to the operator discretion according to standard recommendations.[20]

The availability of equipment for management of a difficult airway will be checked.[21] The difficulty of intubation will be assessed using the MACOCHA score.[5] The Montpellier intubation protocol[8 22] will be strongly advised to be followed for each procedure. In brief, before intubation will be performed: fluid loading in absence of cardiogenic edema and early introduction of vasopressors, preoxygenation with noninvasive ventilation and high-flow nasal cannula oxygen for apneic oxygenation in the case of acute respiratory failure,[18 23 24] preparation of sedation by the nursing team and the presence of two operators. During the intubation period, recommended induction will be rapid sequence induction using short acting hypnotics (etomidate or ketamine or propofol in case of hemodynamic stability), and a rapid onset muscle relaxant (succinylcholine or rocuronium in case of hyperkaliemia), with

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

application of cricoid pressure (Sellick maneuver). After the intubation will be performed: verification of the tube's position by capnography, initiation of long-term sedation as soon as possible (to avoid agitation) and low pressure (low tidal volume, low positive end-expiratory pressure (PEEP)) and low rate, with a protective mechanical ventilation and a recruitment maneuver following intubation after hemodynamic stabilization.[25 26] At any time, vasopressors are recommended in the event of severe hemodynamic collapse.

During the procedure, after preoxygenation, the patient will be ventilated in case of desaturation to less than 90 %. In case of inadequate ventilation and unsuccessful intubation, emergency non-invasive airway ventilation (supraglottic airway) will be used. In cases of intubation failure, the intubation algorithm of each unit will be followed.[7]

Participant timeline

The participant timeline is described in Table 1.

Sample size

The primary outcome is the first-attempt success during intubation procedure. For this study, 2 × 485 patients are needed to detect a 10% difference in the first-attempt success rate during intubation procedure (from 70% without stylet to 80% with stylet, difference judged clinically important[2 10]), at a two-sided α level of 0.05 and a statistical power of 95%.[4 27 28] To take into account withdrawn consent after randomisation, inclusions not meeting the inclusion criteria or improvement or death before intubation, 1040 patients will be included: 520 patients in each group.

Recruitment

Patients are expected to be included during a one and half-year inclusion period starting October 2019. Among the 35 participants centre, each one would include 4 to 10 patients per month during the 8 months-study period.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

March 2019-September 2019: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

October 2019 to May 2020: Inclusion of patients.

September 2020: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

Randomization will be managed by the clinical research unit of Montpellier University Hospital with Capture System software (Ennov Clinical, randomization module). The randomization will be centralized and available online. It will be stratified on centre,[5 15] balanced with a 1:1 ratio and blocks of variable sizes.

Blinding

Given the nature of the devices, a blinded design is not possible for the investigator and associate investigator. The methodologist will be blinded to the group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on electronic case report forms by trained local research coordinators or physicians. Methodology will be similar than the methodology used in a previous published paper, showing that intubation procedure is a challenging issue in ICU because strongly associated with cardiac arrest related to intubation occurence.[6] Patients will receive standard ICU monitoring consisting of electrocardiogram analysis, SpO2, and a noninvasive blood pressure cuff. Prior to tracheal intubation, the nurse will set the time intervals on the noninvasive blood pressure cuff monitoring and electronic medical record in the patient's room to run every minute until 15 minutes after successful intubation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The following data will be collected and registered before intubation: demographic and epidemiologic data: age, sex, weight, height, date and hour of intubation, on-call procedure, severity scores (Simplified Acute Physiologic Score (SAPS) II at admission, Sequential Organ Failure Assessment (SOFA) score on the day of the procedure), type of admission, reason of ICU admission, indication of intubation, co morbidities. The following parameters will be recorded during the four hours before intubation: arterial pressure and lowest saturation, arterial blood gases with calculated arterial oxygen tension to FiO2 ratio (PaO2/FiO2) ratio if performed, delay between the time where the intubation is decided and its realization (defining real emergency (endotracheal intubation required without delay), relative emergency (endotracheal intubation required within one hour), deferred emergency (endotracheal intubation required in more than one hour)), presence of vasopressor drugs, prior noninvasive ventilation or high-flow nasal cannula oxygen use, existence of predictive criteria of difficult intubation evaluated by the MACOCHA score.[5]

During preoxygenation, the following data will be recorded: the length of preoxygenation, the vital parameters (SpO2 at the beginning and at the end of the preoxygenation, the type of preoxygenation).

During the intubation procedure, the following parameters will be collected : doses of hypnotic and neuromuscular blocker used, SpO2 at the beginning and at the end, lowest SpO2, lowest and highest arterial pressure and heart rate, total duration of the intubation procedure, number of operators, number of attempts, Cormack grade, traction force on the laryngoscope, Sellick maneuver, difficult intubation (more than 2 attempts), modified Intubation Difficulty Scale score[29] and occurrence of complications related to intubation. The compliance with the Montpellier intubation protocol[8] will be recorded.

After the intubation procedure (until one hour after): arterial blood gases with calculated PaO2/FiO2 ratio if performed at 5-min and 30-min and ventilatory settings will be recorded. Moderate and severe complications occurring and nature, number of operators, and their training, will be collected.[11]

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

From postoperative day 1 to hospital discharge will be assessed: ventilatory settings (lowest SpO2, highest PEEP and highest FiO2 at 1 hour, 6 hours and 24 hours), chest X ray at 24 hours and 48 hours to identify pneumothorax or new pulmonary infiltrate, morbi-mortality by the length of mechanical ventilation, the length of stay in ICU and the mortality at day 28.

Statistical methods

Statistical analysis

The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or improve before intubation and were not intubated. All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.4; SAS Institute; Cary, NC, USA, and R, version 3.6.2). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges.

Primary Analysis

Unadjusted test of intervention effect. Uncorrected chi square test will be used for primary outcome analysis. Endotracheal tube plus stylet group will be compared to endotracheal tube alone.

Secondary Analyses

We will conduct the following pre-specified secondary analyses:

1. Secondary, Safety and Exploratory Outcomes.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

We will perform unadjusted, intention-to-treat analyses comparing patients in the endotracheal tube plus stylet group to the endotracheal tube alone group with regard to each of the pre-specified secondary and exploratory outcomes.

Continuous outcomes will be compared with the Student t test or Mann-Whitney rank-sum test according to the conditions of application and categorical variables with the chi-square test or the Fisher exact test, according to the conditions of application. For repeated data, a mixed linear model will be used, including the subject as a random variable.

2. Per-Protocol Analysis.

We will perform a per-protocol analysis comparing patients in the endotracheal tube plus stylet group to the endotracheal tube alone group (regardless of group assignment).

3. Effect Modification (Subgroup Analyses). We will examine whether pre-specified baseline variables modify the effect of study group on the primary outcome. We will evaluate for effect modification by fitting a logistic regression model for the primary outcome of first-attempt success. Independent variables will include study group assignment, the potential effect modifier variable of interest, and the interaction between the two (e.g., study group*SpO2 at induction). Significance will be determined by the P value for the interaction term, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analysed using cubic splines with 3-5 knots. If the presentation of data requires it, dichotomization of continuous variables for inclusion in a forest plot will be performed.

Pre-specified subgroups that may modify the effect of adding a stylet for tracheal intubation include:[11]

1. SpO2 at induction (continuous variable)[11]
2. Highest FiO2 received in the 6 hours prior to intubation (continuous variable)[11]
3. Receipt of non-invasive ventilation in the 6 hours prior to intubation (yes / no)[11]

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4. Indication for intubation (acute respiratory failure, not acute respiratory failure)[11]

5. Neuromuscular blocking agent (depolarizing, non-depolarizing, none)[11]

6. SAPS II score at enrolment (continuous variable)[11]

7. Body mass index (continuous variable)[30 31]

8. Operator's prior number of tracheal intubations (continuous variable)[11]

9. Operator training (critical care medicine, anaesthesia)[11] and experience[2 5]

10. Obesity (yes / no)[32 33]

11. Difficult intubation (yes / no)[5]

4. Multivariable Modelling to Account for Confounding.

A logistic regression will be used for the analysis of the main criteria with odds ratio of first-attempt success calculation, before and after adjustment on confounding variables despite the randomization. Covariates will be defined as binary variables and continuous variables dichotomised according to their median tested in the model, and will be selected in a backward selection procedure if p<0·15 in the univariate analysis and then presented as adjusted odds ratios with 95% confidence intervals.

A centre effect will be checked using a mixed effect logistic model, considering the centre both as a random and then a fixed variable. Interactions between variables and time will be tested.

Handling of Missing Data

Based on prior trials in similar settings, we anticipate less than 5% missing data for the primary outcome. For the primary analysis, missing data will not be imputed.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. For the exploratory outcomes, a False Discovery Rate method[34] will be used.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICUs will attend formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the technique of intubation used.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ETHICS AND DISSEMINATION

Research ethics approval

This research involving humans will be conducted in compliance with French 'Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (Loi Jardé), 'Loi N°78-17 du 6 janvier 1978 modifiée relative à l'Informatique, aux fichiers et aux Libertés')

This study will be conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation.

The study project has been approved by the ethics committee "Comité de Protection des Personnes Nord Ouest 3 19.04.26.65808 Cat 2 RECHMPL19_0216 / STYLETO 2019-A01180-57". The STYLETO study is conducted in accordance with the declaration of Helsinki and is registered on at http://www.clinicaltrials.gov (NCT04079387).

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki. If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of underlying disease. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial. Informed consent material is available in Supplemental file 2.

Patient and public involvement

The development of the research question and outcome measures was not informed by patients' priorities, experience, and preferences. Patients were not involved in the design, recruitment and conduct of the study. The burden of the intervention was not assessed by patients themselves. The results will be available for study participants on demand. No systematic disseminating of the results for study participants was planned.

Confidentiality

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

For Peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

To the best of our knowledge, the STYLETO trial is the first pragmatic randomised controlled trial powered to investigate if adding a stylet to the endotracheal tube increases first-attempt success during the intubation procedure in ICU.

Intubation in ICU is associated with severe complications,[4 5] the ultimate being the occurrence of intubation-related cardiac arrest.[6] Intubation-related cardiac arrest was found to be an independent risk factor for Day 28 mortality.[6] Optimizing intubation procedure is, therefore, of particular importance, to reduce morbi-mortality in ICU.[7] However, although many efforts have been made to improve the security of intubation procedure in ICU,[8] the devices used for intubating the trachea have been poorly studied. Use of a stylet allows to pre-shape the endotracheal tube, adds rigidity to the endotracheal tube and could help to improve the ability to catheterize the trachea.[35]

The primary endpoint of the trial is the first-attempt success during intubation procedure. The first-attempt success rate in ICU is ranged between 60% and 80% depending on the setting, the population, the level of expertise of operators and the device used.[2 5 18] Increasing first-attempt success could decrease the apnea period length which can last several minutes, especially when the intubation is difficult. Increased length of apnea before successful intubation and ventilation is associated with increased occurrence of hypoxemia.[7] The first-attempt success is of paramount importance in preventing the development of subsequent complications including intubation-related cardiac arrest.[6] The first-attempt success rate is one of the most used main criteria when evaluating devices used for intubation procedure in emergency settings.[2 10] The criterion “first-attempt intubation success” was chosen because directly related to the potential benefits of using a stylet and associated with complications related to intubation. In a large, multicenter database retrospective analysis of complications related to 1844 intubation in the ICU,[36] we recently reported that first-attempt success was associated with fewer complications related to intubation than first-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

attempt failure. The time to successful intubation is also important but was less likely to be affected by the use of a stylet. Moreover, since we collect and report on most complications related to intubation, either severe or moderate, it may still be possible to determine the effects of stylet on other complications associated with intubation. If this trial demonstrates superiority of the endotracheal tube with stylet, intubation without a stylet might decrease significantly worldwide.

Strengths of the study are that all intubation performed around the clock (nights and week-end) will be included. The randomized design of the study, combined to a sufficient power (95%) with large sample size, will allow to conclude to the usefulness of a stylet. Moreover, as it is a pragmatic and multicentre study, the external validity of the study will be high. Limitations of the study are the non-blinded design, even if it will likely not influence the operator, given the vital character of the intubation procedure. We chose not to allow videolaryngoscopy for the first-attempt of intubation, to avoid confounding factors regarding the association between stylet use and first-attempt success.[2 37 38] Besides, according to recent data showing the results of an online nationwide survey in 180 French ICUs,[39] the videolaryngoscopy was used for the first attempt in only 8 (4%) ICUs. Therefore, the external validity of our study will be higher focusing on Macintosh direct laryngoscopy for first-attempt success.

In conclusion, the STYLETO trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that adding a stylet to the endotracheal tube in comparison to the endotracheal tube alone allows to increase first-attempt success and decrease intubation-related complications during the intubation procedure using a Macintosh direct laryngoscopy blade of ICU patients requiring mechanical ventilation.

Trial status

The trial is started and actively enrolling since October 2019.

Abbreviations

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ICU: Intensive Care Unit; MACOCHA score: Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening < 3 cm, Coma, severe Hypoxemia (<80%) and non-Anaesthesiologist status; SpO2: peripheral oxygen saturation; FiO2: fraction inspired in oxygen; PEEP: positive end expiratory pressure; PaO2/FiO2: Arterial oxygen tension to FiO2 ratio; SAPS: Simplified Acute Physiologic Score; SOFA: Sequential Organ Failure Assessment

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. Chan AW, Tetzlaff JM, Gotzsche PC*, et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
2. Lascarrou JB, Boisrame-Helms J, Bailly A*, et al.* Video Laryngoscopy vs Direct Laryngoscopy on Successful First-Pass Orotracheal Intubation Among ICU Patients: A Randomized Clinical Trial. *Jama* 2017;317(5):483-93.
3. Roux D, Reignier J, Thiery G*, et al.* Acquiring procedural skills in ICUs: a prospective multicenter study*. *Crit Care Med* 2014;42(4):886-95.
4. Jaber S, Amraoui J, Lefrant J-Y*, et al.* Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Crit Care Med* 2006;34(9):2355-61.
5. De Jong A, Molinari N, Terzi N*, et al.* Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187(8):832-9.
6. De Jong A, Rolle A, Molinari N*, et al.* Cardiac Arrest and Mortality Related to Intubation Procedure in Critically Ill Adult Patients: A Multicenter Cohort Study. *Crit Care Med* 2018;46(4):532-39.
7. De Jong A, Jung B, Jaber S. Intubation in the ICU: we could improve our practice. *Crit Care* 2014;18(2):209.
8. Jaber S, Jung B, Corne P*, et al.* An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive care medicine* 2010;36(2):248-55.
9. Martin LD, Mhyre JM, Shanks AM*, et al.* 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114(1):42-48.
10. Driver BE, Prekker ME, Klein LR*, et al.* Effect of Use of a Bougie vs Endotracheal Tube and Stylet on First-Attempt Intubation Success Among Patients With Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial. *Jama* 2018;319(21):2179-89.
11. Casey JD, Janz DR, Russell DW*, et al.* Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults. *N Engl J Med* 2019;380(9):811-21.
12. Apfelbaum JL, Hagberg CA, Caplan RA*, et al.* Practice Guidelines for Management of the Difficult Airway: An Updated Report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2013;118(2):251-70.
13. Kotoda M, Oguchi T, Mitsui K*, et al.* Removal methods of rigid stylets to minimise adverse force and tracheal tube movement: a mathematical and in-vitro analysis in manikins. *Anaesthesia* 2019;74(8):1041-46.
14. Jaber S, Quintard H, Cinotti R*, et al.* Risk factors and outcomes for airway failure versus non-airway failure in the intensive care unit: a multicenter observational study of 1514 extubation procedures. *Crit Care* 2018;22(1):236.
15. Quintard H, l'Her E, Pottecher J*, et al.* Intubation and extubation of the ICU patient. *Anaesthesia, critical care & pain medicine* 2017;36(5):327-41.
16. Higgs A, McGrath BA, Goddard C*, et al.* Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth* 2018;120(2):323-52.
17. Griesdale DE, Bosma TL, Kurth T*, et al.* Complications of endotracheal intubation in the critically ill. *Intensive care medicine* 2008;34(10):1835-42.
18. Jaber S, Monnin M, Girard M*, et al.* Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. *Intensive Care Med* 2016;42(12):1877-87.
19. Levitan RM, Pisaturo JT, Kinkle WC*, et al.* Stylet bend angles and tracheal tube passage using a straight-to-cuff shape. *Acad Emerg Med* 2006;13(12):1255-8.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

20. Langeron O, Bourgain JL, Francon D*, et al.* Difficult intubation and extubation in adult anaesthesia. *Anaesthesia, critical care & pain medicine* 2018;37(6):639-51.
21. Jaber S, Bellani G, Blanch L*, et al.* The intensive care medicine research agenda for airways, invasive and noninvasive mechanical ventilation. *Intensive Care Medicine* 2017;43(9):1352-65.
22. De Jong A, Citerio G, Jaber S. Focus on ventilation and airway management in the ICU. *Intensive Care Med* 2017;43(12):1912-15.
23. Baillard C, Prat G, Jung B*, et al.* Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial. *Br J Anaesth* 2018;120(2):361-67.
24. Baillard C, Fosse JP, Sebbane M*, et al.* Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006;174(2):171-7.
25. Pensier J, de Jong A, Hajjej Z*, et al.* Effect of lung recruitment maneuver on oxygenation, physiological parameters and mortality in acute respiratory distress syndrome patients: a systematic review and meta-analysis. *Intensive Care Med* 2019;45(12):1691-702.
26. Constantin JM, Futier E, Cherprenet AL*, et al.* A recruitment maneuver increases oxygenation after intubation of hypoxemic intensive care unit patients: a randomized controlled study. *Crit Care* 2010;14(2):R76.
27. Baillard C, Fosse J-P, Sebbane M*, et al.* Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006;174(2):171-77.
28. De Jong A, Clavieras N, Conseil M*, et al.* Implementation of a combo videolaryngoscope for intubation in critically ill patients: a before-after comparative study. *Intensive care medicine* 2013;39(12):2144-52.
29. Adnet F, Borron SW, Racine SX*, et al.* The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997;87(6):1290-97.
30. Schetz M, De Jong A, Deane AM*, et al.* Obesity in the critically ill: a narrative review. *Intensive Care Med* 2019;45(6):757-69.
31. De Jong A, Verzilli D, Jaber S. ARDS in Obese Patients: Specificities and Management. *Crit Care* 2019;23(1):74.
32. De Jong A, Chanques G, Jaber S. Mechanical ventilation in obese ICU patients: from intubation to extubation. *Crit Care* 2017;21(1):63.
33. De Jong A, Molinari N, Pouzeratte Y*, et al.* Difficult intubation in obese patients: incidence, risk factors, and complications in the operating theatre and in intensive care units. *Br J Anaesth* 2015;114(2):297-306.
34. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)* 1995;57(1):289-300.
35. Gombar S, Ahuja V. Malleable stylet in difficult intubation: a modified technique. *Br J Anaesth* 2014;113(2):298-9.
36. De Jong A, Rolle A, Pensier J*, et al.* First-attempt success is associated with fewer complications related to intubation in the intensive care unit. *Intensive Care Med* 2020.
37. Jaber S, De Jong A, Pelosi P*, et al.* Videolaryngoscopy in critically ill patients. *Crit Care* 2019;23(1):221.
38. De Jong A, Molinari N, Conseil M*, et al.* Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. *Intensive care medicine* 2014;40(5):629-39.
39. Martin M, Decamps P, Seguin A*, et al.* Nationwide survey on training and device utilization during tracheal intubation in French intensive care units. *Annals of intensive care* 2020;10(1):2.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Author statement

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ, HB, DG and CC. NM and ADJ wrote the statistical analysis plan and estimated the sample size. All authors (ADJ, AR, BJ, GC, HB, DG, CC, NM, SJ) revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Data statement

Technical appendix, statistical code, and dataset available on demand.

Conflicts of interests

Dr. Jaber reports receiving consulting fees from Drager, Fisher & Paykel and Xenios. No potential conflict of interest relevant to this article was reported for other authors.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1. Participant timeline

	Inclusion	Intubation + 5 min + 60 min	48 hours after intubation	Discharge from ICU	Day 28	Day 90
Informed consent	X					
Eligibility: check inclusion and exclusion criteria	X					
Randomisation	X					
Filling of case report forms	X	X	X	X	X	X
Outcomes		X	X		X	X

ICU, Intensive care unit

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure legend

Figure 1: Consort diagram of the STYLETO trial

ICU: Intensive Care Unit.

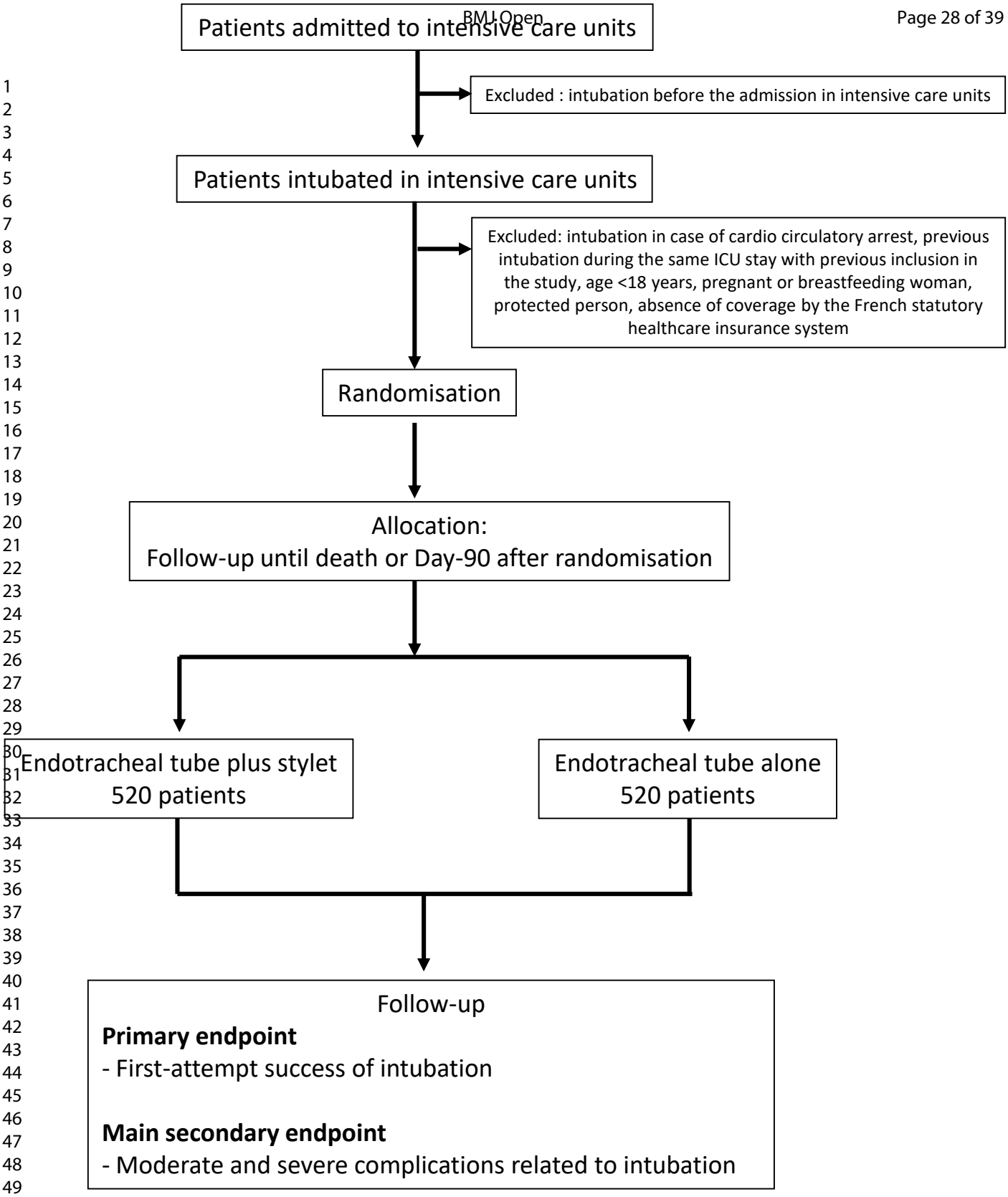
Figure 2

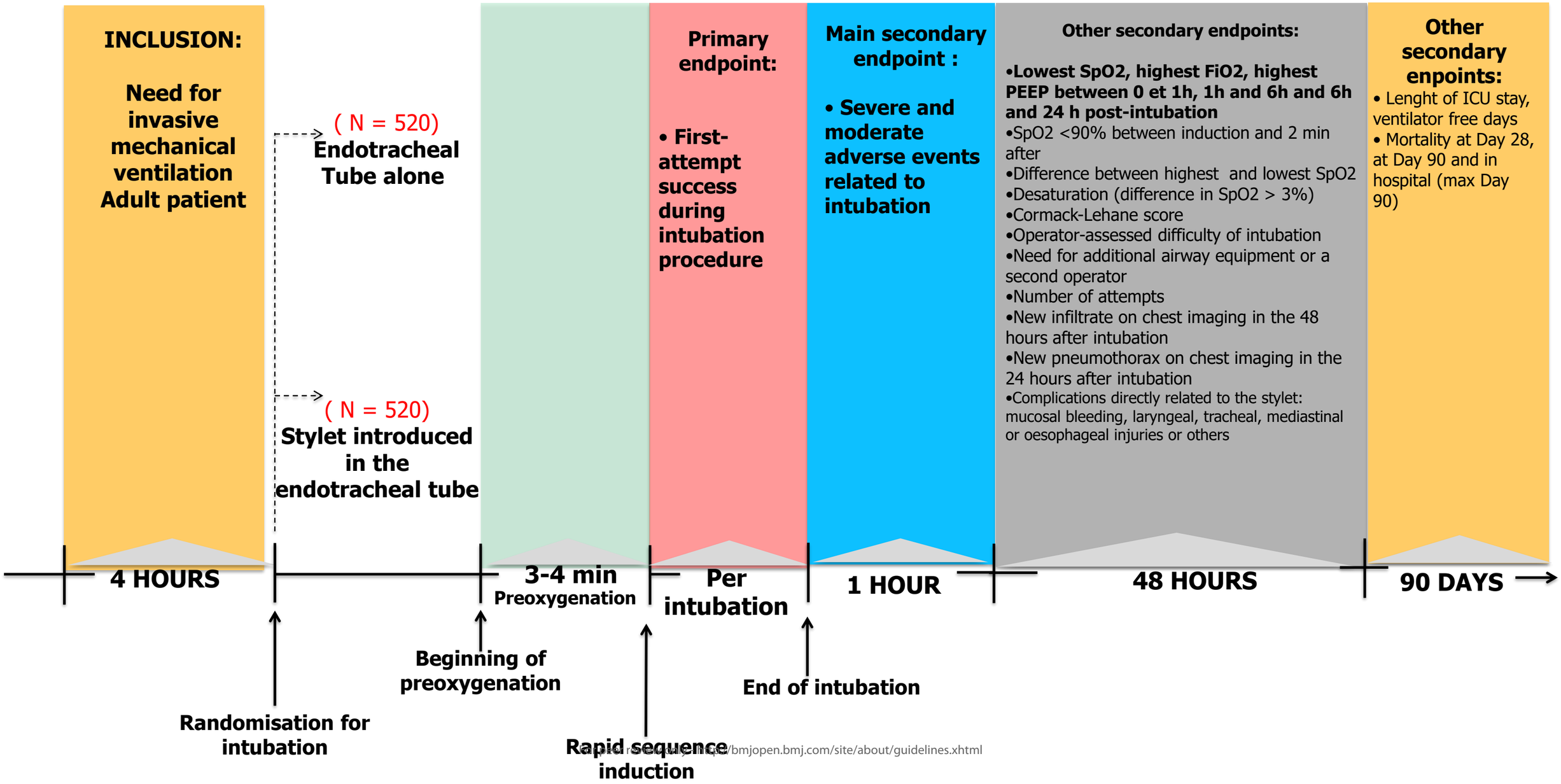
Study design of the STYLETO trial

ICU: Intensive Care Unit.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

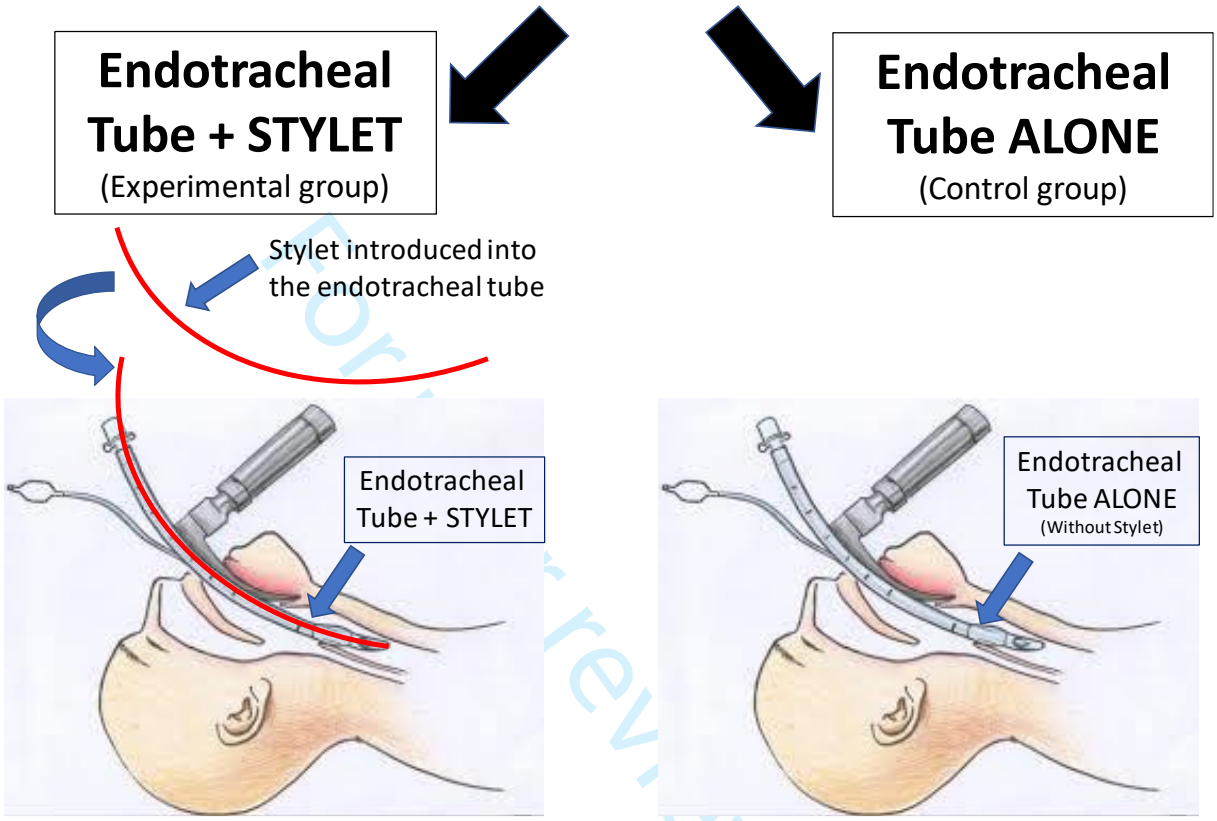

Patients admitted to intensive care units
Excluded : intubation before the admission in intensive care units
Patients intubated in intensive care units
Excluded: intubation in case of cardio circulatory arrest, previous intubation during the same ICU stay with previous inclusion in the study, age <18 years, pregnant or breastfeeding woman, protected person, absence of coverage by the French statutory healthcare insurance system
Randomisation
Allocation:
Follow-up until death or Day-90 after randomisation
Endotracheal tube plus stylet
520 patients
Endotracheal tube alone
520 patients
Follow-up
Primary endpoint
- First-attempt success of intubation
Main secondary endpoint
- Moderate and severe complications related to intubation



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Supplemental Figure S1

Description of the endotracheal intubation procedure according the group of randomisation with (Experimental group) and without the Stylet in red color (Control group).



For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INFORMATION NOTE

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: The multicenter randomised STYLETO study protocol

STYLETO Study

Research promotor: *Montpellier University Hospital*

Main investigator: *Pr Samir Jaber*

For peer review only

Madam, Sir,

Your doctor offers you the opportunity to participate in a research project promoted by Montpellier University Hospital. Before making a decision, it is important that you read these pages carefully as they will provide you with the necessary information concerning the different aspects of this research. Don't hesitate to ask your doctor any questions you may have.

Your participation is entirely voluntary. If you do not wish to take part in this research, you will continue to benefit from the best possible medical care in accordance with current knowledge.

WHY THIS RESEARCH?

You are going to be "intubated", which means that you will be put on an intubation tube ("tubing") to connect you to a ventilator to help you breathe.
Sometimes this tube can be difficult to put in place, and can be complicated by a drop in your blood oxygen level.
A "Stylet" can be added to the tube to make it more rigid to make it easier to insert. The addition of this stylet is intended to reduce the difficulty of intubation.
Both methods (with or without a stylet) are performed in routine practice.
To date, no study has evaluated the impact of the addition of a stylet on the difficulty of intubation and its complications.

WHAT IS THE OBJECTIVE OF THIS RESEARCH?

The objective of this study is to determine whether the addition of a stylet to the intubating tube leads to more frequent successful intubation on the first attempt, i.e. to increase the success rate on the first attempt.

HOW IS THIS RESEARCH GOING TO UNFOLD?

This is a so-called randomized (i.e. by drawing lots) comparative study comparing 2 groups: a control group "intubating tube alone" and an intervention group "addition of a stylet to the intubating tube" which will be conducted in 30 centres. 1040 patients will be recruited over a period of 18 months.
After the draw, you will be "intubated" either with an intubating tube alone or with an intubating tube pre-formed by adding a stylet inside.

WHO CAN PARTICIPATE?

Any critically ill patient who needs to be intubated can participate. The latter must be of legal age, must be a beneficiary or be affiliated to a social security scheme.

WHAT YOU WILL BE ASKED?

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

You will be treated according to the recommendations of good practice, just like any other critically ill patient. You will be monitored until you are discharged from the hospital.
There are no special restrictions.

WHAT ARE THE EXPECTED BENEFITS?

This clinical study has a direct benefit for the patients included. Its aim is to reduce the difficulty of intubation and therefore the complications of intubation.

WHAT ARE THE EXPECTED INCONVENIENTS?

There is no additional risk compared to any intubation performed in critically ill patients.
The addition of a stylet may in exceptional cases, when incorrectly positioned, lead to tracheal injury. Every precaution will be taken to ensure that the stylet is correctly positioned.

WHAT ARE THE POSSIBLE MEDICAL ALTERNATIVES?

An intubating tube is mandatory for intubation. The only two modalities are the presence of an intubating tube alone or with a stylet inside.

WHAT ARE THE MODALITIES OF MANAGEMENT RELATED TO THE STUDY?

Once the intubating tube is in place, no further procedures will be performed. You will be monitored throughout your stay in the intensive care unit and then in hospital.
The end of the search, premature discontinuation or exclusion, does not lead to any particular management modalities.
Participation in this research will not generate any additional costs compared to those you would have for the usual follow-up of this disease.

WHAT ARE YOUR RIGHTS?

Your doctor must provide you with all the necessary explanations concerning this research. If you wish to withdraw at any time, for whatever reason, you will continue to benefit from medical monitoring and this will not affect your future monitoring.
In accordance with the regulations, you must be a beneficiary of a social protection scheme in order to participate in research involving humans.

In accordance with Article L.1111-6 of the Public Health Code, you may designate a trusted person who may be a relative, a close friend or your treating physician and who will be consulted in the event that you are unable to express your wishes and receive the information necessary for this purpose. This person is accountable for your wishes. Her testimony prevails over any other testimony. This designation is made in writing and co-signed by the designated person. It may be revised and revoked at any time.
If you wish, your trusted person can accompany you in your steps and attend medical interviews in order to help you in your decisions.

As part of the research in which the Montpellier University Hospital offers you the opportunity to take part, your personal data will be processed in order to analyse the results of the research with regard to the objective of the research that has been presented to you.
The responsible of this treatment is the *Montpellier University Hospital.*

The study investigator and any other study personnel bound by professional secrecy and under the responsibility of the physician in charge of your treatment will collect medical data about you. This information, called "Personal Information", will be recorded on forms, called case report forms, provided by the sponsor. Only the information strictly necessary for the treatment and the purpose of the research

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

will be collected on a secure database and then kept at the end of the research, under the responsibility of Prof. Samir Jaber for 15 months.
In order to ensure the confidentiality of your personal information, neither your name nor any other information that would allow you to be directly identified will be entered in the observation notebook or in any other file that the study's medical investigator will provide to the research sponsor or to persons or companies acting on his behalf, in France or abroad.

This data will be identified by a code (inclusion number and initials). The code is used so that the study physician can identify you if necessary. This data may also be transmitted to the French health authorities under conditions that ensure its confidentiality.

In accordance with the provisions of the law on data processing, data files and individual liberties (law no. 78-17 of 6 January 1978 on data processing, data files and individual liberties as amended by law no. 2018-493 of 20 June 2018 on the protection of personal data) and the general regulations on data protection (EU regulation 2016/679), you have the right to access, rectify, delete or limit the information collected about you in the context of this processing.
In certain cases, you may also refuse the collection of your data and object to certain types of data processing being carried out. You also have the right to object to the transmission of data covered by professional secrecy that may be used in the course of such research and processing.
You may also have direct access, or through the intermediary of the doctor of your choice, to all your medical data pursuant to the provisions of Article L1111-7 of the Public Health Code.

You may withdraw your consent to the collection of your data for this processing at any time. Where applicable, in accordance with article L.1122-1-1 of the Public Health Code, the data concerning you that will have been collected prior to your withdrawal of consent may not be deleted and may continue to be processed under the conditions provided for by the research.

Finally, you may request that the personal information collected be provided to you or a third party in digital format (right of portability).

Your rights mentioned above are exercised with the doctor who is following you in the research and who knows your identity.

If you have any further questions about the collection or use of your personal information or the rights associated with this information, you can contact the Data Protection Officer of Montpellier University Hospital (Tel: 04 67 33 72 71) or the investigating physician at your centre, Dr. Samir Jaber.

If, despite the measures put in place by the sponsor, you feel that your rights are not being respected, you may file a complaint with the competent data protection supervisory authority in France, the Commission Nationale de l'Informatique et des Libertés (CNIL).

If the data controller wishes to further process your personal data for a purpose other than that for which your personal data were collected, you will be informed in advance about this other purpose, the length of time your data will be kept, and any other relevant information to ensure fair and transparent processing.

Searches mentioned in 1° of article L. 1121-1 relating to the products mentioned in article L. 5311-1 :

We inform you that you will be registered in the national file of persons who lend themselves to research provided for in Article L.1121-16 of the Public Health Code. You have the possibility to check with the Minister

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

in charge of Health the accuracy of the data concerning you in this file and the destruction of the data at the end of the period provided for by law.

In accordance with the law n°2012-300 of 5 March 2012 relating to research involving the human person :

- this research has obtained a favourable opinion from the Committee for the Protection of Persons of name of the CPP (category 2)

- The promoter of this research, the CHU de Montpellier (Centre Administratif André Bénech. 191, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 5), has taken out a civil liability insurance policy with Newline Syndicate 1218 at Lloyd's. (Category 2)

- persons who have suffered harm as a result of participation in research involving humans may assert their rights before regional conciliation and medical injury compensation commissions

- When this search is completed, you will be kept personally informed of the overall results by your doctor as soon as they are available, if you wish.

After reading this information note, do not hesitate to ask your doctor any questions you may have. After a period of reflection, if you agree to participate in this research, you must complete and sign the consent to participate form. A copy of the complete document will be given to you.

Thank you.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

CONSENT FORM

Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: The multicenter randomised STYLETO study protocol

STYLETO Study

Research promotor: *Montpellier University Hospital*

Main investigator: *Pr Samir Jaber*

I .....*(name, surname)* certify that I have read and understood the briefing note provided to me.

I had the opportunity to ask all the questions I wished to the Pr/Dr ..... *(name, surname)* who explained to me the nature, objectives, potential risks and constraints associated with my participation in this research.

I am aware of the possibility that I may interrupt my participation in this research at any time without having to justify my decision and I will do my best to inform the doctor who is following me in the research. This will of course not affect the quality of subsequent care.

I have been assured that the decisions that are necessary for my health will be taken at any time, in accordance with the current state of medical knowledge.

I am aware that this research has received a favourable opinion from the Committee for the Protection of Individuals (category 2) and has obtained compliance with the General Data Protection Regulations.

The promoter of the research, the CHU de Montpellier (Centre Administratif André Bénech. 191, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 5), has taken out civil liability insurance with Newline Syndicate 1218 at Lloyd's (Category 2).

I accept that the persons collaborating in this research or mandated by the promoter, as well as possibly the representative of the Health Authorities, have access to the information in the strictest respect of confidentiality.

I accept that the data recorded in the course of this research may be subject to computerised processing under the responsibility of the promoter.

I have noted that, in accordance with the provisions of the law relating to data processing, files and freedoms, I have the right to access, rectify, limit the processing of my data and make a complaint to the Commission Nationale de l'Informatique et des Libertés (CNIL): https://www.cnil.fr/. I also have the right to oppose the transmission of data covered by professional secrecy

Having had sufficient time for reflection before making my decision, I freely and voluntarily agree to participate in the research "Determination of optimal spontaneous ventilation testing during mechanical ventilation withdrawal: a physiological cross-over study in the resuscitation patient and perioperative medicine".

I may at any time ask for further information from the doctor who proposed me to participate in this research, telephone number:

For peer review only

STYLETO Study

Done in .....the ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ Done in .....the ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Patient signature :

Physician signature :

For peer review only

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	16
	2b	All items from the World Health Organization Trial Registration Data Set	16
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 23
	5b	Name and contact information for the trial sponsor	23
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

For peer review

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	16
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml