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Evaluation of a bronchoalveolar lavage procedure with a flexible disposable bronchoscope, Ambu® aScope™ 3 Large in patients in an intensive care unit setting

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1. INTRODUCTION

Flexible bronchoscopy is a valuable tool in the evaluation and management of critically ill patients in the intensive care unit (ICU) as well as to evaluate complications of invasive mechanical ventilation (IMV), especially atelectasis and ventilator associated pneumonias (VAP). Flexible bronchoscopes (Ambu® aScope™ 3 Large) facilitate inspection of the upper airways and bronchial tree in these patients.

The most common indications for bronchoscopy in the ICU treatment are lobar collapse in the format of lobar atelectasis, management of hemoptysis/hemorrhage and diagnosis of the type of infection. It is not uncommon to perform diagnostic and therapeutic bronchoscopies simultaneously[1,2]

Numerous bronchoscopy procedures can be applied to critically ill patients. This investigation will focus on the therapeutic bronchoalveolar lavage (BAL) procedure by the use Ambu® aScope™ 3. The aim of the therapeutic BAL procedure is to suction retained secretions in order to aid the resolution of atelectasis.

The Clinical Investigation Plan (CIP) was made according to the Council Directive 93/42 EEC of 14 June 1993 and amendment 2007/47/EC[3], the guidelines set out in ISO 14155[4], ISO 14941[5], 21 CFR Part 812[6] and 50[7] and the Helsinki Declaration[8].

2. OBJECTIVE AND HYPOTHESIS OF THE INVESTIGATION

The objective of this investigation is to determine recovery of collapsed lobar segment based on improvement in oxygenation and/or on radiographic revelation to show effectiveness in management of secretion by the use of Ambu® aScope™ 3 Large bronchoscope.

- Improvement in oxygenation is defined as:
  - Increase in saturation by 17.5% within 4 hours post-procedure (determined by the PaO_2/FiO_2 ratio) which is considered as clinical significant

or

- Radiographic revelation is defined as:
  - Recruitment of lobar collapse seen on an X-ray, CT scan or ultrasound

The hypothesis is that aScope™ 3 Large is able to manage the secretion and thereby facilitating the resolution of atelectasis.

3. ENDPOINT(S)

Primary end-point

- Resolution of atelectasis measured by improvement in oxygenation after a bronchoalveolar lavage treatment (measured within 4 hours after the BAL treatment)

Secondary end-points

- Resolution of atelectasis measured by radiographic revelation and increased lung compliance 30 minutes, 1 hour, 2 hours and 3 hours after the BAL treatment

    - Radiographic revelation defined as recruitment of lobar collapse seen on an X-ray, CT scan or ultrasound, applicable for the US only

- Settings prior to the BAL treatment (baseline) and settings post BAL treatment (30 minutes, 1 hour, 2 hours and 3 hours post treatment)
    - Blood measurements:
        - Blood gas tension values of arterial oxygen tension (PaO_2)
        - Partial pressure of carbon dioxide (PCO_2)
        - Oxygen saturation (SaO_2)
    - Ventilator settings:
        - Ventilation mode: assist control or pressure support
        - Fraction of inspired oxygen (FiO_2)
        - Respiratory rate (RR)
        - Tidal volume ($_{inspir}Vt$)
        - Tidal volume ($_{expir}Vt$)
        - Inspiratory pressure (PIP)
        - Positive end-expiratory pressure (PEEP)
        - Plateau pressure (P Plat)
        - Lung compliance (static compliance)
        - Resistance
- Intra- and post procedural complications

Other assessments

- Prior to the BAL procedure a manual recruitment should be performed once without satisfactory result
- Qualitative assessment of need for tracheal suction procedures post BAL procedure should be measured as minimal, moderate or excessive

4. DESIGN OF THE INVESTIGATION

4.1 Design of investigation

This is an open, single-centre investigation without a comparator group. The investigation will include critically ill adult patients admitted to an ICU.

The investigational centre is: University of Chicago Medicine, Chicago, United States of America. The investigational centre will include 90 patients during 6 months, starting as soon as IRB approval is obtained.
The first subject will not be included before the local IRB duly approves the CIP. If the number of subjects cannot be included in time, the sponsor will decide whether another investigational centre should be added, or if the investigation should be closed.

Only patients who can be clinically evaluated as eligible for a BAL procedure i.e. complies with the listed in- and exclusion criteria may be included in the investigation.

The intention of the investigation is a quality assessment of the aScope™ 3 Large during the BAL procedure. If subjects or their legal representatives do not consent to the investigation the procedure will be performed regardless – however off this investigation as the BAL procedure is a standard procedure during IMV and hence not an unusual procedure at the ICU.

Each patient enrolled in the investigation can only participate in the investigation once. The study duration for each subject is counting from diagnosis and indication of the need of a BAL until the effect of the BAL treatment is documented either by radiological evaluation (≤24 hours) and/or blood gas analysis post-procedure (≤4 hours).

The clinical centre is experienced with the use of Ambu® aScope™.
However, before investigation start, all Investigators must document their experience in the use with the flexible scopes, and the minimum requirement is that each Investigator has performed at least 50 BAL procedures in patients, and according to local procedures, also with any Ambu® aScope™.

The user's clinical qualification will be verified by gathering CV's from all professional participants. Investigational product training will be recorded on a separate form, and stored in the Sponsor File.

A Case Report Form (CRF) must be filled in for each subject that has signed the Informed Consent, and therefore is included in the investigation.

4.2 Sample size

- Number of subjects and type of population to be studied: 90 subjects (refer to Section 7.1)

4.3 Expected time schedule

- First subject in: As soon as reasonably possible after the IRB approval
- Last subject out: 6 months after the first subject has been enrolled into the investigation

4.4 Randomisation

Not applicable for the investigation.

5. TEST PARTICIPANTS

5.1 Inclusion criteria

- Patient's ≥18 years
- Clinical indication and eligible for a bronchopulmonary lavage procedure, as judged by the Investigator
- Patients being admitted in the ICU at the investigational centres
- Provision of signed informed consent by subject, or subject´s legal representative, e.g. next of kin

5.2 Exclusion criteria

- Patients where a BAL treatment cannot be clinically justified, judged by the Investigator
- ETT >7 mm and ≤8.5 mm in diameter
- Participating in other interventional clinical investigations or have previously participated in this investigation

5.3 Recruitment

The patients included in this investigation will be under treatment in the ICU department, and clinically judged by the Investigator to be eligible for a BAL procedure. This has to be confirmed by a radiograph revelation ≤24 hours prior to the treatment.

The BAL procedure is a standard procedure during IMV and hence not an unusual procedure at the ICU. The intention of the investigation is a qualitative assessment of the aScope™ 3 Large during the BAL procedure. If subjects or their legal representatives do not consent to the investigation the procedure will be performed regardless – however off this investigation.

The subject, or if the subject is unable to, the subject´s legal representative, will receive information orally and in writing about the investigation (see Patient Information) from the Investigator or a person named by the Investigator. If the patient agrees to participate, or patient´s legal representative agrees on behalf of the patient, the Informed Consent Form (see **Error! Reference source not found.**) needs to be signed before start of the investigation.

A subject is considered included in the investigation as soon as both parties have signed the informed consent.

If a subject is replaced, the new subject is given a new subject number.

Participation in the investigation is voluntary and the subject or the subject's legal representative can at any time withdraw from the investigation without any consequence for further examinations and treatment.

When a subject is included, the Investigator assures that the subject meets all inclusion criteria and none of the exclusion criteria, by checking the relevant boxes in the CRF.

5.4 Exclusion during the examination

Due to the investigation being a qualitative assessment of the performance of aScope™ 3 Large during the BAL procedure, subjects shall be excluded if:

- Another bronchoscope than Ambu® aScope™ 3 Large is used during the BAL procedure which can be related to the revelation of atelectasis treatment

The reason for exclusion will be stated in the CRF, but other data besides primary and secondary endpoints will not be collected in the CRF.

6. PROCEDURE

6.1.1 Method

The investigational procedure will consist of the following components:
- Bronchoalveolar lavage using a aScope™ 3 Large bronchoscope
- Recording of intra- and post-procedure complications

The patients will be recruited as explained in section 5.3.

After signing the informed consent form, the following demographic data and airway assessment parameters will be collected in the CRF, as well as the primary and secondary endpoints:

- Gender (f/m)
- Age (years)
- Height (cm)
- Weight (kg)
- ASA class
- APACHE II Score
- ETT size
- Tracheostomy
- Reason for IMV

Furthermore, the baseline ventilator settings and the blood measurements must be noted in the CRF and settings and measurements 30 minutes, 1 hour, 2 hours, 3 hours and 4 hours after the BAL treatment must be recorded (See 1, Secondary Endpoints).

The PaO_2/FiO_2 ratio will be noted in the CRF prior to (at baseline) and again 4 hours after the BAL treatment.

6.1.2 Preparation

The following materials will be ready on a preparation table before the procedure is initiated:

Investigational device:
The Ambu® aScope™ 3 Large bronchoscopes (item number: 414001000) will be prepared following the manufacturer´s instructions. Furthermore, the specific aScope 3 Large bronchoscopes' lot numbers will be collected in the CRF.

The bronchoscopes´ functions will be checked in advance, to ensure that the scope is working properly. If a bronchoscope has a malfunction, it has to be replaced before starting the procedure. This information will be collected in the CRF and a device deficiency (DD) form must be filled out.

Auxiliaries:
- aView™ monitors (item no.: 405002000)
- 3 x 20 ml sterile syringes
- Sterile saline 0,9% NaCl solution
- 2-10 ml sterile syringes with Lidocaine 2%
- Water-based gel K-Y Gel or other lubrication

The patient will be placed in a supine position.

6.1.3 Monitoring

The patients will be monitored according to local routines, including heart rate (HR), pulse oximetry (SaO_2), blood pressure (BP) and end-expiratory arterial blood gas analysis (ABG).

6.1.4 Start of procedure

All patients will be pre-oxygenated for at least two minutes with 100% oxygen (FIO_2 100%).

A satisfactory SaO_2 and CO_2 trace must be obtained before induction of sedation.

To ensure minimal gastric fluids, the gastrointestinal tube will be used to empty stomach prior to BAL procedure per Investigator's discretion.

Adequate sedation and analgesia should be applied for patients undergoing bronchoscopy in an ICU setting.

6.1.4.1. The BAL procedure

Bronchoalveolar lavage (BAL) can be performed by wedging the tip of the scope into the desired bronchus. This will be done per local procedure and at the Investigator's discretion.

Saline in 20 ml aliquots are instilled up to three times (a total of maximum 60 ml) and after two respiratory cycles, the fluid is intermittently suctioned out to a trap with low suction (<60 mmHg).

The total number of aliquots, total amount of saline instilled as well as wall suction in mmHg, are collected in the CRF.

It is expected that the returned BAL liquid will be in the range of approximately half of the total instilled volume[1]. An estimation of the returned volume must be recorded in the CRF but is not a limitation for the qualitative assessment and the clinical investigation.

Care must be exercised to ensure adequate ventilation and oxygenation is maintained during bronchoscopy in intubated patients – see 6.1.3.

6.1.4.2. Intra- and post procedural complications

Patients in the ICU is considered at high risk from complications when undergoing bronchoscopy, thus this procedure should be clinically justified.

Any complications or premature discontinuation during the procedure shall be recorded in the CRF.

Data to be recorded in the CRF covering intra- and post procedural complications:

- Aspiration
- Airway obstruction
- Laryngospasm
- Bronchospasm
- Tracheospasm
- Hypoxia (SpO_2 <85%)
- Reason for change of the bronchoscope
- Others, as deemed relevant by the Investigator for this investigational outcome

7. DATA MANAGEMENT AND STATISTICAL ANALYSIS

7.1 Sample size

The goal is to improve the "oxygenation" (measured as the ratio PaO_2/FiO_2) by at least 17.5% compared to the baseline value.
The assumed oxygenation baseline value is 200 (called expected baseline value and estimated as the mean value of all patients in the study) and hence a 17.5 % increase means that the goal is to get an end value of ≥200×1.175=235, i.e. an absolute increase of at least 35.
The primary hypothesis to be tested is if the absolute change (from baseline until 4 hours post baseline) is more than 35:

H_0: μ ≤ 35
H_1: μ > 35

In these hypotheses, μ is the expected absolute change from baseline until 4 hours post baseline.
The following formula has been used to calculate the number of patients needed (n=number of patients in the group)[12]:

$$n = \frac{\sigma_D^2 \times \left(\lambda_\alpha + \lambda_\beta\right)^2}{35^2}$$

In the formula above, σ_D is the expected standard deviation for the change over time, Δ is the expected change over time, λ_α is the $1-\alpha$ percentile of the standardized normal distribution and λ_β is the $1-\beta$ percentile of the standardized normal distribution. The test is one-sided and the significance level should then be 0.0250 and then $\lambda_\alpha = 1.9600$. If the power is 80% then $\lambda_\beta = 0.8416$ and if the power is 90% then $\lambda_\beta = 1.2816$.
The assumed standard deviation at baseline and end of study is 80. Then the standard deviation for the change over time is $\sqrt{80^2 + 80^2} = \sqrt{2} \times 80$=113.1371.
The sample size needed is then (80% power, one-sided significance level of 0.0250):

$$n = \frac{113.1371^2 \times (1.9600 + 0.8416)^2}{35^2} = 83.$$

Assuming a drop-out rate of 7% implies 90 patients needs to be recruited.

7.2 Statistical analyses

7.2.1 General aspects

Descriptive statistics, i.e. number of subjects, mean, median, standard deviation, minimum and maximum values for continuous data and frequencies and percentages for categorical data will be presented as applicable.

7.2.2 Demographics and other baseline characteristics

Baseline data will be presented by means of descriptive statistics.

7.2.3 Covariates and prognostic variables

No considerations to potential covariates and/or prognostic factors are taken in the design of the investigation. Potential influence on any covariates and/or prognostic variables to the outcome of the investigation will be investigated in the statistical analysis.

7.2.4 Handling of dropouts and missing data

Subjects dropping out will be compensated for in the sample size estimation. In case of higher drop-out than accounted for (5%), it is recognized that recruitment may be extended to involve at least the minimum number of evaluable subjects. Missing data will not be imputed.

7.2.5 Centre analyses

This investigation is a single centre investigation. However, there is no a priori reason to suspect that there will be any qualitative differences between the study sites regarding any of the outcome variables in the study. Therefore, primary statistical analysis will not include centre in the model but analyses may be stratified by centre as applicable.

7.2.6 Analysis sets

All treated subjects will be included in the Safety Analysis Set (SAS).

All correctly, included patients will be included in the Intention-To-Treat (ITT) analysis set.

Subjects who have been treated according to the CIP without any major deviations will be included in the Per Protocol (PP) analysis set.

The primary efficacy analysis set will be PP.

The primary efficacy objective of the investigation will be analysed using data from patients in the PP analysis set as well as using data from patients in the ITT analysis set. The conclusion will be based on data from the primary efficacy analysis set and the analysis based on data from the other efficacy analysis set will be considered as a sensitivity analysis.

The secondary efficacy objectives will be analysed using data from the primary efficacy analysis set only.

The analyses of the safety objectives will be based on data from the SAS.

Demographic data will be presented using data from SAS, ITT and PP.

7.2.7 Method of statistical analysis in relation to objectives

Primary objective
The primary objective is to test the hypothesis

H_0: $\mu \leq 35$

H_1: $\mu > 35$

In these hypotheses, μ is the expected absolute change of "oxygenation" (measured as the ratio PaO_2/FiO_2) from baseline until 4 hours post baseline.

The p-value will be calculated using the Wilcoxon signed rank test.

Secondary objectives
The change from baseline until each time of measurement past baseline will be tested using the Wilcoxon signed rank test for all continuous and ordered categorical variables.
The change over time for binomial data will be tested using the McNemar test.

Safety objectives
All safety data will be presented using descriptive statistics and if applicable changes over time will be analysed using the same statistical methodology as for the primary and secondary efficacy hypotheses.

7.2.8 Level of significance and handling of multiplicity

All tests and confidence intervals will be two-sided. P-values below or equal to 5% will be denoted "statistically significant" even though it is recognized that multiple hypotheses are tested. The risk for multiplicity errors will be taken into account when conclusions are drawn and the efficacy conclusion will be based on the results of the analysis of the primary objective.

The analyses of the secondary efficacy objectives will be considered hypothesis generating.

7.2.9 Statistical analyses during the course of the study

No analyses will be conducted during the course of the study.

8. LIST OF REFERENCES

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