PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Apnoeic oxygenation with nasal cannula oxygen at different flow rates in anaesthetised patients – a study protocol for a non-inferiority randomised-controlled trial
AUTHORS	Theiler, Lorenz; Schneeberg, Fabian; Kaiser, Heiko; Riva, Thomas; Greif, Robert

VERSION 1 - REVIEW

REVIEWER	Lafi Olayan Institute of Inflammation and Ageing, College of Medical and Dental Science, University of Birmingham, United Kingdom
REVIEW RETURNED	14-Aug-2018

GENERAL COMMENTS	This study evaluates ventilatory effects during apnoeic oxygenation using nasal cannulas at different flow rates. The study addresses an important clinical question. I congratulate the authors for doing this work that could provide deeper understanding about the CO2 accumulation during apnoeic oxygenation. I have a few comments/questions. I'm wondering why tcpCO2 is your primary outcome measure while you will be measuring PaCO2 which is more reliable in measuring the CO2. Patients' recruitment is not well described in the method section and it is not clear where and when participants will be invited. This is very important point to consider as patients need sufficient time to read and understand Participant Information Sheet (PIS) or informed consent before they decide to take part in the study.

REVIEWER	Sherran Milton School of Healthcare Sciences College of Biomedical and Life Sciences Cardiff University >Room 616, 6th Floor, Eastgate House 35 - 43 Newport Road, Cardiff, CF24 0AB
REVIEW RETURNED	29-Oct-2018

GENERAL COMMENTS	There is no recognition of who is going to be doing the jaw thrust. How many anaesthetic rooms will be used and will they all have the same monitoring and will this all be calibrated. Why is consent in German only?

REVIEWER	R. David Hayward Ascension St. John Hospital Detroit, Michigan USA
REVIEW RETURNED	19-Dec-2018

GENERAL COMMENTS	This study protocol describes a single-site, single-blind randomized controlled trial comparing four anesthetic techniques (1 control using laryngoscopy, 3 alternative intervention groups using nasal administration with varied rates of oxygen flow) in a sample of elective surgery patients. My review focuses only on the statistical aspects of the protocol. Overall, the statistical design appears to be well-designed and appropriate to the study aims. There are some elements of the description of the planned analyses, as well as the randomization methods, that need to be presented in greater detail. 1.The Statistical Plan section is not specific enough. The current text describes a general approach to analysis without reference to any of the specific variables of interest in this study. For each of the planned primary and secondary endpoints, you should describe: (1) specifically what hypothesis you plan to test, (2) the procedures you anticipate using based on expectations about the data distribution (along with any additional supplementary procedures you plan to use if the data do not fit these expectations), and (3) the results anticipated. 2.A large number of variables are described on pages 13 – 14 in the Procedure section, but only three of these are included in the primary and secondary objectives. There are two issues here. First, it is difficult to follow all of the data points that will be collected. A table listing all variables to be assessed, along with their timing and type of measurement, would be very helpful for organizing this information for those reading. Second, if the rest of the variables are going to be analyzed, they should be included among the secondary endpoints. 3.The measurement of the patient-reported quality of recovery outcomes mentioned on page 14 needs to be described in more detail. You should include the specific questions that will be asked, or cite a previously-published instrument that will be used. Additionally, the timing of administration of this measure is unclear; there may be important differences in self ratings depending on the setting and on when the assessment is made, so it is important to specify the circumstances under which patients will answer these questions in the hospital vs. by telephone, and how long post-operatively the phone version may be administered. 4.It is not clear from the description of the randomization procedures on page 8 whether you plan to pre-stratify the patients (on the three sets of criteria indicated) before randomization, or if you mean that these factors will be used to stratify the analyses. If you plan to use pre-stratification, then you need to describe the procedures in greater detail, because this will make the randomization process more complex. If stratification will be used analytically, then this needs to be described in more detail in the planned analysis section.

REVIEWER	Lucas Oliveira J. e Silva Universidade Federal do Rio Grande do Sul, Brazil
REVIEW RETURNED	29-Dec-2018

GENERAL COMMENTS	This is an important study that will significantly improve our understanding of the physiological effects of apneic oxygenation. Although this is a study in a healthy population, it will give us valuable data towards a safer use in critically ill patients in settings like the ED or ICU. The use of apneic oxygenation with low-flow devices also make this intervention more feasible in places where high-flow devices are not financially possible. Few comments/suggestions: 1.Title: authors should identify as a non-inferiority randomized trial in the title. 2.Outcomes: I'd suggest to specify whether hypotheses for main and secondary outcomes are non-inferiority or superiority. It was specified only for primary outcome (increase in mean transcutaneous CO2). 3.Intention-to-treat vs per-protocol analysis: in non-inferiority trials, intention-to-treat analysis may cause a misleading inference of non-inferiority given the fact that patients in the "standard" treatment who, for whatever reason, may not follow the protocol and then this would underestimate the benefit of the "standard" treatment. The per-protocol analysis, which focuses only on those who follow the standard treatment more or less as directed, likely introduces prognostic imbalance but can nevertheless provide some reassurance regarding non-inferiority. If the results of such an analysis are consistent with those from the intention-to-treat approach and if both lie below the non-inferiority threshold, the inference regarding non-inferiority is strengthened. I'd suggest to include both.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I'm wondering why tcpCO2 is your primary outcome measure while you will be measuring PaCO2 which is more reliable in measuring the CO2.

Our response: We chose transcutaneous pCO2 over arterial pCO2 as it allows more measurement points and it has been used in previous work (Gustafson et al, BJA 2017, Riva et al. BJA 2018, Humphrey et al. BJA 2017) as well as in daily clinical routine. While invasive arterial measurements are more precise, they are rarely used in daily clinical practice. On the other hand, non-invasive transcutaneous pCO2 represents daily practice. In the research setting, we have the opportunity to measure both, invasive and non-invasive CO2. Indeed, we do both and we use the arterial pCO2 to show a possible gap between the two measurements.

Patients' recruitment is not well described in the method section and it is not clear where and when participants will be invited. This is very important point to consider as patients need sufficient time to read and understand Participant Information Sheet (PIS) or informed consent before they decide to take part in the study.

Our response: Thank you for this comment. We clarified our recruitment maneuver and the consent procedure accordingly on page 8 and 9, lines 126-129 and 133-136.

Reviewer: 2

There is no recognition of who is going to be doing the jaw thrust.

Our response: We added this information on page 12, line 219

How many anaesthetic rooms will be used and will they all have the same monitoring and will this all be calibrated.

Our response: All five anaesthetic rooms used in this study are equipped with the same standard anaesthesia monitoring according to and beyond ASA recommendations (ECG, blood-pressure, end-tidal CO2, heart rate, pulse oximetry, temperature, processed EEG), which is calibrated according to hospital regulation through dedicated personnel. Any additional specific study monitoring is brought in by the study personnel and is calibrated before every study patient according to manufacturer's instructions before measurements begin. We do not add this information in the protocol because this is standard operating procedure for anaesthesia safety and good clinical practice.

Why is consent in German only?

Our response: We are not sure whether we understand this question correctly. In Bern, Switzerland, the local language is German. Therefore, as we describe in the protocol under exclusion criteria on page 9, line 132, we exclude patients with limited knowledge of German language.

Reviewer: 3

1. The Statistical Plan section is not specific enough. The current text describes a general approach to analysis without reference to any of the specific variables of interest in this study. For each of the planned primary and secondary endpoints, you should describe: (1) specifically what hypothesis you plan to test, (2) the procedures you anticipate using based on expectations about the data distribution (along with any additional supplementary procedures you plan to use if the data do not fit these expectations), and (3) the results anticipated.

Our response: Thank you for this comment. We improved the manuscript and we clarify now how we will analyze the primary outcome parameter (page 15, line 289). The hypothesis is already defined on page 7, lines 103-105, as well as the anticipated results on page 7, lines 96-98.

For the many secondary outcome parameters that we measure, we would prefer to not list the statistical procedure in details, with a hypothesis, an analysis procedure with alternatives according distribution and the anticipated results. It would lengthen the protocol without any benefits to the reader as it will be highly repetitive. If the editor wishes, we could deliver a very long table with this information. Additionally, our ethical committee did not ask for these details, either.

2. A large number of variables are described on pages 13 – 14 in the Procedure section, but only three of these are included in the primary and secondary objectives. There are two issues here. First, it is difficult to follow all of the data points that will be collected. A table listing all variables to be assessed, along with their timing and type of measurement, would be very helpful for organizing this information for those reading. Second, if the rest of the variables are going to be analyzed, they should be included among the secondary endpoints.

Our response: We copied all these parameters from pages 13 and 14 into the section with the secondary outcome on page 15, secondary outcomes.

We would prefer to not add a table as it would be unusual in an investigator-driven anesthesia study protocol to add a table for all these parameters. They are now written in the appropriate sections.

3. The measurement of the patient-reported quality of recovery outcomes mentioned on page 14 needs to be described in more detail. You should include the specific questions that will be asked, or cite a previously-published instrument that will be used. Additionally, the timing of administration of this measure is unclear; there may be important differences in self ratings depending on the setting and on when the assessment is made, so it is important to specify the circumstances under which patients will answer these questions in the hospital vs. by telephone, and how long post-operatively the phone version may be administered.

Our response: Thank you for this comment. The measurements of these parameters will be following an already published protocol, which now is referenced (Theiler et al, Trials 2013, our new reference No. 22) We now describe the time in further detail, on page 14, line 255-256). The entire interview will be taken place at one single point in time, which should adequately reduce any possible bias the reviewer addresses.

4. It is not clear from the description of the randomization procedures on page 8 whether you plan to pre-stratify the patients (on the three sets of criteria indicated) before randomization, or if you mean that these factors will be used to stratify the analyses. If you plan to use pre-stratification, then you need to describe the procedures in greater detail, because this will make the randomization process more complex. If stratification will be used analytically, then this needs to be described in more detail in the planned analysis section.

Our response: The randomisation process is now described in great detail to clarify the stratification and randomisation on page 10, lines 156-158

Reviewer: 4

Reviewer Name: Lucas Oliveira J. e Silva

Few comments/suggestions:

1. Title: authors should identify as a non-inferiority randomized trial in the title.
2. Our response: The title has been changed according the suggestion

2. Outcomes: I'd suggest to specify whether hypotheses for main and secondary outcomes are non-inferiority or superiority. It was specified only for primary outcome (increase in mean transcutaneous CO2).

Our response: As explained in the comment 1 for reviewer 3, we now describe this in great details for the primary outcome. We did not describe a hypothesis for every secondary outcome, as reasoned in the answer to reviewer 3.

3. Intention-to-treat vs per-protocol analysis: in non-inferiority trials, intention-to-treat analysis may cause a misleading inference of non-inferiority given the fact that patients in the "standard" treatment who, for whatever reason, may not follow the protocol and then this would underestimate the benefit of the "standard" treatment. The per-protocol analysis, which focuses only on those who follow the standard treatment more or less as directed, likely introduces prognostic imbalance but can nevertheless provide some reassurance regarding non-inferiority. If the results of such an analysis are

consistent with those from the intention-to-treat approach and if both lie below the non-inferiority threshold, the inference regarding non-inferiority is strengthened. I'd suggest to include both.

Our response: Thank you for this important comment. We did so and included this in the protocol. The changes are visible on page 16, lines 293-297.

VERSION 2 – REVIEW

REVIEWER	R. David Hayward, PhD Ascension St. John Hospital, Detroit, MI USA
REVIEW RETURNED	02-May-2019

GENERAL COMMENTS	Thank you for addressing most of the points raised in my review.

REVIEWER	Sherran Milotn Cardiff University South Wales United Kingdome
REVIEW RETURNED	22-May-2019

GENERAL COMMENTS	Concerns have been addressed

REVIEWER	Lucas Oliveira J. e Silva Universidade Federal do Rio Grande do Sul, Brazil.
REVIEW RETURNED	22-May-2019

GENERAL COMMENTS	Authors have followed all instructions from the reviewers and the protocol has improved significantly.