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The effects of iron deficiency on red blood cell transfusion requirements in non-bleeding critically ill patients.

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Abstract

Introduction: Critically ill patients often need blood transfusion, but no reliable predictors of transfusion requirements are available at Intensive Care Unit (ICU) admission. We hypothesized that ICU patients admitted with Iron Deficiency (ID) may be at higher risk for developing anemia, requiring blood transfusion. The aims of this study were to determine the frequency of ID in ICU patients admission and to investigate its relationship with transfusion requirements in ICU patients.

Methods: Two hundred ninety-six patients admitted to the general ICU were enrolled in the prospective observational study. We studied 268 patients, after excluding those transfused on or before ICU admission. The patients recorded age, gender, diagnosis, severity scores, presence of sepsis, ICU complications, ICU treatments, and transfusion-free interval. ID was assessed on the basis of several parameters, including hemoglobin, hematocrit, levels of serum iron, transferrin saturation, levels of ferritin, soluble transferrin receptor, C-reactive protein.

Results: The mean age was 48 years. Of 268 patients (138 male/ 130 female), 114 (42.8%) had ID with outcomes of blood samples were used at ICU admission. The overall transfusion rate was 38.8%, being higher in ID patients than in normal iron profile patients (40.3 vs. 18.9%, P=0.001). After adjusting for severity of illness and hemoglobin level, ID patients remained significantly associated with transfusion, with a hazard ratio of 5.3 (95% CI, 1.8-14.8; P=0.001).

Conclusion: ID is common at ICU admission and is associated with higher transfusion requirements. These findings have important implications for transfusion practices for in ICU patients.

Keywords: Iron deficiency, Anaemia, Blood transfusion, Critical illness.

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Introduction

Intensive care (ICU) patients often need blood transfusion, but no reliable predictors of transfusion requirements are available at ICU admission [1]. Anemia is a common condition in critically ill patients and results in a high requirement for blood transfusions associated with poor outcomes [2]. Iron Deficiency (ID) is known as the first cause of anemia worldwide and prevalence of ID at ICU admission is around 25 to 40% [3]. However, effects of ID on transfusion requirements at ICU are unknown and, to the best of our knowledge, there are no data available.

The main objective of this prospective observational study was to determine the prevalence of ID on ICU admission and to investigate the clinically significant relationships between ID and the need for blood transfusion requirements.

Material and Methods

After approval by the Ethics Committee of the Inonu University in Malatya, and written informed consent was obtained from the patients, a prospective observational study was undertaken consisting of 296 consecutive adult ICU patients between September 1, 2014, and March 1, 2015. All patients admitted to our 20-bed ICU and if their stay in ICU was expected to last more than 7 days. Exclusion criteria were: estimated survival of fewer than 28 days, prescription of erythropoietin, iron, or blood product transfusions during the previous month, iron overload. Data derived from medical charts were collected for all consenting patients, including age, gender, type of admission (postoperative, unplanned surgical or medical). Significant comorbidities were also recorded. Blood samples were obtained on the day of ICU admission. All hematologic variables were measured using an automated analyzer (Beckman-Coulter/LH780,USA). Serum iron and transferrin saturation levels were measured using commercially available kits (Abbott, Milano, Italy), and ferritin concentration was determined using nephelometry on an Immune Light 2000 (Siemens Company, USA). High-sensitivity CRP was measured using immunonephelometry on the automated analyzer. Anemia was defined as Hb concentration of <130 g/L in men and <120 g/L in women, in accordance with the World Health Organization criteria. Using this approach, ID was defined as either a serum ferritin level of <80 μg/L or a ferritin

level of 80-150 µg/L combined with either a Transferrin Saturation (TSI) (serum iron per total iron binding capacity) of <20% or a CRP level of <5 mg/L. When CRP was >5 mg/L, The protocol for transfusion in our ICU uses restrictive criteria: stable patients are transfused only when hemoglobin reaches 7 g/dL, whereas patients in septic shock or with acute cardiac conditions are transfused when hemoglobin reaches 9 g/dL [4].

Statistical analyses

Power analysis indicated that a minimum of 48 patients were required in each group based on type I error α of 0.05; type II error β of 0.20; difference of 2.8, Standard Deviations (SD) of group I of 4.5 and SD of group II of 1.6, respectively. Normality distribution of our data was confirmed using the Kolmogorov-Smirnov test. All variables between 2 groups were compared using the Mann-Whitney U test, and the distribution of gender with respect to the groups was analyzed using Yates' corrected chi-square test. A value of $P<0.05$ was considered to be statistically significant. All values are presented as means ± SD or number (%).

Result

A total of 296 consecutive ICU patients who fulfilled the inclusion criteria were considered for this study. Twenty eight patients were excluded for the following reasons: 14 patients were diagnosed with iron overload; 12 patients non-anemic; 2 patients blood transfusions during the previous month. Ultimately, 268 adult patients ICU admission were included in the study. Table 1 presents the remaining 268 patients were divided into 2 groups according to their baseline iron status: iron-deficient (ID; n=114; 42.8%) and non-ID (normal iron profile; n=144; 57.2%). Median Hb concentration on ICU admission was 10.6 (8.4 to 9.5) g/dL. At ICU admission ID patients was associated with low hemoglobin levels (P=01, Table 1). Clinical and demographic data for the 268 patients are presented in Table 2. The median number of PRBC units transfused was associated with a higher transfusion rate in the ID group than in the non-ID group (3 and 1 U/patient, respectively; P<0.0001). The median ICU length of stay was longer among the ID than the non-ID group (15 and 10 days/patient, respectively; P=0.0017).

Table 1. *Hematological and iron parameters on ICU admission.*

Variable	Normal ranges	ID (n=114)	Non-ID (n=144)	P-value
Reticulocyte percentage (%)	<5	2.1 ± 0.3	2.4 ± 0.2	0.182
Hb (g/dL)	13.5-17.5	8.4 ± 1.1	9.5 ± 2.4	0.01
Serum iron (mmol/L)	12-35/	56 ± 13.2	180 ± 35.7	0.012
TSAT (%)	20-50	32 ± 1.2	34 ± 2.1	0.542
Serum ferritin (mg/L)	30-300	64 (12-120)	253 (175-382)	0.002
Soluble serum transferrin receptor (mg/L)	0.83-1.76	0.94 (0.81-1.21)	1.02 (0.91-1.36)	0.754
C- reactive protein (mg/L)	<10	2,5 ± 0.2	2.8 ± 1.2	0.256

Table 2. *Patients' characteristics at ICU admission.*

Variable	ID (n=114)	Non-ID (n=144)	P-value
Age (year)	54.8 ± 17	53.6 ± 12	0.458
Female	56 (49.1%)	74 (51.3%)	0.642
Body mass index (kg/m^2)	26.5 ± 14.8	25.3 ± 13.5	0.565
Trauma	19 (16%)	36 (25%)	0.347
Acute coronary syndrome	15 (13%)	24 (17%)	0.654
Clinical bleeding	5 (4%)	12 (9%)	0.454
Surgery before ICU admission	3 (2%)	6 (4%)	0.363
Surgery during ICU stay	15 (13%)	24 (17%)	0.627
Sepsis	21 (18%)	35 (31%)	0.047

Discussion

In this prospective observational study, we found that ID was highly prevalent at ICU admission patients (42.8%) and that it was associated with higher PRBC transfusion requirements. To the best of our knowledge, this is the first report of the clinical relationship between ID and transfusion in ICU admission patients.

ID is a common cause of anemia in outpatients and inpatients. In the present study, the prevalence of ID is relatively high. Indeed, because of the blood losses regularly observed in critically ill patients, one could have expected a higher prevalence of ID. Previous studies assessing ID using different biomarkers (that is, hypochromic red cells, reticulocyte Hb content, soluble transferrin receptor, zinc protoporphyrin, transferrin saturation and ferritin) [5]. However, ID diagnosis is difficult in the context of inflammation [6]. There is no consensus to define ID in critically ill patients [7]. Thus, we choose to use an ID definition that has already been used in an intervention study and that is commonly accepted in surgery patients. However, we could have used more recent biological markers that have been proposed for ID diagnosis in the presence of inflammation [8].

There are few studies of the epidemiology of anaemia admission ICU. In a recent large multicentre study the mean Hb among ICU patients who remained in hospital longer than

24 days after ICU admissions was 96-98 g/L [2]. In addition, blood transfusion is commonly used in the treatment of anemia. For a long period, hemoglobin of 10.0 g/dL was the threshold for transfusion [9]. In a landmark multicenter Canadian trial, Hebert and colleagues randomized 838 critically ill patients to either a liberal protocol where transfusions were administered to maintain hemoglobin levels above 9 g/dl or a restricted strategy where hemoglobin levels were kept between 7 and 9 g/dl [10]. Overall, the 30-day mortality rate was 19% in the restricted group and 23% in the liberal transfusion group, with a significant difference in outcome among younger patients. Our data are consistent with Hb concentration less than 100 g/L. Fernandez et al. [1] reported that 37% presented with low Reticulocyte hemoglobin content (CHr) on ICU admission and is associated with higher transfusion requirements. Therefore, it could be concluded that limiting the use of blood products should lead to improvements in patient outcome. Accordingly, reduction of ID and ID-related anemia during the ICU admission is likely to be beneficial. Most prior studies have quantified blood losses indirectly, reporting blood transfusion requirements necessary to maintain or reach a trigger value. Hb concentration is the most frequently cited criterion for transfusion [4]. This study focused on admission iron data, and the goal was to maintain Hb levels between 70 and 90 g/L. We showed that higher rates of transfusion are required for ID patients compared to non-ID patients. More importantly, this study identified ID as an important prognostic factor for predicting transfusion requirements in ICU admission patients.

Moreover, in some observational studies on ICU patients, blood transfusions were associated with a number of complications, including an increased risk for infections, and with poor outcome [11]. Thus, considering this "blood transfusion anemia paradox", the optimal Hb level to trigger ICU patients has not been defined yet [12]. Determining who and when to transfuse this patients population is thus a challenge and recent years have seen continuing debate and discussion regarding the optimal transfusion, 'trigger'. Although blood transfusion can be lifesaving in extreme circumstances, in the absence of life threatening hemorrhage, the indications for transfusion are somewhat controversial. Blood transfusions have well-recognized problems, including the need to type and cross match, and the potential transmission of diseases, or the development of transfusion-related complications (such as transfusion-related acute lung injury or transfusion associated circulatory overload) and immunosuppression. Studies have shown that for most critically ill patients, there is no advantage to maintaining a higher hemoglobin concentration [13].

Our study has several limitations. First, we did not measure inflammatory markers on admission, such as interleukin-6. Therefore, the biochemical parameters we used for diagnosis not only are markers for ID but also can indicate activation of acute-phase responses. In our study, patients with evidence of iron homeostasis were further evaluated using peripheral blood smears to correlate biochemical data. A second important limitation is that, because this is an observational study, and, therefore, causality cannot be inferred and multiple adjustments for all comorbidities could not have been performed. Finally, this study had a relatively small sample size. Future studies should be carried out with larger numbers of patients to verify our results. This study suggests a methodology that can be used to analyze ID in other clinical trials.

Conclusion

Iron deficiency is common in patients admitted to the ICU. Moreover, we found that ID is strongly associated with higher transfusion requirements at ICU admission patients. We believe that it is important to avoid transfusion during at ICU stay when possible. At ICU admission ID anemia may be able to be used to identify patients who should receive transfusion and the number of PRBC units required. Our findings may have implications for PRBC transfusion management strategies in ICU patients.

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