This protocol has regard for the HRA guidance and order of content.

FULL TITLE OF THE STUDY

Preoxygenation with high-flow nasal oxygen using Optiflow™ - does speech have an effect on end-tidal oxygen achieved when compared to closed-mouth nasal breathing?

SHORT STUDY TITLE

Preoxygenation with Optiflow™ – the effect of speech on oxygenation.

PROTOCOL VERSION NUMBER AND DATE

v 0.2 26/9/2018

RESEARCH REFERENCE NUMBERS

IRAS Number: 231097

SPONSOR'S Number: RHM CR10369

NHS
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date: 26/9/2018

Name: Dr Patrick Butler

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LIST of CONTENTS

KEY STUDY CONTACTS

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Key Protocol Contributors Dr Patrick Butler	patrick.butler@uhs.nhs.uk

STUDY SUMMARY

Study Title	Preoxygenation of the lungs with high-flow nasal oxygen using Optiflo ™ - does speech have an effect on end-tidal oxygen w achieved when compared to closed-mouth nasal breathing?

Short title	Preoxygenation with Optiflow™ – the effect of speech on lung oxygenation.
Study Design	Randomised controlled trial
Study Participants	Elective booked surgical patients having a general anaesthetic
Planned Size of Sample	28
Follow up duration	none
Planned Study Period	Sept 2018 to January 2019
Research Question/Aim(s)	If a patient speaks during the process of preoxygenation with high-flow nasal oxygen via the Optiflow™ system, is the efficacy reduced as measured by end-tidal lung oxygen content?

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
Fisher & Paykel Healthcare Limited Unit 16, Cordwallis Park Clivemont Road, Maidenhead Berkshire SL6 7BU United Kingdom	F&P have given free disposable equipment for use in this and other research studies.

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ROLE OF STUDY SPONSOR AND FUNDER

PROTOCOL CONTRIBUTORS

Dr Patrick Butler and Sophie Brindley (medical student) are responsible for the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The sponsor and equipment provider do not control the final decision regarding any of these aspects of the study.

KEY WORDS: Preoxygenation
Optiflow™
End-tidal oxygen

STUDY FLOW CHART

Patients in preassessment unit given patient information sheets

↓

On day of surgery patients asked by their anaesthetist if they are willing to be recruited to study

↓ Willing

↓ Not willing

↓

Researcher explains project, answers queries, checks inclusion/exclusion suitability

↓

Patient not included in study and

↓

Suitable for study

↓

Not suitable for study → Patient not included in study

↓

Researcher completes consent form with subject

↓

Researcher randomises subject (sealed envelopes)

↓ Mouth closed group

↓ Speech group

↓

In anaesthetic room subject has nasal Optiflow™ device placed and is preoxygenated for 3 minutes with a closed mouth

↓

In anaesthetic room subject has nasal Optiflow™ device placed and is preoxygenated for 3 minutes reciting text from written sheet

↓

After 3 minutes Optiflow™ is ceased and subject exhales and then inhales through anaesthetic equipment with oxygen sampling to register the end-tidal oxygen content

↓

Optiflow™ device removed and subject released from study

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STUDY PROTOCOL

Preoxygenation with high-flow nasal oxygen using Optiflow™ - does speech have an effect on endtidal oxygen achieved when compared to closed-mouth nasal breathing?

1 BACKGROUND

Before anaesthetists commence anaesthetising patients it is common practice in many cases to ask the patient to breathe 100% oxygen for a few minutes (this is called preoxygenation). The reason for this is that the percentage of oxygen in the lungs can be raised from about 21% to 90%. If / when patients stop breathing as the anaesthetic drugs are injected, the oxygen in the lungs acts as a reservoir to keep them well oxygenated whilst the anaesthetist inserts a breathing tube into the airway. If this process of intubating the airway proves to be difficult and prolonged (e.g. due to anatomical problems) the preoxygenation will have given a larger reservoir of oxygen in the lungs and the patient will be less likely to become poorly oxygenated and come to harm.

Preoxygenation can be done with a normal anaesthetic circuit or with other oxygen delivery equipment such as high-flow nasal oxygenation with the Optiflow™ device. The latter is commonly used to support awake patients with breathing difficulties but is increasingly used in anaesthesia to maintain a high flow of oxygen via a patient's nasal airway and may be useful to prevent falls in oxygen levels during difficult intubation of the airway.

The amount of oxygen in the lungs after a period of preoxygenation can readily be measured with standard anaesthetic monitoring equipment.

Preoxygenation is commonly done with the patient breathing through their nose with a closed mouth. However, people often tend to talk during this process and this may result in less efficient preoxygenation if they breathe in room air whilst doing so.

This study aims to investigate whether there is a measurable difference in the efficiency of Optiflow™ preoxygenation (as measured by expired oxygen content) when the patient either breaths only through their nose or when they talk during the process. Talking will be standardised by reading aloud a poem.

2 RATIONALE

During induction of anaesthesia, one of the primary aims of the anaesthetist is to continue to keep the patient well oxygenated whilst the patient passes from the situation of breathing for them self to being anaesthetised and having their breathing controlled or supported by the anaesthetist. This will often entail a period of time when from when the patient stops breathing (an apnoeic period) until an airway device is inserted and the anaesthetist can oxygenate the lungs. If that apnoeic period is prolonged, the amount of oxygen remaining in the lungs will start to fall and this will result in a fall in the amount of oxygen in the bloodstream and then the oxygenation of vital organs. To try to prevent this happening it is common practice to increase the oxygen content in the lungs before the patient is anaesthetised by asking them to breathe 100% oxygen for a short period of time (about 3 minutes) before the start of the anaesthetic. Research has shown that the amount of oxygen in the lungs can be raised to 85-90% by this process – an increase to over 4 times the usual amount – which will allow the patient to remain well oxygenated for several minutes without breathing.

An alternative technique which can be used alongside preoxygenation is to use high-flow nasal oxygenation (in which a high flow of warmed, humidified oxygen is provided from nasal prongs) to keep oxygenating the lungs during a period of apnoea. It has been possible to continue oxygenating

apnoeic patients for up to 30 minutes during airway surgery using such a technique but this can only happen if the airway from nose/mouth through the larynx and into the trachea remain open and patent.

It is therefore becoming common practice to use a device such as Optiflow™ to perform both preoxygenation and apnoeic oxygenation since the device can remain in place from the start of preoxygenation until the airway has been secured and hopefully extend the safe apnoeic period in those cases where the anaesthetist has either expected or unexpected difficulty in passing an endotracheal tube.

Despite the value of high-flow nasal oxygenation during apnoea, preoxygenation remains important because, if the airway become not fully patent (a not uncommon situation in anaesthesia) the highflow nasal oxygenation becomes ineffective and then we become reliant on the oxygen stores already produced by preoxygenation to prevent falls in systemic oxygenation and potential patient harm.

In circumstances when we are using Optiflow™ to provide preoxygenation it is important that the patient breathes 100% oxygen into their lungs. If they start to speak during the process there is the possibility that they might breath in some room air through their mouth despite the high flow of oxygen via their nose. If they dilute the inspired oxygen in this manner it may be that the lung oxygen content at the end of preoxygenation is not as high as it might otherwise be and the safe apnoeic period will therefore be shorter.

By measuring the expired lung oxygen content after Optiflow™ preoxygenation in groups with either solely nasal breathing or with speech encouraged we hope to quantify any difference in efficacy. Publication of this information may help to guide clinical practice especially if a large difference in mean values between the 2 groups is demonstrated.

3 THEORETICAL FRAMEWORK

Previous studies including those involving the principal investigator have shown that the end tidal oxygen content of the lungs can be reliably measured by asking a subject to exhale and then breathe normally via a mouthpiece which has a side sampling port connected to a standard gas monitor (as used during anaesthesia) which will measure and display the expired oxygen percentage.

We have also shown that Optiflow™ can preoxygenate volunteer females to a comparable level to traditional facemask oxygenate within 3 minutes. In that trial all subjects breathed through their nose with a closed mouth and no vocalisation.

The planned study moves on from previous studies by comparing 2 groups of subjects (patients not volunteer medical students) who either breathe with a closed mouth or recite a standardised text, reading from a sheet. The study is designed to address the gap in knowledge about whether speech adversely affects the efficacy of this preoxygenation technique.

4 RESEARCH QUESTION

The research question being addressed is: Does speaking during preoxygenation with Optiflow™ have an effect on the expired oxygen fraction in the lungs at the end of 3 minutes preoxygenation.

4.1 Objectives

The objective is to quantify the end-tidal oxygen after 3 minutes of Optiflow™ preoxygenation in groups of either closed-mouth, nasal breathers or ones who speak throughout the process.

4.2 Outcome

The outcome will be that we will produce a mean (range/SD) value for the end-tidal oxygen content of the lungs after 2 styles of Optiflow™ preoxygenation. We can give guidance to the practical use of high-flow nasal oxygen for preoxygenation particularly with respect to whether efficacy is improved if patients are instructed to refrain from talking during the process.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

For each subject demographic data will be collected: age, gender, height, weight, body mass index.

For both study group arms, the end tidal oxygen fraction of the first expired breath after 3 minutes of preoxygenation will be recorded.

Demographic data will be analysed with descriptive statistics.

The findings generated (mean end-tidal oxygen levels) will be quantitative/parametric data and a t-test will be used to compare the groups.

Data will be anonymised and stored on password protected NHS computers.

Access to the study data will only be available to the researchers.

6 STUDY SETTING

The study will be a single centre study at University Hospital Southampton.

The study will be conducted in the operating theatre anaesthetic room prior to anaesthesia and surgery.

Participants will have been recruited from the patients booked on the elective surgical list who have been to the preassessment clinic in advance of the operating day.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

The study population will be from booked, elective surgical patients who have been preassessed and given a patient participation sheet to read in advance.

7.1.1 Inclusion criteria

Age 18 to 65

ASA category 1 and 2 for cardiorespiratory fitness

BMI 18 to 35

Able to understand instructions and read aloud in English

7.1.2 Exclusion criteria

ASA 3 or above for cardiorespiratory fitness

Outside age or BMI range

Unable to understand and follow detailed instructions from the researcher.

Inability to read aloud the standardised poem.

Prescribed a sedative premedication.

7.2 Sampling

7.2.1 Size of sample

A power calculation has been performed which gives a sample size of 28 (estimated mean for control group 0.85, estimated mean for test group 0.75 {SD 0.1}, p=0.05, power 0.8 [actual power 0.824]).

The control group value comes from a previous volunteer study using the same technique. The lower mean value for the speech group is a conservative estimate based on experience with mask preoxygenation by the chief investigator.

7.2.2 Sampling technique

The selection of participants will be at random from the population of preassessed elective surgical patients on any particular day that the research team is available to conduct the study in any particular theatre location. Any patient who reaches the inclusion criteria and is willing will be included.

7.3 Recruitment

7.3.1 Sample identification

Potential subjects will be identified by asking the nurses in preassessment clinic to give patient participation sheets to all patients booked on certain operating lists (from a diary/list provided by the researcher for when she is available to conduct the study). There will be no recruitment by publicity, posters, leaflets, adverts or websites.

On the day of surgery the routine anaesthetist for that operating session will ask patients who have been given participation sheets if they are willing to be spoken to about the research by the researcher and if they are willing to be screened by them to check eligibility.

If they are willing, the researcher will approach them; discuss the study in more detail, answering any questions. She will also screen them for (in)eligibility.

7.3.2 Consent

If, after discussion with the researcher, they are still willing to participate and are eligible to do so, the researcher will ask them to read and sign the consent form, again providing further explanation when needed.

8.1 Assessment and management of risk

Preoxygenation is a standard safety technique, commonly employed before many general anaesthetics. Optiflow™ is a commonly used alternative to traditional facemask preoxygenation. The technique can therefore be considered a safe one with no additional risks for a patient about to undergo a general anaesthetic.

There are no additional risks to the researcher or other hospital staff.

Subjects will not directly benefit from participation in the study

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant documents.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

All correspondence with the REC will be retained.

It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the study.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before any patients are enrolled into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

Any amendments that might need to be made to the study will be made via the REC by the principal investigator who will also be responsible for amending the protocol and other paperwork. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

8.3 Peer review

Peer review will be undertaken in line with the University of Southampton guidance for Medical Student research projects and include 2 reviewers who have relevant knowledge of the field of research, have experience in research including that involving medical student researchers and are suitably independent of the conduct of the study.

8.4 Patient & Public Involvement

A similar related study on the use of high-flow nasal oxygen for preoxygenation of term pregnant subjects is underway at the same study site. Prior to starting that study patient feedback about the design of the patient information sheet was obtained from patients who had undergone caesarean section and would have been suitable for enrolment. Knowledge of that feedback has guided the design of the present study.

8.5 Protocol compliance

Accidental deviations from the protocol will be recorded and reported to the CI.

8.6 Data protection and patient confidentiality

Only members of the patient's routine care team will see the participant before the day of surgery. Only information used as part of the routine process for assessing patients pre-operatively would be used to identify them as suitable for inclusion in the study. The researcher will only approach subjects who have indicated to their anaesthetist a willingness to participate in the study. The consent form will explain that the researcher has access to certain demographic data from patient notes (e.g. name, age) but personal identifiable information will not be stored for the study.

To protect personal data, hospital identification numbers will be anonymised. A list of hospital identification numbers with cross reference to their research ID numbers will be kept in a locked NHS office.

All investigators and study site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Data generated by the study, which will be anonymised, will be kept on NHS password protected computers. This data will be retained for 5 years by the CI.

8.7 Indemnity

As an NHS organisation has agreed to act as sponsor and as researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes.

8.8 Access to the final study dataset

The full anonymised data set will be accessed only by the research team.

9 DISSEMINATION POLICY

9.1 Dissemination policy

At the end of the study the researcher will produce a full written report which will be submitted to the University of Southampton as part of her BM degree work. An abstract and presentation at an annual medical student conference will be made.

Further publication of the study may be made in peer reviewed publications or at conferences as a poster or oral presentation.

Fisher and Paykel, as providers of the disposable equipment, will be provided with copies of reports and potential publications but will not have rights to review or edit publications.

Participants who are interested will be sent a copy of the researcher's report.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship of reports and publications will be limited to the researcher and principal/chief investigator.

10 REFERENCES

Mir F, Patel A, Iqbal R, Cecconi M, Nouraei S. A randomised controlled trial comparing transnasal humidified rapid insufflations ventilator exchange (THRIVE) with facemask pre-oxygenation in patients undergoing rapid sequence induction of anaesthesia. *Anaesthesia* 2016; **72:** 439 – 43

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11. APPENDICES

Text chosen for reading aloud is the opening pages from The Chronicles of Narnia by CS Lewis

13.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	0.2	26/9/18	p butler	Subject exclusion criteria to include those having a sedative premedication