**Research Protocol**

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| DATE4 May 2022 | VERSION NUMBER6 |
| **STUDY TITLE** | Cerebral Oximetry when VEntilated oR Spontaneouslybreathing  |
| **Short title** | The COVERS trial |

**PRINCIPAL INVESTIGATOR**

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***A) Project summary / Abstract***

Data from observational series suggests that ventilatory strategy may affect cerebral oxygenation during shoulder surgery in the beach chair (sitting) position.[[1]](#endnote-1),[[2]](#endnote-2) This has not previously been tested through a randomised control trial. We propose to undertake a patient-blinded, randomised control trial comparing cerebral oximetry in patients who are spontaneously breathing under anaesthesia with those who are ventilated with intermittent positive pressure ventilation. The primary outcome would be mean change from baseline cerebral oximetry. We plan to recruit 40 ASA 1-2 patients aged 18-70 undergoing arthroscopic shoulder surgery in the beach chair position. Recruitment and follow up is anticipated to take six months or less. We expect to show that intermittent positive pressure ventilation is associated with a reduction in cerebral oximetry.

***B) Background / Rationale***

The ‘beach chair’ or sitting position is commonly used during shoulder surgery. Maintenance of adequate cerebral perfusion is a key goal of anaesthetic technique. Rare but catastrophic outcomes (stroke, brain death) have been reported. Further concern has been raised that relative hypoperfusion could lead to subclinical cerebral damage in vulnerable patients[[3]](#endnote-3).

Cerebral oximetry is a non-invasive monitor which can be used to measure cerebral oxygenation. Over the past decade, this monitor has been used to explore the impact of many elements of anaesthetic technique in those at higher than average risk of cerebral events – including neonates and patients undergoing vascular, cardiac and shoulder surgery. Among patients undergoing shoulder surgery, studies have looked at the impact of position, regional techniques, and anaesthetic agent.[[4]](#endnote-4) Only two randomised control trials have considered the impact of ventilatory technique – they studied the effect of inspired oxygen concentration and end tidal CO2.[[5]](#endnote-5),[[6]](#endnote-6).

Only one study has compared positive pressure ventilation with spontaneous ventilation for surgery in the beach chair position. The study was an observational cohort study (all patients were exposed to both ventilatory strategies) and some elements of anaesthetic care (inspired oxygen fraction, anaesthetic agent, management protocol for hypotension) were not standardised. No difference was found in the incidence of cerebral desaturation events.[[7]](#endnote-7)

***C1) Aims and Objectives***

The objective of our study is to compare the effect of the two ventilatory strategies on cerebral oximetry in the beach chair position. Secondary objectives are

* to see if ventilatory strategy affects the incidence of cerebral desaturation events.
* If possible, to report changes in cerebral oximetry by ethnicity

***C2) Hypotheses***

The null hypothesis is that mean change in cerebral saturation (ΔSctO­2) under general anaesthesia is the same, regardless of whether patients are breathing spontaneously or being ventilated with intermittent positive pressure ventilation.

* ***D) Methodology***
* Study design / type:
	+ This is a patient-blinded randomised control trial. The researcher responsible for data extraction from the anaesthetic record will also be blinded to treatment group assignation. The anaesthetist/co-investigator providing intra-operative patient care will be aware of treatment group assignation.
* Participants:
	+ We plan to enrol 40 patients (20 patients in each treatment arm) across two sites (Counties Manukau Health and MercyAscot).
	+ Inclusion criteria – ASA1-2 patients aged 18-70 undergoing arthroscopic shoulder surgery in the beach chair position under general anaesthesia with interscalene blockade (either ‘single shot’ or catheter-based).
	+ Exclusion criteria
		- known cerebrovascular or peripheral vascular disease,
		- uncontrolled hypertension
		- a history of severe postoperative nausea and vomiting (which may mandate a total intravenous based anaesthetic)
	+ Participants will be identified by through screening of theatre lists 3-4 days prior to surgery.
* Outcomes:
	+ Primary outcome – mean change in cerebral oximetry during the operative period. This will be calculated as the difference between baseline cerebral oximetry values and mean intraoperative values, which are defined as
		- the area under the curve (AUC) for ‘cerebral oximetry versus time’ between anaesthesia induction and application of dressings, divided by duration (measured in seconds) to produce a value (AUC/t).
		- this difference will be calculated for both the right and left hemisphere recordings and mean value defined as [right hemisphere + left hemisphere]/ 2.
	+ Secondary outcome –
		- Incidence of cerebral desaturation events (defined as a fall of 20% below baseline values and/or an absolute measured cerebral oxygenation value of 55% or less in either hemisphere).
		- Mean change in cerebral oximetry for each ethnic group represented.
* Sample size calculations.

A recent series by Cox et al presented a complete dataset of NIRS values in forty patients across multiple phases of arthroscopic surgery in the beach chair position[[8]](#endnote-8). This information was used to derive the mean and associated standard deviations of NIRS values between the baseline (or awake) value to the conclusion of surgery which includes the operative phase during which the patient was anaesthetised and in the beach chair position. The mean change in NIRS value between these two phases was 1.65% with an associated standard deviation of 7.3%.

We consider an absolute difference in NIRS values between the two groups of 6% to be clinically relevant. This is in agreement with the power calculations provided by Picton et al5 for a study comparing the effect of anaesthetic techniques in patients undergoing shoulder surgery in the beach chair position. Here a difference of NIRS values between the two groups of 4-5% was regarded as a clinically relevant difference.

Based on a minimum clinical difference of 6%, a standard deviation of 7.3%, a power of 90% and a two sided alpha value of 0.05 we would need a sample size of 30 patients. Accounting for protocol violations and a study drop out rate of 25%, we would need 20 in each group using a 1:1 ratio.

Our power calculation was completed by Christin Coomarasamay, Biostatistician with the Counties Manukau Health Research Office.

* Procedure – please see Appendix 1.
* Randomisation – a series of opaque envelopes containing treatment group assignations will be prepared by a nurse not otherwise affiliated with the study. These envelopes will be sequentially labelled with the patient study numbers (01-40).
* Recruitment process. Theatre lists will be screened in advance of the surgical date, and patients who meet eligibility criteria will be contacted by phone by one of the investigators, or one of the departmental research nurses. The study will be outlined and patients will be asked if they wish to consider participating. Those who are interested in participating will be emailed a copy of the Patient Information Sheet (Appendix 2). An investigator will subsequently contact them to answer any questions and confirm whether the patient wishes to participate.
* Visit schedule. All data will be collected during the intraoperative period. There will be no additional visits or extensions, no additional surveys or questionnaires and no additional investigations. There will be no extension to any element of the perioperative journey (eg time in PACU).
* Follow-up assessments. There will be no follow up assessments.
* Variables being collected
	+ Preoperatively….
		- Demographic (age, gender, ethnicity)
		- Planned surgical procedure
		- Physical status (height, weight, comorbidities, American Society of Anesthesiologists physical status score)
		- Blood pressure on admission
	+ Intraoperatively…
		- Baseline and intraoperative cerebral oximetry values
		- Intraoperative controlled variables (angle of ‘beach chair’ operating table, end tidal sevoflurane, end tidal O2)
		- Physiological variables (heart rate, blood pressure, end tidal CO2).
		- Intraoperative medication administered.
* Analysis plan

Patient data will be stored in a password protected Microsoft Excel spreadsheet on a secure research server within the Department of Anaesthesia and Pain Medicine at Counties Manukau Health. The statistical analysis will be completed on an intention to treat basis with those completing the process blinded to group allocations. To avoid the assumption of normality of data, non-parametric statistical tests will be used to compare the two groups. Continuous variables will be compared using the Mann-Whitney U test and discrete or binomial variables compared with the Fisher Exact or the Chi Square test with or without the Yates correction as appropriate. A two-tailed p-value of less than 0.05 will define statistical significance. The statistical analysis will be completed with SPSS Version 27.0 (IBM, New York, United States) by a researcher who is versed in the analysis of trial information in Anaesthesia and Perioperative Medicine. The analysis will be completed using blinded data whereby the researcher is unaware of the group allocation meaning bias is not introduced to the analysis.

Baseline demographic data will be collected including age, sex, comorbidities, baseline drug consumption (e.g., antihypertensives etc), indication for surgery, surgical procedure

performed, duration of surgery, drugs and doses used for anaesthesia induction and maintenance and the conduct and performance of the regional anaesthetic block procedure. This will help derive a baseline dataset to ensure the randomisation procedure has produced two groups with comparable demographics.

For the primary outcome (cerebral oximetry values for both the right and left hemisphere and the mean value) will be treated as both time dependent and time independent variables. For the time dependent analysis, the area under the curve (AUC) for cerebral oximetry versus time between anaesthesia induction and surgical wound closure and application of dressings with the patient still in the beach chair position will be calculated for both the right and left hemisphere recordings and mean value defined as [right hemisphere + left hemisphere]/ 2. This value will be divided by the duration of the operation (in seconds) to produce a value for AUC/t. For the time independent analysis, the average cerebral oximetry recording over a thirty second window at the time of anaesthesia induction and at the time of surgical wound closure with the patient still in the beach chair position will be subtracted from one another to define the difference in cerebral saturations between the two times. For both analyses, the Mann Whitney U test will be used to detect a difference between the two groups.

Should enough information be available, the data from both the spontaneously breathing and intermittent positive pressure ventilation groups will be pooled to conduct a multivariate analysis of factors predictive of changes in the mean cerebral oximetry values over time (AUC/t). Patient and anaesthetic specific factors will be entered to this model to determine the predictors of changes in cerebral oximetry over time

***E) Ethics and safety***

* **Participant safety**

Regardless of treatment arm, all patients will receive anaesthetic care which is entirely consistent with safe, contemporary practice.

* **Informed consent**;

Refer Appendix 2 (Patient Information Sheet and Consent Form)

* **Confidentiality**;

Refer Appendix 3 (Data Management Plan)

* **Safety monitoring**

Major adverse events will be reported to the CMH Research Office. All adverse events will be reported to the CMH Department of Anaesthesia Quality Assurance Committee.

* **Relevant consultation**

Refer Appendix 4 (Letter of Recommendation – Taia te Hauora)

* **Data Storage / Data Protection / Data Privacy**:
* Refer Appendix 3 (Data Management Plan)

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|  | **By checking the boxes below I confirm that I Agree:** |
|  | [x]  | I have read “Health Research and Privacy: Guidance notes for health researchers and ethics committees”\*  |
|  | [x]  | For all non-CM Health members of the research team who will have access to the research data: Signed confidentiality agreement(s) *(downloaded from the Research Office Registry Templates page under “Additional Resources”)* have been uploaded with the research application on the online Research Registry. |
|  | [x]  | I will only transfer Health Information\*\* by email to those within the regional secure network (any Middlemore, Waitemata or ADHB email) who are members of the research team.  |
|  | [x]  | I will encrypt or password-protect any data storage devices (e.g. USB flash drives) used to store health information.  |
|  | [x]  | I will password-protect any files containing Health Information.  |
|  | [x]  | I will keep any hardcopy Health Information that relates to identifiable individuals for 10 years and then destroy it in a secure bin.  |
|  | \* http://www.hrc.govt.nz/sites/default/files/Research%20involving%20personal%20health%20information.pdf\*\*Note: anonymised information which cannot be linked to identifiable individuals is not regarded as Health Information by the Health Information Privacy Code (1994). |

***F) Project Management***

Participating site(s)

 Manukau Surgery Centre, Manukau, Auckland.

MercyAscot Hospital, Greenlane, Auckland.

Investigators (and responsibilities of each)

 Andrew Cameron Anaesthetist (lead investigator)

Adam Durrant Orthopaedic Surgeon (recruitment)

Nicholas Lightfoot Anaesthetist (statistical analysis)

David Choi Anaesthetist (data handling, publication)

Jennifer Stephens Anaesthesia Fellow (data handling, publication).

Data ownership;

Data remains the property/responsibility of Counties Manukau Health, the investigators and the individual participants (for their own data). There are no external sponsors.

Risk management of project.

The risks have been assessed and, wherever possible, minimised as part of the HDEC application process. A process for adverse event monitoring is in place. Participants will be eligible to apply for ACC support if affected by and adverse event.

***G) Timetable***

The overall aim to have the study completed by mid 2022.

Jan - May 2021 Ethics and funding applications

Jun - Jul 2021 Site approval, ‘trial run’ patients

Aug 2021 - Mar 2022 Recruitment

Apr – May 2022 Data analysis

Jun - Jul 2022 Write-up and publication.

***F) Resources***

The cerebral oximetry probes cost $280 per person (two probes). We budget an equipment cost of $11200. All investigator time will be donated. There are no other costs associated with the trial.

***G) Research Output***

The outcome of the study will be presented at conferences (provisionally the European Society of Regional Anaesthesia Congress in September 2022) in addition to Orthopaedic Surgical Conferences. The study will be submitted to medical journals for publication. The study will be presented at the Counties Manukau Research Week.

1. Moerman AT, De Hert SG, Jacobs TF, De Wilde LF, Wouters PF. Cerebral oxygen desaturation during beach chair position. Eur J Anaesthesiol 2012; 29: 82-7. [↑](#endnote-ref-1)
2. Salazar D, Sears BW, Andre J, Tonino B, Marra G. Cerebral desaturation during shoulder arthroscopy: a prospective observational study. Clin Orth Relat Res 2013; 471: 4027-34. [↑](#endnote-ref-2)
3. Salazar D, Hazel A, Tauchen AJ, Sears BW, Marra G. Neurocognitive deficits and cerebral desaturation during shoulder arthroscopy with patient in beach-chair position: a review of the current literature. Am J Orthop 2016; 45: E63-8. [↑](#endnote-ref-3)
4. Orebaugh S, Palermi S, Lin C, YaDeau J. Daring discourse: is nerve block with sedation the safest anesthetic for beach chair position? Reg Anesth Pain Med 2019; 44: 707-12. [↑](#endnote-ref-4)
5. Picton P, Dering A, Alexander A, Neff M, Miller BS, Shanks A, Housey M, Mashour GA. Influence of ventilation strategies and anesthetic techniques on regional cerebral oximetry in the beach chair position: a prospective interventional study with a randomized comparison of two anesthetics. Anesthesiology 2015; 123: 765-74. [↑](#endnote-ref-5)
6. Murphy GS, Szokol JW, Avram MJ et al. Effect of ventilation on cerebral oxygenation in patients undergoing surgery in the beach chair position: a randomized controlled trial. Br J Anaesth 2014; 113: 618-27. [↑](#endnote-ref-6)
7. Ya Deau JT, Kahn RL, Lin Y, Goytizolo EA et al. Cerebral oxygenation in the sitting position is not compromised during spontaneous or positive pressure ventilation. HSSJ 2019; 15: 167-75. [↑](#endnote-ref-7)
8. Cox RM, Jamgochain GC, Nicholson K, Wong JC, Namdari S, Abboud JA. The effectiveness of cerebral oxygenation monitoring during arthroscopic shoulder surgery in the beach chair position: a randomized blinded study. J Shoulder Elbow Surg 2018; 27: 692-700. [↑](#endnote-ref-8)