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Daily Lowest Hemoglobin and Risk of Organ Dysfunctions in Critically Ill Patients

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Abstract

Objective—To determine the association between hemoglobin levels and the daily risk of individual organ dysfunctions in critically ill patients.

Design—We performed a post-hoc analysis of prospectively collected data in medical and surgical ICU patients admitted with respiratory failure or shock. Baseline demographic data, and detailed in-ICU and hospital data, including daily lowest hemoglobin, were collected up to hospital day 30. We assessed patients daily for brain dysfunction [delirium, using Confusion Assessment Method for ICU (CAM-ICU)], for renal and respiratory dysfunction [using the ordinal renal and respiratory Sequential Organ Failure Assessment (SOFA score)], and for ICU mortality. Associations between the lowest hemoglobin on a given day and organ dysfunctions the following day were assessed using multivariable regressions, adjusting for age, APACHE II score, Charlson comorbidity index, Framingham stroke risk profile, ICU day, ICU type, sepsis, and current organ dysfunction status. A sensitivity analysis further adjusted for daily transfusions and fluid balance in a subset of our patients.

Measurements and Main Results—We enrolled 821 patients with a median (interquartile range, IQR) age of 61 (51, 71) years, APACHE II score of 25 (19, 31), and hemoglobin level of 10.0 (9.0, 11.1) g/dl. There was no evidence of an association between lowest daily hemoglobin and brain dysfunction ($p=0.69$ for delirium), renal dysfunction ($p=0.30$) or ICU mortality ($p=0.95$). The lowest hemoglobin on a given day was significantly associated with the respiratory SOFA score the following day; for each increasing hemoglobin unit, the odds of worsened respiratory SOFA score the following day were decreased by 36% (OR 0.64, 95% CI: 0.53, 0.77, $p < 0.001$). The sensitivity analysis including daily transfusions and fluid balance (in a subset of 518 patients) did not qualitatively change any of these associations.

Conclusions—In this study in ICU patients, lower hemoglobin was associated with a higher probability of worsening respiratory dysfunction scores the following day. There was no evidence

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of association between hemoglobin and brain or renal dysfunction, or ICU mortality. The possible differential effects of anemia on organ dysfunctions seen in this hypothesis generating study will have to be studied in a larger prospective study before any alterations to present restrictive transfusion guidelines can be recommended.

Keywords

anemia; critical illness; restrictive transfusion; delirium; respiratory dysfunction; renal dysfunction

Introduction

The balance between oxygen supply and demand is a daily challenge in the care of critically ill patients. While tissue oxygen demand is often increased in critical illness, many patients are unable to increase oxygen supply to match this demand (1). Insufficient oxygen delivery leads to tissue ischemia and end-organ dysfunction. One of the major contributors to oxygen delivery is the oxygen-carrying capacity of blood, which in turn depends on its hemoglobin concentration.

Anemia is common in the ICU patient population and has a multifactorial etiology (2) (3) (4) (5) (6) (7). The physiological consequences of anemia can be seen in both healthy and diseased individuals, and anemia has been associated with poor outcomes in the critically ill including failure to wean from mechanical ventilation, myocardial infarction, and increased mortality (8) (9) (10) (11).

Despite the risks associated with anemia, treatment of anemia with red blood cell (RBC) transfusions is also not without risk. RBC transfusions are associated with several well-known complications including immunosuppression (12), Transfusion Related Acute Lung Injury (TRALI) (13), Transfusion Associated Cardiac Overload (TACO) (14). This has led some investigators to hypothesize that anemia associated with chronic disease states and inflammation could be an adaptive response (15). Blood products are also a scarce and expensive resource and need to be conserved (16).

Recent large randomized controlled studies (17) (18) have demonstrated that restrictive transfusion strategies that recommend transfusing only when hemoglobin levels fall below 7g/dl are safe in critically ill patients and septic patients, and are not associated with increased mortality. This has led to widespread adoption of restrictive transfusion guidelines, yet it is unclear if anemia may put certain organs at risk for dysfunction, while others may have more reserve.

We hypothesized that anemia would differentially affect the daily risk of developing brain, renal and respiratory dysfunction and sought to test this hypothesis in a large cohort of medical and surgical ICU patients.

Materials and Methods

Study design and patients

We performed a post-hoc analysis of prospectively collected data from the “Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors” (BRAIN-ICU) study (19). The eligibility criteria for the parent BRAIN-ICU study have been previously reported (19). Briefly, we enrolled adult medical and surgical ICU patients with respiratory failure or shock and excluded patients who had been critically ill for a prolonged period of time prior to enrollment, those with significant prior cognitive impairment, those who were moribund and not expected to survive and those in whom follow-up would be difficult because of substance abuse, psychosis, homelessness, or residence more than 200 miles from Nashville. Informed consent was obtained from patients or their health-care proxy; if consent was initially obtained from a health-care proxy, the patient provided informed consent when mentally competent. The institutional review boards at the two enrolling sites—Vanderbilt University Medical Center and Saint Thomas Hospital—approved the study.

Procedures

Detailed in-ICU and hospital data, including daily lowest hemoglobin levels, were collected in the study up to hospital day 30. Both enrolling institutes had adopted restrictive transfusion practices prior to study initiation. Hemoglobin was directly measured immediately after collection of patient whole blood samples. Hemoglobin level was determined by Sysmex(R) automated analyzer which utilizes fluorescent flow cytometry to obtain blood component cell counts. “Daily lowest hemoglobin level” was defined as the single lowest value of hemoglobin if multiple measurements were made for one patient over the course of one day. In patients with only one measurement per day, daily lowest hemoglobin represents their single hemoglobin measurement for that day. The area under the hemoglobin-time curve was also calculated, using a trapezoid rule on the daily lowest hemoglobin values, to ascertain whether time spent anemic and overall severity of anemia (ICU day $\times$ lowest daily hemoglobin over the patient’s ICU course) related to ICU mortality. Patients were evaluated daily for brain dysfunction (delirium) using the validated Confusion Assessment Method for the ICU (CAM-ICU) (20). Patients, who were responsive to voice, whether on sedation or not, were assessed for delirium with the CAM-ICU and those scored positive, were considered delirious in this analysis. Patients unresponsive to voice were deemed comatose, irrespective of its etiology. We assessed patients daily for renal dysfunction using the renal SOFA score (based on creatinine and urinary output) and for respiratory dysfunction using the respiratory SOFA score (based on the PaO₂/FiO₂ ratio) (21). The SOFA score is validated as a measure of organ dysfunction (21). We also collected data on baseline illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE) II score (22), comorbidities with the Charlson Comorbidity Index (23), and risk for ischemia by the Framingham Stroke Risk profile (24). We also assessed daily mechanical ventilation status, time on mechanical ventilation, time to death and in-ICU mortality.

Statistical analysis

On each study day, brain dysfunction was categorized as “normal”, “delirious”, or “comatose”. Separate categories were used to indicate study withdrawal, death, or discharge from the ICU. The adjusted association between the current day lowest hemoglobin level and brain organ dysfunction the following day was assessed using multinomial logistic regression. We used ordinal (proportional odds) logistic regression for the renal and respiratory dysfunction outcomes, since the renal and respiratory SOFA scores are measured on an ordinal scale ranging from 1 to 4, where higher values indicate greater organ dysfunction. Logistic regression was used to evaluate ICU mortality and daily requirement for mechanical ventilation. All logistic regression analyses were implemented in a “transition model” or “Markov” configuration. In each transition model, the outcome (e.g., current day respiratory SOFA score) was modeled conditionally on the previous day’s lowest hemoglobin level, previous day’s outcome (e.g. previous day respiratory SOFA score), the previous day’s daily covariates, and baseline covariates (e.g., APACHE II score). Cox proportional hazards regression with time-varying covariates was used to assess the adjusted association between current day lowest hemoglobin and time to death in the ICU.

In each analysis, we adjusted for covariates that would potentially confound the relationship between the lowest hemoglobin level and the corresponding outcome. These included age, weight, APACHE II score, Charlson comorbidity index, Framingham stroke risk profile, ICU day, ICU type (medical vs. surgical), current sepsis, and current day organ dysfunction status. We further evaluated the interaction between lowest hemoglobin and ICU day (1, 2, up to 30) to determine if the effect of hemoglobin differed according to early versus late ICU course, and the interaction of lowest hemoglobin and current day organ dysfunction on next day outcomes. The interactions considered were fully prespecified before statistical analysis on the basis of expert opinion. For each quantitative regressor, we sequentially evaluated the possibility of nonlinear association using a restricted cubic spline basis with three knots spaced evenly at the quartile boundaries. If there was significant evidence of nonlinear association using a likelihood ratio test, the nonlinear components were retained and otherwise omitted. Statistical significance was indicated for p-values less than 0.05, or for 95% confidence intervals that fail to include the relevant null value. All statistical analyses were implemented in the R framework (version 3.1; <http://www.R-project.org/>).

To determine whether daily red cell transfusion and daily net fluid balance confounded the association between lowest daily hemoglobin and organ dysfunction outcomes, we conducted a sensitivity analysis with adjustment for number of red cell transfusions (units transfused per day) and daily net fluid balance (fluid intake and output measured/charted hourly and totaled every 24 hours) as potential confounders in separate sensitivity analyses. Fluid intake included intravenous and enteral fluids, total parenteral nutrition, albumin, and blood products; fluid output included urine output, estimated blood loss, and drain output. In the sensitivity analyses, we reimplemented the primary regression analyses by additionally adjusting for the effect of daily fluid balance (L), and separately for daily RBC transfusion amount (350mL units). We could obtain these additional data from the electronic medical record only in patients enrolled at Vanderbilt University (518 of the 821 cohort). The

patients included in the sensitivity analysis did not differ significantly from the full cohort in baseline demographics or severity of illness at enrollment.

Results

Between March 1, 2007 and June 30, 2010, 826 patients were enrolled in the BRAIN-ICU study; five withdrew consent and permission to use collected data, thus we had 821 patients with in-hospital data and assessments. Baseline demographics and in-hospital course for the entire cohort are shown in Table 1. The enrolled patients had a median (IQR) age of 61 (51, 71) years, high severity of illness with a median APACHE II score of 25 (19, 31) and median lowest hemoglobin of 10.0 (9.0, 11.1) on study day 1.

We found no evidence of association between daily lowest hemoglobin and the likelihood of transition between normal, delirious, and comatose mental states (all $p > 0.2$, see Table 2). Similarly daily lowest hemoglobin was not associated with the odds of worsening renal SOFA score (worse renal dysfunction) [OR 0.95 (0.87, 1.04), $p = 0.30$] the following day (Table 2). However, daily lowest hemoglobin was significantly associated with worsening respiratory SOFA score [OR 0.64 (0.53, 0.77), $p < 0.001$], such that for every unit (g/dl) increase in hemoglobin the odds of worsening respiratory dysfunction were reduced by 36% (Table 2). This association was attenuated in patients with more severe respiratory dysfunction (i.e., an interaction between current day respiratory SOFA score and lowest daily hemoglobin, $p < 0.001$) such that patients with more severe respiratory dysfunction were less sensitive to worsening respiratory dysfunction as a consequence of lower hemoglobin levels. There was also an association between lower hemoglobin levels and being on mechanical ventilation the following day ($p = 0.01$). However, there was an interaction with study day, such that the effect of hemoglobin level on mechanical ventilation was greater at later ICU days. On ICU day 5 for example, the odds of mechanical ventilation the following day were increased by day 2% (OR: 1.02, 95% CI: 0.95, 1.09) for each lower unit of hemoglobin and by Day 10, the odds of mechanical ventilation the following day were increased by 8% (OR: 1.08, 95% CI: 1.00, 1.15). There was no evidence of statistical interactions between the daily lowest hemoglobin and ICU day on any of the other organ dysfunction outcomes (all p values > 0.2). Neither the lowest hemoglobin over the full ICU course ($p = 0.95$), nor the area under the hemoglobin-time curve ($p = 0.45$) was associated with ICU mortality ($p = 0.95$). The hemoglobin level in the ICU was not associated with time to death ($p = 0.40$) in the Cox proportional model with time varying covariates (Table 2). The sensitivity analysis including daily transfusions and fluid balance (in a subset of 518 patients) did not qualitatively change any of these associations. Specifically, daily lowest hemoglobin was still significantly associated with worsening respiratory SOFA score in the models incorporating red blood cell transfusions [OR 0.64 (0.50, 0.81), $p < 0.001$], and those incorporating daily fluid balance [OR 0.65 (0.51, 0.82), $p < 0.001$].

Discussion

The focus of this hypothesis-generating study was to investigate the association of lowest hemoglobin and acute organ dysfunctions. In this large cohort of medical and surgical ICU patients with respiratory failure or shock, a lower hemoglobin level on a given day was

associated with a worsening respiratory function score the following day, and a continuing need for mechanical ventilation, especially in the later part of their ICU stay. There was no evidence that lower hemoglobin levels were associated with risk of developing delirium, renal dysfunction, or ICU-mortality. These data suggest that anemia does not consistently increase the risk for end organ dysfunction or mortality, and corroborates a growing body of literature (11) (17).

While prior work that has shown that anemia in critical illness is associated with worse outcomes (8) (9) (10), more recent observational and randomized controlled trials (RCTs) have shown that transfusions are associated with worse clinical outcomes as well (24) (26) (27) (28) (29), and that a restrictive transfusion strategy does not portend worse outcomes (17) (11). Thus, while anemia is not desirable, red blood cell transfusions can be harmful too and should not be advocated for all patients who are anemic. Our data suggest that in the patients who have some underlying respiratory dysfunction, lower hemoglobin levels are associated with worsening respiratory dysfunction score and ongoing need for mechanical ventilation. However, at this point, these data are purely hypothesis generating and no alterations to present restrictive transfusion guidelines should be made.

There are a number of plausible hypotheses that may support our findings that anemia is associated with worse respiratory dysfunction score and should be considered. Iron deficiency anemia in ventilated COPD patients, and in those with chronic respiratory failure, is known to increase work of breathing and minute ventilation, (30) (31) (32) and transfusion may help to wean these patients from mechanical ventilation (33) (34). There is also a correlation between pulmonary function (Forced expiratory volume, FEV₁) and iron status, exacerbated by inflammation and nutritional deficiencies, which many critically ill patients have (35). Transfusion of blood products has been associated with increased probability of worse respiratory scores the following day (13) (14). Therefore, it is important to differentiate whether anemia itself contributed to worse respiratory scores or blood products administered secondary to anemia contributed to worse outcomes. Our sensitivity analysis performed to determine whether red cell transfusion confounded the relationship between anemia and worsened respiratory status found that the associations between low hemoglobin levels and respiratory dysfunction persisted even after accounting for transfusion of blood products and fluid balance. We did find an association between lower hemoglobin levels and the need for mechanical ventilation, though there was an interaction with study day, and the association was driven by patients with longer durations of mechanical ventilation (10% of our patients had > 10 days of mechanical ventilation though). While this could be a statistical finding of low clinical importance, it may also be that chronic anemia may be a risk factor for longer duration of mechanical ventilation when other elements of critical illness (such as sepsis, hemodynamic instability etc.) have resolved. So, early in critical illness when there are hemodynamic and metabolic perturbations, the impact of anemia—while still seen on higher probability of worsening respiratory scores—may not be a substantial driver for increasing probability of being on mechanical ventilation; however later in the course of critical illness when those factors have abated, the independent effect of anemia on mechanical ventilation may become more pronounced.

Clinicians, however, need to use this information with caution and should not use these hypotheses generating data to challenge or change restrictive transfusion practices in their ICUs that have been shown to be safe, while at the same time cost and resource effective. The possible differential effect of anemia on organ dysfunction seen in this cohort would first need to be revalidated in a much larger clinical cohort or tested in a prospective comparative trial and hopefully these data may serve as an impetus for researchers to do just that. In the interim, perhaps it can be reasoned that anemia should be considered in the differential diagnosis of ongoing and prolonged respiratory insufficiency in patients who have completed the resuscitative phase of their critical illness and once all other apparent causes are addressed.

Low hemoglobin levels were not associated with worsened delirium, renal function or mortality in our study population. While the pathogenesis of delirium is not known, it is plausible that the degree of anemia in our patient population did not impact cerebral oxygen delivery and any potential for brain organ dysfunction. Our findings corroborate studies where red blood cell transfusions have shown to have no impact on delirium rates (36) (37) (38). While anemia and red blood cell transfusions have both been implicated in acute kidney injury (39), a degree of anemia may be protective for the kidney due to decreased viscosity and rheology, and there is evidence that correcting anemia with either erythropoietin or transfusion, does not improve renal function (28) (29) (39).

Our study has many strengths and a few limitations that need to be considered. This was a large prospective cohort of medical and surgical ICU patients and patients in the study had a wide distribution of daily hemoglobin levels, with at least a quarter being below 8.7 g/dl and 5% < 7 g/dl, allowing comparisons between patients who were anemic by traditional definitions and those who were not. However, the development of anemia during chronic illness may relate to a multitude of factors including hemodilution, frequent blood drawing, bone marrow dysfunction due to cytokines, malnutrition, medications, and bleeding -factors which may also influence organ function and outcome parameters, making it difficult to take these multiple interactions into account in a single analysis. We used the renal and respiratory SOFA as our measures for organ dysfunctions. While well validated, other scoring systems may have yielded different results. Nevertheless, anemia was not associated with increased probability mortality, thus any possible associations would not have had significant clinical significance. We were also unable to account for confounding due to cardiac ischemia in our models due to the sparseness of cardiac enzymes drawn in this cohort. Finally, as in any observational study, there can always be residual confounding, though our large sample size allowed us to adjust for a wide range of confounders that we believed may have impacted the relationship. Finally, there was no a priori sample size calculation for this specific study aim, though the parent BRAIN-ICU study was adequately powered for the outcomes that were measured (19) (40). We selected covariates a priori based on available degrees of freedom to avoid model overfitting and listed 95% confidence intervals throughout the manuscript, for all of the important findings, to provide the reader with a gauge of statistical precision.

Conclusion

In this cohort of critically ill medical and surgical ICU patients, anemia was associated with an increased probability of worse respiratory function the following day and a need for ongoing mechanical ventilation. There was no evidence of an association between hemoglobin levels and brain and renal dysfunction outcomes or ICU mortality. Studies focusing on the outcomes of anemia and transfusions in critically ill patients with significant lung injury will be needed to confirm our findings and until then no changes in restrictive transfusions can be recommended.

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Table 1Demographic and In-hospital data ^a

	In-hospital cohort (N=821)
Age at enrollment (years)	61 (51–71)
Caucasian, N (%)	740 (90%)
Males, N (%)	420 (51%)
Medical ICU (versus surgical ICU), N (%)	559 (68%)
Charlson comorbidity index	2 (1–4)
Severity of illness (APACHE II score) at enrollment	25 (19–31)
Organ failure (SOFA score) at enrollment	9 (7–12)
Lowest hemoglobin on study day one	10.0 (9.0–11.1)
Admission Diagnosis, N (%)	
Sepsis	244 (30%)
Acute respiratory failure ^b	135 (16%)
Cardiogenic shock, myocardial ischemia or arrhythmia	141 (17%)
Upper airway obstruction	87 (11%)
Gastric/colonic surgery	63 (8%)
Neurological diseases/seizures	11 (1%)
Other surgical procedures ^c	82 (10%)
Others	58 (7%)
Days of mechanical ventilation (among those on MV)	3 (1–8)
Prevalence of delirium	606 (74%)
Delirium days (among those with delirium)	4 (2–7)
Coma days (among those with coma)	3 (2–6)
Hospital length of stay (days)	10 (6–17)
Average fluid balance (mL) (N=518)	484 (–228 – 1260)
Cumulative RBC units (N=518)	0 (0 – 0.33)

^aMedian (Interquartile range) unless otherwise indicated

^bAcute respiratory failure: Due to acute respiratory distress syndrome, acute exacerbations of chronic obstructive airway disease or asthma, or pulmonary edema, embolus, fibrosis, etc.

^cOther surgical procedures: hepatobiliary surgery, liver transplant, orthopedic, obstetrical/gynecological, vascular, otolaryngeal, urologic etc.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Score; MV, mechanical ventilation

Table 2

Daily Hemoglobin Levels and Outcomes the Following Day

Outcome (N=821)	Point Estimate*	P value
Brain Dysfunction		
Delirium vs. Normal	0.97 (0.86–1.1)	0.69
Coma vs. Normal	1.03 (0.88–1.22)	0.69
Renal Dysfunction	0.95 (0.87, 1.04)	0.30
Respiratory Dysfunction	0.64 (0.53, 0.77)	<0.001
ICU Mortality	1.0 (0.86, 1.16)	0.95
Time to Death	1.06 (0.91– 1.25)	0.40

* Point estimates represent Odds Ratios and 95% Confidence Intervals except for the time to death outcome where the point estimates represent the Hazard Ratio and the Confidence Interval