International Journal of Clinical Trials
Wood MD et al. Int J Clin Trials. 2016 Aug;3(3):98-105
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: http://dx.doi.org/10.18203/2349-3259.ijct20162792

Research Article

Assessing the relationship between brain tissue oxygenation and neurological dysfunction in critically ill patients: study protocol

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Received: 10 May 2016
Revised: 08 June 2016
Accepted: 20 June 2016

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ABSTRACT

Background: Acute and chronic neurological complications amongst survivors of critical illness is common, however, the underlying etiology of this neurological dysfunction is unknown. This is the first study to use near-infrared spectroscopy to non-invasively measure brain tissue oxygenation, as a surrogate marker of cerebral perfusion, and correlate these values with subsequent neurological dysfunction. We will test the hypothesis that poor cerebral oxygenation during the first 24 hours of critical illness is correlated with acute and chronic neurological complications.
Methods: This single-centre prospective observational study will be performed in a 33-bed medical/surgical intensive care unit (ICU). Adult patients are eligible for enrolment if they are admitted to the ICU within 24 hours, require mechanical ventilation, and/or vasopressor support. For 24 hours, cerebral oxygenation levels will be measured with the FORESIGHT oximeter; vital signs and tissue oxygenation will be captured with data monitoring software. Participants will be screened daily for delirium with the confusion assessment method-ICU. Long-term neurological function will be assessed with the Repeatable Battery for the Assessment of Neuropsychological Status and the kinesiological instrument for normal and altered reaching movements (KINARM) robot.
Conclusions: This study will provide novel information regarding the determinants of cerebral oxygenation during the acute phase (i.e. 24 hours) of critical illness, and its potential relationship with subsequent neurological complications. Should a relationship exist between cerebral oxygenation and neurological complications, future studies will be aimed at using brain tissue oxygenation as a therapeutic target to prevent acute and chronic neurological dysfunction.

Clinical Trial Registration: This trial is registered on clinicaltrials.gov (Identifier: NCT02344043), retrospectively registered January 8, 2015.

Keywords: Near-infrared spectroscopy, KINARM, Delirium, CAM-ICU, Cognitive impairment, Post-intensive care syndrome

INTRODUCTION

Survivors of critical illness often have newly acquired cognitive impairments for which the underlying cause is poorly understood. The first sign of neurological dysfunction during critical illness may be the onset of delirium, which is defined as an "acute, fluctuating change in mental status, with inattention and altered levels of consciousness or disorganized thinking".[1] The prevalence of delirium can be as high as 80% in critically ill patients.[2] The presence of delirium has been associated with increased mortality, increased intensive care unit

(ICU) length of stay, increased duration of mechanical ventilation and cognitive impairments amongst survivors.[2-4] The duration of delirium has been identified as an independent predictor of long-term cognitive impairment in survivors of critical illness, with increased duration of delirium leading to more severe impairments.[4] Specific cognitive domains particularly affected include memory, executive function, attention, and language.[5,6] Some form of cognitive impairment has been observed in roughly half of survivors.[5] These impairments are persistent, being observed for at least a decade after hospital discharge.[7,8] These deficits have been compared to moderate traumatic brain injury or patients suffering from mild Alzheimer's disease4. These acquired impairments are associated with impaired quality of life8, and negatively impact independent living.[7]

To identify and characterize cognitive dysfunction among survivors of critical illness, both screening tests and higher-level neuropsychological tests have been used. The incidence of cognitive dysfunction is higher in cohorts who have undergone formal neuropsychiatric testing, compared to screening tests alone.[9,10] This suggests that screening tests alone are insufficient to completely document the degree of cognitive dysfunction following critical illness. Therefore, we are proposing the quantification of neurological dysfunction in survivors of critical illness using a neuropsychological battery and the kinesiological instrument for normal and altered reaching movements (KINARM).

The KINARM is a robotic device that provides an objective and quantitative method for assessing sensory, motor, and cognitive function, using only the patient's upper limbs. The KINARM has been used in stroke survivors to identify subtle neurocognitive deficits not apparent on routine clinical testing11, and has been used to describe sensory motor deficits in patients with stroke patients with traumatic brain injury, and children with fetal alcohol syndrome.[12-15] This research program will test the hypothesis that poor cerebral perfusion during the resuscitative phase (first 24 hours) of critical illness contributes to the development of delirium and subsequent long-term cognitive dysfunction among ICU survivors. We will use near-infrared spectroscopy (NIRS) to monitor brain tissue oxygenation (BtO_2) as a surrogate marker for cerebral perfusion. This technique was chosen since it is simple, non-invasive, and previous evidence suggests that poor BtO_2 during cardiac surgery correlates well with poor post-operative cognitive function.[16] We have recently published the feasibility of long-term recordings of BtO_2 in critically ill patients.[17]

METHODS

Study location and participants

This prospective observational study, cerebral oxygenation and neurological outcomes following critical illness (CONFOCAL) study, is registered on clinicaltrials.gov (Identifier: NCT02344043). The study flow is depicted in Figure 1.

A completed "standard protocol items: recommendations for interventional trials (SPIRIT)" checklist is available as supplemental material. Participants will be recruited from an academic 33-bed general medical/surgical ICU. The local health sciences research ethics board has approved the study protocol, which includes deferred consent for the first 24 hours of the patient's stay. Patients are considered eligible if they are over the age of 17, and admitted to the ICU within 24 hours of having respiratory failure requiring invasive mechanical ventilation with an expected duration >24 hours, and/or having shock of any etiology. Shock is defined by the need for one of the following vasopressors: dopamine ≥7.5 mcg/kg/min, dobutamine ≥5 mcg/kg/min, nor-epinephrine ≥5 mcg/min, phenylephrine ≥75 mcg/min, epinephrine at any dose, milrinone at any dose (if used in conjunction with another agent), vasopressin ≥0.03 u/min if used in conjunction with another agent. This inclusion criterion was adapted from the BRAIN-ICU study, which is currently one of the largest studies conducted to analyze cognitive impairments amongst critical illness survivors.[4] The exclusion criteria are a life expectancy <24 hours, an underlying diagnosis of cognitive dysfunction, primary neurological/neurosurgical admitting diagnoses, or any reason that the subject may not be able to participate in the follow up assessments (i.e. limb amputation, paresis). Participant recruitment began in March 2014. At that time, inclusion criteria required that patients meet the society of critical care medicine (SCCM) definition of severe sepsis/septic shock.[18] However, due to the low recruitment rates (1.4 patients/month), the inclusion criteria were broadened to those described above in December 2014.[17]

Data capture-BtO_2

Immediately following enrolment, patients will undergo BtO_2 monitoring with the FORESIGHT monitor (CASMED, Caster Medical, Canada). This device was chosen since the 5 cm sensor allows for the greatest tissue penetration of all commercially available sensors. Treating clinicians will not have access to the BtO_2 data. The FORESIGHT monitor captures BtO_2 data every two seconds, and patients will have their data recorded for the first 24 hours of their ICU stay. We will use this granular, high fidelity data, as extrapolating a single hourly value of BtO_2 does not always accurately reflect what was occurring during the 1-hour epoch (Figure 2). Sensors will be placed both on centre and side of the forehead.

Our pilot project used the centre position to demonstrate decreased oxygenation in delirious patients.[17] This may include an oxygenation signal from the superior saggital sinus (Figure 3). We will use an additional sensor in the parasaggital position, a more traditional sensor position used for patients undergoing cardiac surgery.[16]

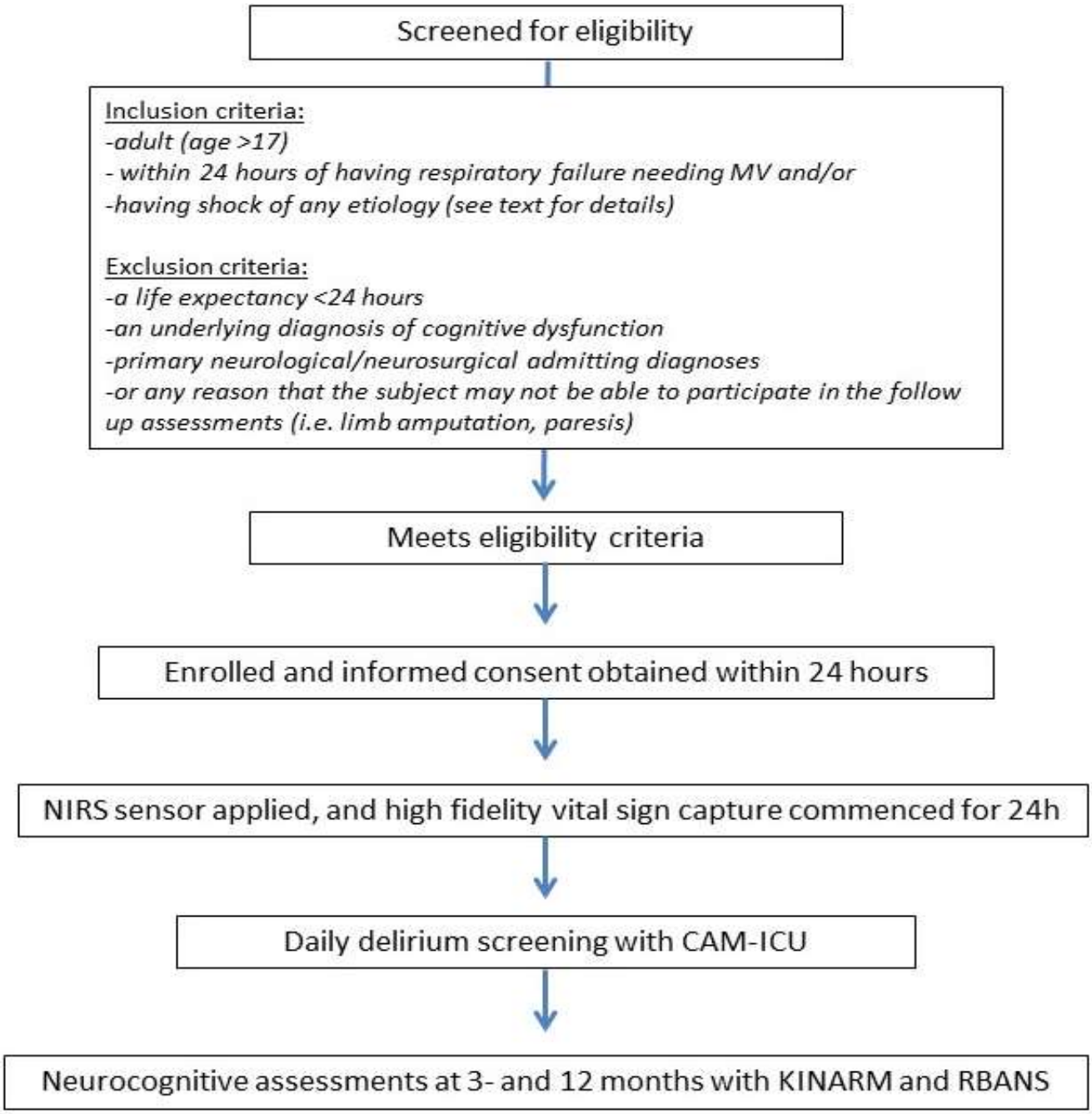

Figure 1: Cerebral oxygenation and neurological outcomes following critical illness (CONFOCAL) study flow diagram.

CAM-ICU; Confusion assessment method-intensive care unit, KINARM; Kinesiological instrument for normal and altered reaching movements, RBANS; repeatable battery for the assessment of neuropsychological status.

Data capture: patient hemodynamics and medications

To correlate patient hemodynamics with the high-fidelity BtO2 recordings, we will use a commercially available system to capture high fidelity vital signs (including heart To correlate patient hemodynamics with the high-fidelity BtO2 recordings, we will use a commercially available system to capture high fidelity vital signs (including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, peripheral oxygen saturation) from enrolled patients (Bedmaster, Excel Medical Electronics, FL, USA).

These data are captured locally, and stored on dedicated servers at the Queen's University Centre for Advanced Computing (www.hpcvl.org). We will also record the vasoactive and sedative/analgesic medications administered to participants, which will be converted to either "fentanyl equivalents" for narcotics, or "midazolam equivalents" for benzodiazepine medications. The

conversion formulas have been previously described.[4] Both continuous infusion doses and intermittent doses of medications will be recorded.

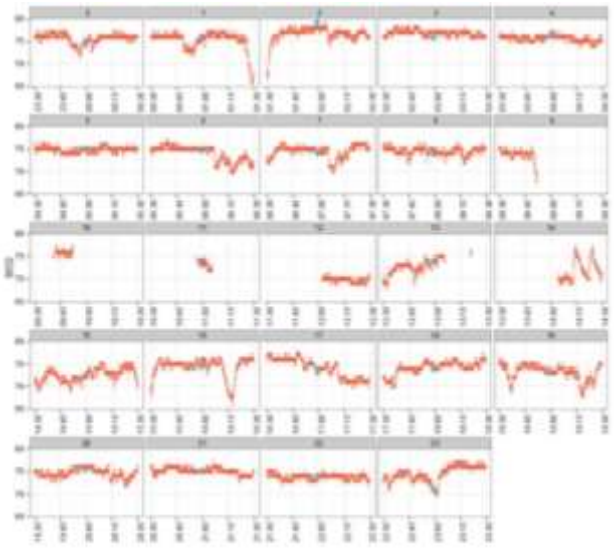

Figure 2: BtO_2 levels.

Hourly data entry of BtO_2 levels may not always accurately reflect dynamic changes. The BtO_2 levels are captured every 2 seconds with the NIRS monitor (small red dots) over the 24 hour period. We record the hourly data (large green dots) in our electronic case response form. In areas where there are no red dots, the NIRS signal had degraded and the monitor stopped recording data. For most hours, the "on hour" BtO_2 was reflective of the hourly epoch, but for others (e.g. hour 23), the "on hour" BtO_2 clearly does not reflect the hourly epoch. Additionally, there are many peaks and valleys that occur with BtO_2, which has provided the rationale for high frequency vital sign recording to identify the underlying determinants of these high frequency changes.

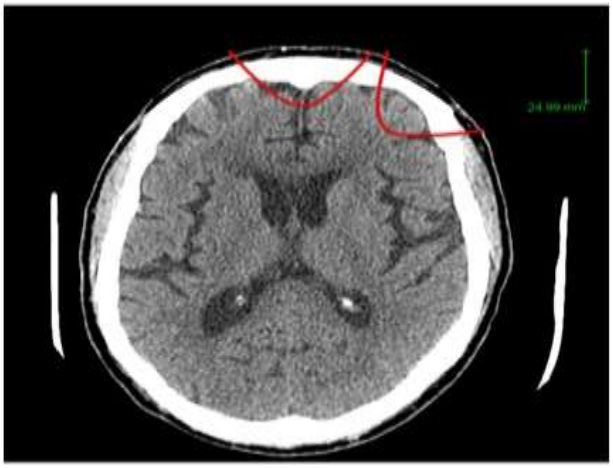

Figure 3: Sensor records both on centre and side of the forehead.

Two sensor placement on a patient's forehead demonstrates that the center sensor may derive its signal from brain tissue and the superior sagittal sinus, whereas the frontotemporal sensor derives its signal from brain tissue and avoids the sinus. The red lines represent the approximate depth (2.5 cm) and region that the cerebral oximeter sensor records.

Delirium screening and adjudication of primary endpoint

Patients will be assessed daily for delirium throughout their entire ICU stay, using a validated screening tool, the confusion assessment method (CAM)-ICU.[19–21] Trained researchers will administer the CAM-ICU once daily, at a time that is convenient for the patient, their family, and the medical team directing their care. On the basis of this screening, patients will be assigned to one of 3 groups: 1) comatose and not assessable for the duration of the ICU stay, 2) delirious for the majority of the ICU stay, or 3) neurologically intact for the majority of the ICU stay. As comatose (Richmond Agitation Sedation Scale; (RASS) -4 or -5) patients cannot be screened for delirium (by definition), we will use the number of non-comatose days as the denominator in calculating the relative proportion of ICU stay spent either delirious or intact. The ICU discharge day is considered to be the day that the attending physician considers the patient to be ready for discharge to avoid the influence of delayed ICU discharge because of lack of ward beds.

Neuropsychological assessment: repeatable battery for the assessment of neuropsychological status (RBANS)

Survivors will complete a 3 and 12-month follow up assessment in which the RBANS will be administered by a trained researcher. The RBANS assesses cognition across several domains, including: immediate memory, visuospatial/constructional, language, attention, and delayed memory. These five indices have been described previously.[22] Survivors will be compared to age, education, and gender matched controls.

Robotic set-up and assessment at follow up

The bimanual KINARM end-Point robot (BKIN technologies Ltd, Kingston, ON, Canada) (see Figure 4 A) has a comprehensive battery of behavioral tasks that quantify sensory processing of the limb, basic motor skills, and various cognitive processes (e.g. executive function and attention). The subject is seated at the device (see Figure 4 B) and grasps onto handles attached to the End-Point robot (see Figure 4 C) that permits movement of the hand in the horizontal plane with an augmented/virtual reality system that projects objects (i.e. visual targets) onto this plane (see Figure 4 D). The subjects' vision of both their hands and arms are occluded (see Figure 4 E), and visual feedback of their hands is represented by a white circle (0.4 cm radius) in the middle of their grasp. A trained operator selects a task from the software (Dexterit-E) menu, instructs the subject on how to perform the task (see Figure 4 F), and visually monitors performance as the Dexterit-E software

completes data acquisition of the subject's performance in real time. The KINARM assessment takes approximately 1 hour to complete and subject performance is quantified using 6 to 12 metrics for each task. This technology also has a representative data set of healthy control subjects, with which survivors of critical illness can be matched on age, gender, and education.

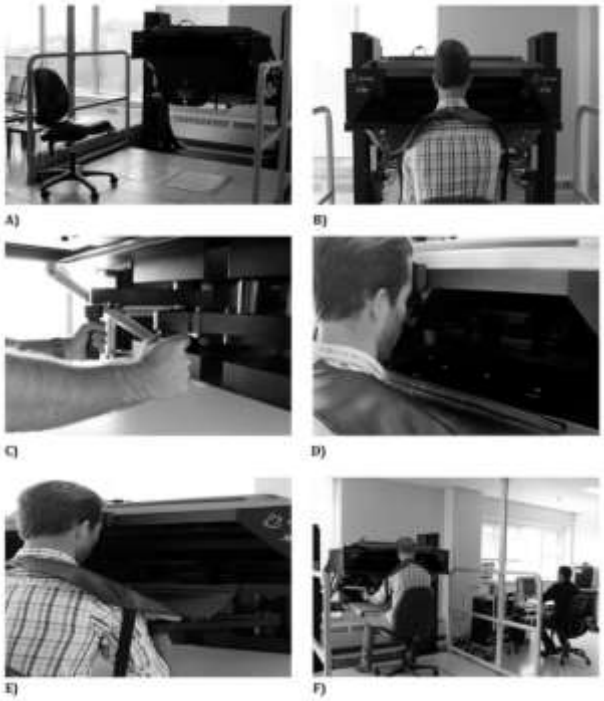

Figure 4 (A-F): Robotic set-up for neurocognitive assessment.

A) Front view of the KINARM end-point robot. B) The participant is seated during the assessment. C) The participant grasps onto the robotic handles, which permits movement in the horizontal plane on the virtual reality display. D) A 2 dimensional virtual reality workstation displays the current task (E.g. Object Hit) to the participant. E) A vision blocker occludes the subjects' hands and arms during each task. F) An operator selects each task from the Dexterit-E menu, instructs the participant on how to complete each task, and observes performance in real time.

KINARM task descriptions

Visual-guided reaching: Participants are asked to grasp and move the arm of the End-Point robot (represented visually by a white circle) to one of four target locations (represented by red circles, 1.0 cm radius), and back to the start position (Figure 5 A). This task assesses visuomotor control of the upper limbs.[11]

Reverse visually guided reaching (inverted): This task is similar to Visual-Guided Reaching, except the visual feedback on screen is inverted to the actual hand position (Figure 5 B). This task requires subjects to inhibit their automatic movement response, via intact executive function, and initiate a movement in the opposite direction towards a target.

Arm position matching: During this task, the participant's right/left arm is moved via the KINARM robot to a set of preprogrammed coordinates, and the subject is instructed to move their contralateral limb to the mirror-image position (Figure 5 C). This task assesses limb proprioception.[12]

Object hit: Participant's use 5 cm paddles to hit targets (red circles, 2 cm diameter) that fall from the top of the screen (Figure 5 D). This task progressively increases in difficulty; objects begin to fall more frequently and with increasing velocity. This task assesses spatial attention, sensorimotor control and planning of the upper limbs.[23]

Object hit and avoid: This task is similar to the Object Hit task, however at the beginning of the task the participant observes two shapes (e.g. triangle and horizontal rectangle). The subject is then asked to remember these two shapes, their orientation, and is instructed to hit only those two shapes and avoid all the other objects (e.g. circles, vertical rectangle) (Figure 5 E). In contrast to the Object Hit task, this task involves the use of executive function (e.g. attention, rapid sensorimotor control, and inhibition).

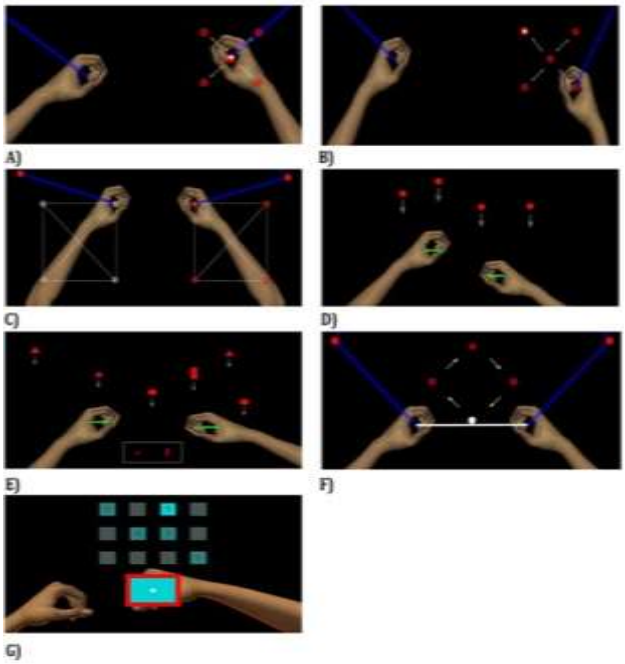

Figure 5 (A-G): Visual representation of the comprehensive KINARM behavioral battery.

A) Visually guided reaching. B) Reverse visually guided reaching. C) Arm position matching (4 Target). D) Object hit. E) Object hit and avoid. F) Ball on bar. G) Spatial span.
Note. The grey targets represent coordinates in which the End-Point robot actively guides a participants' hand, whereas the red targets represent destinations in which the participant must actively move to. Blue bars visually represent the position of the

End-Point robot during a task, with the white dotted lines and arrows representing the path in which the robot or participant will move their left or right hand.

Ball on bar task: The participant sees a white bar (30 cm in length) connecting both their hands, with a white ball (1 cm radius) resting on top. 4 targets are presented one at a time, and the participant has to move to one of the 4 target circles (1 cm radius; Figure 5 F). This task assesses bimanual motor control.[24]

Spatial span: The participant is presented with a 3×4 square grid, the squares briefly light up in a random sequence that the subject must retain, and replicate once the sequence is complete (Figure 5 G). The first trial begins with a 3 square sequence, and with each successive correct answer the next trial increases in length up to a maximum of.[12] If the trial is unsuccessful, the next sequence will become shorter. This task protocol is similar to the Corsi block tapping test and is an assessment of visuospatial working memory.[25]

Statistical plan

Assessment of primary outcome and sample size calculation: The primary hypothesis of this study is the correlation between BtO_2 and proportion of ICU time spent delirious. In order to detect a moderate (r=0.3) correlation between average BtO_2 and proportion of delirium days experienced, 89 evaluable patients would be required to achieve 80% power at a 2-sided alpha = 0.05. In our pilot study, 30% of patients were comatose (RASS -4 or -5) for their entire ICU stay and could not be screened for delirium. Therefore, this study investigating the relationship between BtO_2 and delirium anticipated recruitment of 130 patients (100/0.7 = 127; rounded up to 130). However, since we broadened the inclusion criteria in December 2014 (see above), the number of unevaluable patients (e.g. RASS -4 or -5 for the entire ICU stay) accounted for only 14 of the first 80. Therefore, we will continue enrollment until we have 89 evaluable patients. Initial scatterplots of the primary outcome did not show a normal distribution, so non-parametric testing (i.e. Spearman's rank correlation coefficient) will be used for the primary outcome. A correlation will be considered statistically significant if $p<0.05$.

Assessment of secondary outcomes-physiological variables and medications

Correlation analysis between non-invasive measurements of BtO_2 with hemodynamic and physiological parameters (E.g. MAP, HR, SaO_2, and pCO_2) will be performed by calculating Spearman's rank correlation coefficients. The Wilcoxon rank-sum test will be used to determine if there are significant differences in physiological variables, sedative medications, and narcotics, between delirious and neurologically intact patients.

Assessment of secondary outcomes-KINARM and RBANS

The KINARM provides 6-12 metrics for each task completed by the participants. For each of the 9 tasks described above, a z-score is calculated. Performance will be considered abnormal if the z-score is outside a z-score of +/- 1.65 which represents the 5-95% confidence interval that the performance is within the normal range. The number of metrics outside the normal range will therefore be analyzed as a continuous variable, with higher numbers outside the normal range reflecting worse neurological performance. We will calculate the Spearman's rank correlation coefficient for the median BtO2 and the number of performance metrics outside of the normal range. Similarly, the RBANS has 5 subscores reflecting the various neurocognitive domains (immediate memory, delayed memory, visuospatial, language, and executive functioning) and a total score. All are normalized to age-matched controls. We will correlate the median BtO2 with participant performance on the total RBANS score, as well as for each cognitive domain.

Logistic regression

To determine if BtO_2 is an independent predictor of acute- and long-term dysfunction, we will use logistic regression. On the basis of our pilot data, about a third of enrolled patients will spend the entire ICU stay comatose, with the remaining two thirds evenly divided between patients who spend the majority of their ICU stay either delirious or neurologically intact. Based on our planned enrollment of 150 patients, this means approximately 50 patients will be in each group, which will allow us to control for 4 covariates and our 1 predictor variable (mean BtO_2). We have selected the following covariates, as they are most likely to be associated with acute neurological dysfunction history of hypertension, history of alcohol abuse, total sedative dose (in midazolam equivalents), and total narcotic dose (in fentanyl equivalents).[26]

Bayesian modeling

We have chosen the above statistical plan because correlation coefficients are well-known and robust strategies to assess the relationship between variables. However, we will also explore machine learning strategies to analyze our data, such as naïve Bayes classification. The principle of Bayesian statistics is that the likelihood of an outcome is based on known prior probabilities. For example, our early work with a native Bayes classifier has demonstrated that an algorithm based on BtO_2 variables alone (mean, median, minimum), successfully classified the neurological status of our patients (comatose, delirious, or intact) 82% of the time (17 of 22). We plan to further refine this approach (including adding additional data to improve accuracy), as well as comparing to other physiological measurements (MAP, HR, SaO_2).

Identifying physiological factors that contribute to BtO_2 will be an important component of developing strategies to optimize BtO_2 in critically ill patients. We will also apply Bayesian statistics to BtO_2 data to assess the likelihood of neurological dysfunction, as measured with the KINARM.

Progress to date

Recruitment started in March 2014. As of April 1, 2016, we have recruited 80 participants, with an average recruitment rate of 4 participants/month. At this current recruitment rate, we anticipate the completion of enrollment in September 2016.

DISCUSSION

This study protocol will examine the relationship between non-invasive measurements of BtO_2 and acute- and long-term neurological dysfunction. The results from this single-centre prospective observational study will be used to inform the design of a prospective multi-centered observational study. Should a relationship exist between BtO_2 and neurological functioning, future studies will be aimed at testing clinical practice algorithms that improve BtO_2 with the objective of mitigating acute- and chronic neurological dysfunction.

ACKNOWLEDGMENTS

The authors would like to thank the study coordinators, Ms. Miranda Hunt, Ms. Nicole O'Callaghan, Ms. Ilinca Georgescu, Ms. Suzy Fleury, and Ms. Jenna Polichuck. We would also like to thank the KINARM technologists, Ms. Simone Appaqaq, Ms. Kim Moore, and Ms. Sarah Gregor.

Funding: Physician Services Incorporated and the Southeastern Ontario New Clinician Scientist Program funded this work.
Conflict of interest: None declared
Ethical approval: The study was approved by the Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board, which includes deferred consent for 24 hours.

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Cite this article as: Wood MD, Maslove D, Muscedere J, Scott SH, Day A, Boyd JG. Assessing the relationship between brain tissue oxygenation and neurological dysfunction in critically ill patients: study protocol. Int J Clin Trials 2016;3(3):98-105.