

CLINICAL TRIAL PROTOCOL

STUDY NUMBER:

STUDY TITLE: Anesthesiological management of ventilation with laryngeal mask in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound procedures.

VERSION NUMBER: 1

DATE: December 28th, 2017

COMPOUND: Laryngeal mask versus no device in ERCP and endoscopic ultrasound procedures

Promoter: xxx

Principal Investigator: xxx

Signature

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1. SYNOPSIS

COMPOUND: Laryngeal mask versus no device in endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound procedures

STUDY No.: Seomask1

Anesthesiological management of ventilation with laryngeal mask in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound procedures	
TRIAL LOCATION	P.I. Dott. xxx Department of Anesthesia and Intensive Care
STUDY OBJECTIVE(S)	Primary: Partial Pressure of Carbon Dioxide (PaCO ₂) at the end of the endoscopic procedure
	Secondary: <ul style="list-style-type: none"> - Number needing pressure support ventilation (PSV) in the treatment group - pH, Partial Pressure of Oxygen (PaO₂) at the end of the procedure -Time to recover after the procedure -Satisfaction of the procedure operator -Satisfaction of the patient
STUDY DESIGN	Single Centre Comparative No profit 1:1 randomized Single blind (patient)
STUDY POPULATION Main selection criteria:	INCLUSION CRITERIA <ul style="list-style-type: none"> -age >18 years -written informed consent -elective ERCP and endoscopic ultrasound procedure EXCLUSION CRITERIA <ul style="list-style-type: none"> -pregnancy -contraindication to propofol administration -contraindication to mask insertion (e.g. malformation) - emergency operation (not scheduled) - preexisting causes of hypoventilation (e.g. cronic obstructive pulmonary disease, neuromuscular disease...)
Total expected number of patients:	60
INVESTIGATIONAL PRODUCT(S)	LMA® Gastro™ Cuff Pilot™ The device allows the access to the esophagus with separation of the airways. The ventilation tube has an anatomical shape and a laryngeal mask (LMA) at the extremity. The cuff is adaptable to the pharyngeal shape with an open in front of the larynx. It has a parallel channel for the endoscope that ends under the cuff at the level of the upper esophageal sphincter (UES).
EFFICACY CRITERIA	Primary: Partial Pressure of Carbon Dioxide (PaCO ₂) at the end of the endoscopic procedure

	Secondary: <ul style="list-style-type: none"> - Number needing pressure support ventilation (PSV) in the treatment group - pH and PaO₂ at the end of the procedure -Time to recover after the procedure -Satisfaction of the procedure operator -Satisfaction of the patient - Completion of the endoscopic procedure
SAFETY CRITERIA	No risk for the study subjects is expected
STUDY PROCEDURES	<p>Patients undergoing ERCP and endoscopic ultrasound will be screened the day before the procedure during the routine anaesthesiological visit. Eligible patients will be enrolled.</p> <p>Immediately before the procedure patients will be allocated according to a simple randomization list to a treatment group and a control group. Patients will be blinded about the treatment, since they will be unconscious during the procedure (single blind study).</p> <p>Patients in the control group will receive the standard anaesthesiological management of ERCP-patients, which is based on total intravenous anesthesia with propofol target controlled infusion (TCI) in spontaneous breathe without any airway devices.</p> <p>In patients in the treatment group a laryngeal mask (LMA) specifically designed to permit gastrointestinal endoscopy will be inserted after the induction of sedation. This allows for expiratory end tidal CO₂ (ETCO₂) monitoring and assisted ventilation if needed.</p> <p>In both groups anesthesia induction and maintenance will be performed according to a TCI protocol with a tailored site-effect target between 4 and 6 mcg/ml. Treatment group will receive PSV in case of ETCO₂ raising above 50 mmHg. At the end of the endoscopic procedure an arterial gas analysis will be performed. Patients will be awakened as usual and then monitored in recovery room until full recovery. Data will be collected intraoperatively and during the recovery room stay.</p> <p>The study will start after Ethical Committee approval.</p>
STATISTICAL CONSIDERATIONS	<p>The PaCO₂ in the treatment group is expected to be around 45 mmHg, due to the study design. A clinically significant hypoventilation is indicated by a PaCO₂ around 50 mmHg and could be expected in the control group. We aim at observing such a 5 mmHg PaCO₂ difference between groups with power 90% and alpha=0.05. PaCO₂ SD during sedation is considered around 5 mmHg¹.</p> <p>This yields a calculated 44 patients (22 per group).</p> <p>We decide to enroll 60 patients (30 per group) taking into account dropouts and possible non-normality.</p> <p>Continuous data will be reported as mean±SD[median(IQR)] and compared with the Student t tests on the equality of means or with the Wilcoxon rank-sum test (Mann-Whitney two-sample statistic) if not normal. Normality will be tested by visual inspection and with the Shapiro-Wilk W test for normality.</p> <p>Categorical data will be reported as number(percentage) and compared with the Pearson's chi-squared test Fisher's exact test if appropriate.</p>
DURATION OF STUDY PERIOD	6 months

2. FLOW CHART

	SCREENING PHASE (day -1)	TREATMENT PHASE (day 0)	RECOVERY ROOM PHASE (day 0)
Clinical Examination	X	X	X
Laboratory Testing (and pregnancy test)	X	X	
Inclusion/Exclusion Criteria	X	X	
Informed Consent	X		
Randomization		X	
Investigational Device Use		X	
AE /SAE recording (if any):		X	X

3. INTRODUCTION AND RATIONALE

Diagnostic and operative procedures of upper gastrointestinal (GI) tract are very common in all patients. The associated level of discomfort is extremely different and often subjective, but some procedures are difficult to tolerate because of long duration, prone position or significant stimulation of the upper airways. In case of obstructive jaundice suspicious for pancreatic lesion which needs cythopatologic determination, endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound are often performed at once. The endoscopic probe is conducted in duodenum, an endoscopic ultrasound and some biopsys are performed and then the biliary tract is investigated with a contrast agent injected from the papilla of Vater. Ducts dilatation or prosthesis placement can be performed if necessary. The more the complexity, the longer the procedure.

The procedure is generally performed with deep sedation. Many pharmacologic regimens are available and described in literature. Our institute adopts propofol target controlled infusion (TCI), setting a tailored target between 4 and 6 mcg/ml. This protocol usually guarantees unconsciousness and unresponsiveness of patients. Propofol is a handy intravenous hypnotic drug but the main adverse event is dose-related respiratory depression. Pre-existing reasons for hypoventilation can exacerbate this event. Specific categories prone to this condition are the elderly and the cronic obstructive pulmonary disease-patients. The possibility to ventilate the patient with a pressure support ventilation (PSV) is an interesting perspective. Laryngeal mask (LMA) is a useful tool when an invasive ventilation is not necessary and when neuromuscular block is not required.

This specific type of LMA allows to separate the gastric and respiratory tract and, allows the anesthesiologist to support patient's ventilation as (and only if) necessary.

BACKGROUND and PRELIMINARY DATA

A review of 33.854 GI endoscopy in Scotland underlines that for upper GI endoscopy in ASA 3-5 patients, the participation of an anesthesiologist, particularly for airway management and sedation, is mandatory. Complications can occur during the procedure and the percentage of death is 0.059%.²

A recent trial concerning the use of a gastro-laryngeal tube for airway management versus no devices found higher satisfaction, less degree of desaturation and faster recovery after anesthesia in the treatment group.³

Another study regarding a novel method of positive pressure ventilation (mask adaptor) in upper GI procedures reported an incidence of 3/30 (10%) carbon dioxide end-tidal (ETCO₂) > 50 mmHg⁴. This value exceeds the normal range of 35-45 mmHg and has several physiological implications (e.g. cerebral vasodilatation, tachycardia, lethargy)

ORIGINALITY OF THE PROPOSAL

Patients in spontaneous breathe without airway devices could reach a high level of carbon dioxide (CO₂) totally unknown to the anesthesiologist which has no tool to measure it. The introduction of a LMA in upper GI procedures could improve not only the monitoring but also the management of these patients. Literature has very few examples of airway management during GI procedures. Nowadays, new devices have been patented and are currently used in anesthesia. Our proposal is to introduce LMA in GI endoscopy to improve patient and clinicians satisfaction, reduce procedure-related complications and shorten recovery after anesthesia.

MAIN EXPECTED RESULTS AND IMPACT

This randomized controlled trial aims to demonstrate a beneficial effect of LMA in GI endoscopic procedure. In details we hypothesize:

- a faster recovery because of maintenance of normal level of CO₂.
- a higher satisfaction for patient, anesthesiologist and endoscopic operator because of deep level of sedation also in more fragile population
- an increased safety for all patients and in particular in the specific population at significant risk for hypoventilation

The results of this study can support the use of LMA in all ERCP and/or GI endoscopic procedures also in other centers.

4. STUDY OBJECTIVES

4.1 Primary

Partial Pressure of Carbon Dioxide (PaCO₂) at the end of the endoscopic procedure

4.2 Secondary

Secondary endpoints will be:

- Number needing pressure support ventilation (PSV) in the treatment group
- pH and PaO₂ at the end of the procedure
- Time to recover after the procedure
- Satisfaction of the endoscopy operator
- Satisfaction of the patient

5. STUDY DESIGN

5.1 Description of the protocol

This is a monocentric randomized controlled trial of superiority of LMA use in GI endoscopic procedures. Randomization is centralized. The study is single blind (patient). The study is no-profit.

5.2 Duration of study

Every patients undergoing scheduled ERCP and endoscopic ultrasound will be screened and consecutive eligible patients will be enrolled. The study starts after randomization and ends after discharge from the recovery room.

6. SELECTION OF PATIENTS

6.1 Number of patients planned : 60

6.2 Inclusion criteria

- age ≥ 18 years
- written informed consent
- elective ERCP and endoscopic ultrasound procedures

6.3 Exclusion criteria

- pregnancy
- emergency procedure
- contraindication to propofol administration
- contraindication to mask insertion (e.g. malformation)
- preexisting causes of hypoventilation (e.g. chronic obstructive pulmonary disease, neuromuscular disease...)

7. TREATMENTS

7.1 Investigational Medicinal Product (IMP)

All patients in both groups will receive propofol TCI with a tailored target between 4 and 6 mcg/ml until the end of the procedure.

The treatment group will also receive LMA insertion after induction of anesthesia and ET-CO₂ monitoring. In case of hypoventilation with an ET-CO₂ higher than 50 mmHg the patient will receive PSV to normalize this value.

Both group will receive a laboratory testing (peripheral arterial sample) at the end of the procedure, when the patient is still sedated, to obtain important data about ventilation.

7.2 Other products

Intraoperatively, there will not be any limitation to the use of any drugs as in general practice.

7.3 Description of blinding methods.

All the patients will be blinded to treatment assignment for the duration of the study. This study is single blind.

7.4 Method of assigning patients to treatment group (if applicable)

Randomization will be performed centrally by a simple randomization list.

7.5 Responsibilities

There is no specific drug under investigation.

7.6 IMP accountability and compliance

There is no drug company involved and there is no specific drug under investigation.

8. STUDY PROCEDURES

Subjects will be allocated according to a simple randomization list. Data will be collected by the investigators or trained colleagues.

After peripheral venous catheter insertion and vital parameters monitoring, patients will receive propofol TCI with a tailored target between 4 and 6 mcg/ml. The treatment group will receive LMA insertion and ETCO₂ monitoring throughout the procedure. In case of hypoventilation, with an ETCO₂ above 50 mmHg, the patient will be supported as necessary with PSV. The control group will not receive any airway device, according to the standard treatment. At the end of the procedure, both group will receive a laboratory testing (peripheral arterial sample), when the patient is still sedated. Vital parameters monitoring will continue in recovery room. Patients will be discharge as usual with an Aldrete score > 9.

Data will be collected during the procedure and in recovery room.

Data will be stored in electronic database without mention to patient's name.

8.1 Efficacy

The primary endpoint of the study will be the PaCO₂ at the end of the endoscopic procedure.

Secondary endpoints will be:

- Number needing pressure support ventilation (PSV) in the treatment group
- pH and PaO₂ at the end of the procedure
- Time to recover after the procedure
- Satisfaction of the procedure operator
- Satisfaction of the patient
- Completion of the endoscopic procedure

9. PATIENT SAFETY

No risk for the study subjects is expected.

10. TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION

Does not apply.

11. STATISTICAL CONSIDERATIONS

11.1 Determination of sample size

The PaCO₂ in the treatment group is expected to be around 45 mmHg, due to the study design. A clinically significant hypoventilation is indicated by a PaCO₂ around 50 mmHg and could be expected in the control group. We aim at observing such a 5 mmHg PaCO₂ difference between groups with power 90% and alpha=0.05. PaCO₂ SD during sedation is considered around 5 mmHg (Yamakage M, Kamada Y, Toriyabe M, Honma Y, Namiki A. Changes in respiratory pattern and arterial blood gases during sedation with propofol or midazolam in spinal anesthesia. J Clin Anesth 1999; 11:375–9).

This yields a calculated 44 patients (22 per group).

We decide to enroll 60 patients (30 per group) taking into account dropouts and possible non-normality.

11.2 Statistical Methods

All data will be analyzed according to the intention-to-treat principle, beginning immediately after randomization. Data will be stored electronically and analyzed by use of the R software (R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>).

All data analysis will be carried out according to a pre-established analysis plan.

Continuous data will be reported as mean±SD[median(IQR)] and compared with the Student t tests on the equality of means or with the Wilcoxon rank-sum test (Mann-Whitney two-sample statistic) if not normal. Normality will be tested by visual inspection and with the Shapiro-Wilk W test for normality. Categorical data will be reported as number(percentage) and compared with the Pearson's chi-squared test Fisher's exact test if appropriate.

11.3 Interim analysis

Not needed.

12. ETHICAL AND REGULATORY CONSIDERATIONS

This clinical trial will be conducted in accordance with the Helsinki declaration, all applicable amendments and the guidelines for Good Clinical Practice. This clinical trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country in which the clinical trial is performed, as well as any applicable guidelines.

12.1 Informed Consent

The investigator, or a trained colleague will fully inform the patient about all the aspects of the clinical trial, in language and terms the subject is able to understand. Patients will be informed about the possibility to withdraw from the study. Written informed consent will be obtained and it will be stored together with Investigator's file. A copy of the consent will be given to the patient.

12.2 Independent Ethics Committee Approval (IRB/IEC)

This clinical trial protocol as well as the Informed Consent have been submitted to the Ethics Committee.

12.3 Responsibilities of the investigator(s)

The investigator undertakes to perform the clinical trial in accordance with this clinical trial protocol, ICH /Good Clinical Practice and the applicable regulatory requirements.

The investigator will provide any missing information requested in the Case Report Form (CRF).

12.4 Responsibilities of the sponsor/promoter

Does not apply.

13. DATA MANAGEMENT

13.1 Source Documents

According to the ICH /Good Clinical Practice, the monitoring team must check the Case Report Form entries against the source documents.

13.2 Case Report Forms (CRFs)

It is the responsibility of the investigator to maintain adequate and accurate web based CRFs (a printed copy is attached to this application). All CRFs will be completed electronically in their entirety to ensure accurate interpretation of data.

14. DATA PROTECTION

Data will be stored in electronic database without indicating the name of the patients (a numeric code will be used).

The promoter (OSR) has the ownership of the data, in particular stored and secured by the Department of Anesthesia.

15. CLINICAL TRIAL RESULTS

The Promoter will be responsible for preparing a Clinical Study Report.

When the data from all investigational sites have been fully analyzed, the results of the clinical trial will be communicated to all the investigators and to Competent Authority.

16. BIBLIOGRAPHIC REFERENCES

1. Yamakage M, Kamada Y, Toriyabe M, et al. Changes in respiratory pattern and arterial blood gases during sedation with propofol or midazolam in spinal anesthesia. *J Clin Anesth* 1999; 11:375–9

2. Thompson A. M., Wright D. J., Murray W., et al. Analysis of 153 deaths after upper gastrointestinal endoscopy: room for improvement? *Surg endosc* 2004; 18: 22–25
3. Daşkaya H., Uysal H., Çiftçi T. et al, Use of the gastro-laryngeal tube in endoscopic retrograde cholangiopancreatography cases under sedation/analgesia. *Turk J Gastroenterol* 2016; 27: 246-51
4. Cong Y., Sun X., Mask adaptor-a novel method of positive pressure ventilation during propofol deep sedation for upper GI endoscopy. *Gastrointestinal Endoscopy* 2008; 68: 127-31