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Low hemoglobin levels are associated with lower cerebral saturations and poor outcome after cardiac arrest☆

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ABSTRACT

Purpose: Post-cardiac arrest (CA) patients have a large cerebral penumbra at risk for secondary ischemic damage in case of suboptimal brain oxygenation during ICU stay. The aims of this study were to investigate the association between hemoglobin, cerebral oxygenation ($SctO_2$) and outcome in post-CA patients.
Methods: Prospective observational study in 82 post-CA patients. Hemoglobin, a corresponding SctO2 measured by NIRS and SVO2 in patients with a pulmonary artery catheter ($n = 62$) were determined hourly during hypothermia in the first 24 h of ICU stay.
Results: We found a strong linear relationship between hemoglobin and mean $SctO_2$ (SctO2 = 0.70 × hemoglobin + 56 (R^2 0.84, $p = 10^{-6}$)). Hemoglobin levels below 10 g/dl generally resulted in lower brain oxygenation. There was a significant association between good neurological outcome (43/82 patients in CPC 1–2 at 180 days post-CA) and admission hemoglobin above 13 g/dl (OR 2.76, 95% CI 1.09:7.00, $p = 0.03$) or mean hemoglobin above 12.3 g/dl (OR 2.88, 95%CI 1.02:8.16, $p = 0.04$). This association was entirely driven by results obtained in patients with a mean SVO2 below 70% (OR 6.25, 95%CI 1.33:29.43, $p = 0.01$) and a mean SctO2 below 62.5% (OR 5.87, 95%CI 1.08:32.00, $p = 0.03$).
Conclusion: Hemoglobin levels below 10 g/dl generally resulted in lower cerebral oxygenation. Average hemoglobin levels below 12.3 g/dl were associated with worse outcome in patients with suboptimal SVO2 or SctO2. The safety of a universal restrictive transfusion threshold of 7 g/dl can be questioned in post-CA patients.

Introduction

Post-cardiac arrest (CA) patients have a large cerebral penumbra at risk for secondary ischemic damage in case of suboptimal brain oxygenation during ICU stay.[1] Additionally, many post-CA patients have a depressed left ventricular function and cannot increase cardiac output to ensure adequate cerebral oxygenation as a compensation for an anemic status.[1] Moreover, brain oxygenation depends even more on hemoglobin levels during therapeutic hypothermia due to a leftward shift of the hemoglobin dissociation curve.[2] Previous large randomized controlled trials in critically ill patients failed to show benefit of a liberal (hemoglobin 9 g/dl) compared with a restrictive transfusion strategy (hemoglobin 7 g/dl).[3–6] Based on these findings and a Cochrane meta-analysis,[7] many clinicians apply a uniform hemoglobin transfusion threshold of 7 g/dl among all critically patients.[8] It can be questioned whether the results of these trials can be extrapolated to post-cardiac arrest (CA) patients since patients with myocardial infarction or CA were excluded from these trials and are phenotypically clearly different from the trial patients. We hypothesize that cumulative exposure to anemia induced cerebral desaturation is associated with poor outcome in post-CA patients. The aims of this prospective observational study were to investigate the association between hemoglobin, cerebral oxygenation by near-infrared spectroscopy (SctO2) and outcome in post-CA patients during therapeutic hypothermia. We also aimed to investigate whether a

Abbreviations: ACS, acute coronary syndrome; CA, cardiac arrest; CPC, cerebral performance category; SctO2, cerebral saturation; SVO2, mixed venous oxygen saturation; TBI, traumatic brain injury.

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potential harmful effect of a lower hemoglobin would be more pronounced in patients with insufficient cardiac reserve to compensate for their anemic status (reflected by a mixed venous oxygen saturation (SVO2) below the recommended target of 70%) and in patients with low brain saturations (SctO2 below 62.5%).

Methods

Study population

All comatose survivors after non-traumatic CA treated in our tertiary care hospital (Ziekenhuis Oost-Limburg, Genk, Belgium) are prospectively enrolled in our database. Patients could have been resuscitated in-hospital, referred by another hospital or admitted by our own emergency ward. All patients were treated uniformly according to the institutional post-CA protocol. As part of this protocol, cerebral saturation (SctO2) is routinely monitored on admission in the intensive care unit. Written informed consent was obtained from a next of kin. The local medical ethics committee approved the study protocol (15/2/2011).

General management

Our institutional post-CA protocol has been described previously.[1,9] Briefly, all patients were intubated, mechanically ventilated and sedated with propofol and remifentanil if hemodynamically tolerated. Cisatracurium was administered in case of shivering. Unless an obvious non-cardiac cause could be identified, all patients were referred for urgent coronary angiography followed by percutaneous coronary intervention when indicated. Therapeutic hypothermia was induced shortly after admission by cold saline (4 °C – 30 ml/kg) and further mechanically induced and maintained in the coronary care unit by endovascular (Icy-catheter, CoolGard® 3000, Alsius, Irvine, CA, USA) or surface (ArcticGelTM pads, Arctic Sun® 5000, Medivance, Louisville, Colorado, USA) cooling systems at 33 °C for 24-h. After rewarming (0.3 °C/h) sedation was titrated toward patient's comfort with efforts toward minimizing sedation. Patients were extubated when their neurological, respiratory and hemodynamic status had sufficiently recovered.

Data collection

Cerebral tissue oxygen saturation (SctO2) was continuously measured with near infrared spectroscopy (NIRS), using the FORE-SIGHT™ technology (CAS Medical systems, Branford, CT, USA). During hypothermia and rewarming cerebral saturation data were transmitted electronically to a personal computer with a two seconds time interval. Cerebral saturation data were not used to guide any form of hemodynamic management. An arterial blood gas with determination of hemoglobin was taken hourly during the 24 h hypothermia period. The simultaneously obtained $SctO_2$ values (by averaging the left and right $SctO_2$ sensor) were collected from our electronic records. Unless contra-indicated or considered inappropriate by treating physicians, a pulmonary artery catheter (CCOmbo PAC®, Edwards Life Science, Irvine, CA, USA) was used to measure cardiac output by continuous thermodilution and SVO2. Because we previously reported a marked inaccuracy of cardiac output measurements using thermodilution during therapeutic hypothermia, we prefer SVO2 as a surrogate parameter for cardiac output and for the balance between oxygen supply and demand.[10] The continuous SVO2 monitoring system was calibrated as prescribed by the manufacturer. These data were transmitted electronically to a personal computer with a 2 s time interval.

Statistics

Results are expressed as mean (±SD, standard deviation) unless otherwise stated. All simultaneously obtained hemoglobin-SctO2-SVO2 triplets collected during the first 24 h after ICU admission were pooled together. The mean SctO2 was calculated per g/dl hemoglobin. Linear regression with calculation of Pearson correlation coefficient was used to describe the relationship between SctO2 and hemoglobin. All obtained hemoglobin values were divided in quartiles and the average MAP, cardiac output, SVO2, pO2, pCO2 and SctO2 were calculated per quartile. A multivariate linear regression model was constructed including these parameters. Survival analysis was performed in four steps. First, the mean hemoglobin during the first 24 h was calculated per patient. Good neurological outcome was defined as a cerebral performance category score (CPC) 1–2 at 180 days post-CA. To determine the admission and average hemoglobin level per 24 h that discriminates best between good (CPC 1–2) and bad (CPC 3–5) neurological outcome, odds ratios (and 95% confidence intervals) were calculated per g/dl hemoglobin (forest plot). To test for significance, a chi-square test was performed for the suggested hemoglobin cut-off with the highest odds ratio. These were defined as the optimal admission hemoglobin and average hemoglobin levels. Second, patients were stratified according to their average SVO2 (above or below 70%) and SctO2 (above or below 62.5%) to investigate whether a detrimental effect of anemia would be more pronounced in patients with suboptimal brain saturation or insufficient cardiac reserve to compensate for an anemic status. Third, odds ratios were calculated per percentage of time under each hemoglobin level after stratification according to whether the mean SctO2 during the study period was below or above 62.5%. Fourth, multivariate models were constructed to correct for cardiac arrest variables, hemodynamic parameters and co-morbidity. Co-morbidity was quantified by means of a modified Charlson co-morbidity index based on the presence of myocardial infarction, congestive heart failure (ejection fraction <45%), chronic lung disease, chronic kidney disease (admission creatinine >1.5 g/dl), malignancy and age (0–4 points).[11] Finally, to asses fluid induced hemodilution, the mean hemoglobin decrease was calculated ($[Hb]_{initial} - [Hb]_{24\ hours}$). Patients who received blood transfusions were not included in the hemodilution calculation. Statistical analysis was performed using Matlab software (version R2010b, Mathworks, USA). A p-value <0.05 was considered significant.

Results

Study population

Eighty-two patients were included in the study. Patient characteristics are summarized in Table 1.

Hemoglobin–SctO2

The mean hemoglobin concentration among all study patients during the 24 h study period was 13.4 ± 1.9 g/dl. Only four patients received a total of nine units packed cells during the 24 h study period. To investigate the correlation between hemoglobin and SctO2, all paired hemoglobin-SctO2 measurements hourly obtained during the 24 h study period were pooled together (1990 pairs, 82 patients, mean 24.3 per patient) and the average SctO2 was calculated per g/dl hemoglobin (Fig. 1). We found a strong linear relationship between hemoglobin and mean SctO2 ($SctO2 = 0.70 \times hemoglobin + 56$ (R^2 0.84, $p = 10^{-6}$)). Therefore, the cerebral saturation increases with 0.7% per g/dl hemoglobin. In