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Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: A prospective observational study

The Cerebral Oxygenation and Neurological Outcomes Following Critical Illness (CONFOCAL) Research Group, on behalf of the Canadian Critical Care Trials Group.
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ABSTRACT

Purpose: To test the hypothesis that poor brain tissue oxygenation (BtO_2) during the first 24 h of critical illness correlates with the proportion of time spent delirious. We also sought to define the physiological determinants of BtO_2.

Materials and methods: Adult patients admitted to the ICU within the previous 24 h were considered eligible for enrollment if they required mechanical ventilation, and/or vasopressor support. BtO_2 was measured using near-infrared spectroscopy, for 24 h after enrollment. Hourly vital signs and clinically ordered arterial and central venous blood gases were collected throughout BtO_2 monitoring. Patients were screened daily for delirium with the confusion assessment method for the intensive care unit (CAM-ICU).

Results: BtO_2 and the proportion of time spent delirious did not result in a significant correlation ($p = 0.168$). However, critically ill patients who spent the majority of their ICU stay delirious had significantly lower mean BtO_2 compared to non-delirious patients, ($p = 0.017$). BtO_2 correlated positively with central venous pO_2 ($p = 0.00003$) and hemoglobin concentration ($p = 0.001$). Logistic regression indicated that lower BtO_2, higher narcotic doses and a history of alcohol abuse were independent risk factors for delirium.

Conclusions: Poor cerebral oxygenation during the first 24 hours of critical illness contributes to the development of delirium.

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

1. Introduction

Delirium is common during critical illness and manifests as an acute fluctuating change in mental status characterized by an altered level of consciousness or disorganized thinking [1]. Delirium has been associated with increased mortality, longer intensive care unit (ICU) length of stay and mechanical ventilation duration [2,3] and long-term cognitive impairment [4]. Although the underlying etiology of delirium is unknown, neuropathological studies suggest that diffuse neuronal ischemia is common in critically ill patients, primarily affecting brain areas susceptible to hypoxic-ischemic injury such as watershed areas in the frontal cortex [5]. Therefore, poor cerebral perfusion may contribute to delirium. Reliable cerebral perfusion measurements during critical illness have only recently become available.

Near infrared spectroscopy (NIRS) is a non-invasive strategy to measure regional brain tissue oxygenation (BtO_2) [6], and has been used as

Abbreviations: 95% CI, 95% confidence interval; BtO_2, brain tissue oxygenation; CAM-ICU, confusion assessment method-intensive care unit; DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; M, mean; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; RASS, Richmond Agitation Sedation Scale; ROC, receiver operating characteristic; SD, standard deviation; SpO_2, peripheral oxygen saturation; SBP, systolic blood pressure.

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a surrogate marker for cerebral perfusion during cardiac surgery. In this clinical setting, low BtO_2 levels are associated with worse post-operative cognitive outcomes [7]. Low BtO_2 has also been associated with poor neurological outcomes in cardiac arrest survivors [8]. NIRS derived BtO_2 may serve as a marker and predictor of delirium. For example, in a small cohort of septic shock patients, lower BtO_2 was observed in delirious patients compared to non-delirious patients [9]. In another small sample of patients with septic shock, BtO_2 recordings over 72 h were lower in patients who spent the majority of their ICU stay delirious, relative to non-delirious patients [10]. Although poor perfusion may contribute to delirium, the association between BtO_2 and delirium requires further study.

Our study tested the hypothesis that poor cerebral oxygenation during the resuscitative phase (i.e. first 24–48 h) of critical illness is associated with the subsequent development of delirium throughout a patient's ICU stay. Additionally, we aimed to identify the physiological determinants related to BtO_2, such as hemodynamics and clinical measures of tissue oxygenation.

2. Materials and methods

2.1. Study design and participant recruitment

The Cerebral Oxygenation and Neurological outcomes FOllowing CriticAL illness (CONFOCAL) study (NCT02344043 clinicaltrials.gov) is a single-centre prospective observational study. The full protocol has been previously published [11]; the acute neurological findings in this cohort are described herein. Adult patients (≥18 years) admitted to a 33-bed general medical/surgical and trauma ICU were eligible if they required mechanical ventilation with an expected duration > 24 h, and/or having shock of any etiology and were admitted to the ICU within the previous 24 h. Shock was defined by vasopressor requirement with infusions of: dopamine ≥ 7.5 mcg/kg/min, dobutamine ≥ 5 mcg/kg/min, norepinephrine ≥ 5 mcg/min, phenylephrine ≥ 75 mcg/min, epinephrine at any dose, milrinone at any dose (only in conjunction with another agent), or vasopressin ≥ 0.03 u/min (in conjunction with another agent) [4]. Participants were excluded if they had a life expectancy < 24 h, a pre-ICU diagnosis of cognitive dysfunction as indicated by their medical records on admission, or a primary central nervous system diagnosis (e.g. neurosurgical admission).

2.2. Data capture: demographics, BtO_2, medications, and vital sign recording

At the time of enrollment, basic clinical and demographic information was collected. Thereafter, patients underwent BtO_2 monitoring with the FORESIGHT monitor (CASMED, Caster Medical, Canada). A single 5 cm sensor was placed in the centre of the patients' forehead and BtO_2 data was captured every 2 s for 24 h. The BtO_2 recordings were not revealed to the treating clinicians. Hourly physiological variables (e.g. blood pressure) were collected simultaneously. These BtO_2 and hourly physiological variables were then converted to mean values for statistical analysis. Sedative/analgesic medications administered during the first 24 h of critical illness either by continuous infusion or bolus doses were tallied and converted to "fentanyl equivalents" for narcotics, and "midazolam equivalents" for benzodiazepine medications [12].

2.3. Delirium screening

Patients were assessed once daily for delirium throughout their ICU stay or (up to 30 days), using the confusion assessment method (CAM)-ICU [13], which was administered by trained researchers. Patients were assigned to one of 3 pre-defined subgroups: 1) comatose (Richmond Agitation Sedation Scale; (RASS) −4 or −5) and not assessable for the ICU stay, 2) delirious for the majority (≥50%) of the ICU stay, or 3) non-delirious for the majority of the ICU stay. As comatose patients cannot be screened for delirium, we used the number of non-comatose days as the denominator in calculating the proportion of ICU stay spent either delirious or non-delirious. We have chosen to consider coma as a distinct entity, rather than an extreme of cognitive dysfunction. For example, a patient may be admitted with respiratory failure due to pneumonia and is mechanically ventilated with pharmacological paralysis/heavy sedation, but would otherwise be neurologically intact if not for the iatrogenic coma. This contrasts significantly with the patient who has profound shock and remains comatose for the first 24 h despite aggressive resuscitation and little or no sedation. We feel that including the number of days a patient spends in this highly heterogeneous state would dilute any putative relationship between BtO_2 and delirium. ICU discharge was documented as the day the discharge was ordered, as delayed discharges occur due to lack of ward beds.

2.4. Data analysis

2.4.1. Sample size calculation and assessment of primary outcome

Our primary hypothesis was that there is a negative association between BtO_2 recordings and the proportion of ICU time spent delirious (i.e. days CAM-ICU positive). Our primary analysis used Spearman's correlation coefficient to test the correlation between the average BtO_2 during the first 24 h in the ICU and the proportion of ICU days with delirium. We used Spearman's rank correlation coefficient rather than Pearson's correlation coefficient, because the scatterplot of BtO_2 versus proportion of ICU days with delirium clearly showed the data was not normally distributed.

We enrolled 89 patients (i.e. at least 1 day of CAM-ICU screening) so that we would achieve approximately 80% power to detect a moderate correlation ($\rho = 0.3$; [14]) using Spearman's rank correlation coefficient at a 2-sided alpha = 0.05. The actual power for a given correlation depends on the distribution of the two variables being correlated. For example, if the variables were distributed bivariate normally we would have about 78% power, while if the variables were distributed uniformly with BtO_2 ranging from 50 to 80 and proportion of delirium days ranging from 0 to 1, we would achieve 81% power (estimated using PASS software with 200,000 simulations [15]).

2.5. Secondary outcomes-physiological variables and medications

A one-way between subjects analysis of variance (ANOVA) determined if mean BtO_2 measurements differed significantly between the three neurological states described above. Post hoc comparisons were performed using Tukey's HSD test. Spearman's rank correlation coefficients were conducted between mean BtO_2 recordings with mean hemodynamic/physiological parameters, that were collected during the 24 h recording period, for all enrolled patients, as these parameters were not normally distributed. The Kruskal-Wallis rank sum test was used to determine if there were significant differences in physiological variables, sedative medications, and narcotics, among delirious, non-delirious, and comatose patients. Dunn's Multiple Comparisons Test was used, with Bonferroni adjustment, when the Kruskal-Wallis rank sum test was significant. Correlations and between group differences were considered significant if $p < 0.05$. When the Bonferroni correction was applied, the corrected p value is stated.

2.6. Logistic regression

To determine if BtO_2 is an independent predictor of delirium, logistic regression was used to estimate the unadjusted effect of each individual predictor on having a majority of ICU days delirious (after excluding comatose days). The models provide odds ratios of having a majority of ICU days delirious with 95% confidence intervals and corresponding p-values estimated by Wald's method. We fitted a multivariable model adjusting for the following covariates specified a priori [11], as they were likely to be associated with delirium [3]: a history of hypertension, a history of alcohol abuse, total sedative dose (in midazolam equivalents), and total narcotic dose (in fentanyl equivalents). Due to the