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Red blood cell transfusion in non-bleeding critically ill patients with moderate anemia: is there a benefit?

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Abstract *Purpose:* This study was undertaken to investigate the efficacy of red blood cell transfusion (RBCT) at reversing the deleterious effects of moderate anemia in critically ill, non-bleeding patients. *Methods:* This was a retrospective, pair-matched (ratio 1:1) cohort study. Non-bleeding critically ill patients with moderate anemia (nadir hemoglobin level between 70 and 95 g/l), admitted to the ICU over a 27-month period, were included. Anemic patients were included upon meeting five matching criteria of having the same nadir hemoglobin (±5 g/l), APACHE II score (±5), SOFA score (±2), admission diagnostic group, and age (±5 years). Outcome events occurring over the whole ICU stay and after RBCT were collected. After hospital discharge, all patients had a 2-year follow-up period. *Results:* Two hundred fourteen non-transfused anemic patients (NTAPs) were successfully matched with 214 transfused anemic patients (TAPs). In addition to the matching criteria, at baseline, both groups were homogenous with respect to multiple comorbidities. Compared with TAPs, NTAPs showed significantly lower rates of hospital mortality (21 vs.13 %, respectively; $p < 0.05$) and ICU re-admission (7.4 vs. 1.9 %, respectively; $p < 0.05$). Additionally, NTAPs had significantly lower rates of nosocomial infection (12.9 vs. 6.7 %, respectively; $p < 0.05$) and acute kidney injury (24.8 vs. 16.7 %, respectively; $p < 0.05$). Similar results were obtained in subgroup analysis where only more anemic patients (68 matched pairs) or patients with cardiovascular comorbidities (63 matched pairs) were considered. *Conclusions:* RBCT does not improve the clinical outcome in non-bleeding critically ill patients with moderate anemia.

Keywords Transfusion · Critically · Anemia · Moderate · Surgery · Coronary

Introduction

Allogeneic red blood cell transfusion (RBCT) remains a cornerstone therapy for treating anemia in critically ill patients. In fact, nearly 50 % of all critically ill patients receive at least one RBCT during their ICU stay [1–4].

Anemia may be well tolerated by healthy volunteers until they reach hemoglobin (Hb) levels of less than 50 g/l [5]. In contrast, severe anemia (Hb < 70 g/l) may induce tissue hypoxia and worsen the clinical outcome of patients presenting with cerebral dysfunction [6], acute coronary artery disease [7, 8], or sepsis [9], as well as of those undergoing major surgical procedures with significant

blood loss [10, 11]. Therefore, as RBCT increases hemoglobin levels and arterial oxygen content [4], alleviating at least in theory oxygen tissue debt, it may benefit patients with severe, acute anemia.

However, at the ICU, more than two-thirds of RBCT are given to patients who presented with mild-to-moderate anemia and without acute blood loss [4]. In addition, although transfusion practices may vary among physicians and clinical settings [12–15], a relatively high transfusion trigger (hemoglobin 8.8 ± 2 g/dl) seems to be consistently applied in most ICUs [1–4], which means that critically ill patients are transfused to maintain hemoglobin levels above 9 g/dl.

In this regard, there is a large body of evidence suggesting that RBCT is in itself associated with increased risks of infectious complications, mortality, and prolonged hospital stays [1–4, 16, 17], whereas it has not been consistently demonstrated that the deleterious effects of moderate anemia may be reverted by RBCT [17]. This paucity of knowledge is at least in part due to the difficulty of separating adverse effects associated with anemia from those associated with RBCT.

We hypothesized that RBTC does not improve clinical outcomes of non-bleeding, moderately anemic critically ill patients. Therefore, this retrospective cohort study was designed to investigate the efficacy of RBCT in two matched populations of non-bleeding, moderately anemic critically ill patients: non-transfused anemic patients (NTAPs) (exposed to the risks of anemia) and transfused anemic patients (TAPs) (theoretically less exposed to the risks of anemia, but exposed to the risks of RBCT).

Materials and methods

Setting

This retrospective study was conducted at the multidisciplinary ICU of the teaching hospital "Virgen del Rocío," which has a total of 40 beds and over 2,000 admissions per year. The Institutional Ethics and Research Committee approved this study and waived the need for requesting patient's written informed consent.

At the ICU, all dedicated medical senior staff, trainees in critical care, and trainees from other specialties (such as anesthesiology, surgery, and other medical specialties) are allowed to make decisions on RBCT indications. A general guideline for blood transfusion (not exclusively for critically ill patients) is available at the hospital intranet and may be consulted at any time. This guideline suggests that transfusion decisions should be individualized in patients with nadir hemoglobin levels between 70 and 90 g/l, according to cardiopulmonary reserve, intra-vascular volume, and clinical symptoms. As a consequence, we [14] and other authors [12, 13, 15] have observed a high variability when prescribing RBCT to non-bleeding, moderately anemic critically ill patients.

Design

All patients admitted to the ICU from 1 January 2008 to 30 March 2010 were initially evaluated for inclusion in this study. Most ICU patients were admitted following general, cardiothoracic, transplant, vascular, or oncological surgeries. Non-surgical admissions included patients presenting with coronary disease, sepsis or decompensated chronic obstructive pulmonary disease.

Demographic, laboratory, and clinical data, including primary ICU admission diagnosis, morbid complications, length of ICU stay, and clinical outcome (during a 2-year follow-up period), were prospectively collected and retrospectively drawn from our database (GESTUCI: GESTion de enfermos de UCI), which has been described elsewhere [14]. GESTUCI incorporates a hemovigilance module, which enables users to continuously check the number of RBCTs, the pre-transfusion hemoglobin level, and multiple RBCT-related variables. Hemoglobin levels were measured daily throughout the patients' ICU stay. GESTUCI was used to check all patients' nadir hemoglobin levels.

Inclusion criteria. Moderately anemic (nadir hemoglobin levels between 70 and 95 g/l), non-bleeding patients were initially assessed to be included in this retrospective study. *Exclusion criteria*. The following patients were excluded: (1) those with nadir hemoglobin <70 g/l since our clinicians believe that these severely anemic, critically ill patients should always be transfused; (2) patients with nadir hemoglobin >95 g/l, since there is a large body of evidence showing no benefit of RBCT for non-bleeding patients with nadir hemoglobin >95 g/l; (3) patients with active severe bleeding at the moment of the possible inclusion. Severe bleeding was defined by overt hemorrhage, hemorrhagic shock (bleeding patient with systolic arterial pressure of less than 90 mmHg) or having received more than five RBCTs within the previous 24 h prior to patient inclusion, and (4) patients with any restriction for receiving medical support.

Included patients were classified into two groups: TAP if they received at least one RBC transfusion while they presented with a nadir hemoglobin level between 70 and 95 g/l; NTAP if they did not receive RBCT while they presented with a nadir hemoglobin level between 70 and 95 g/l. For the propose of this study, included patients were further classified into five subgroups based on their admitting diagnoses: (1) postoperative period following non-cardiac surgery, including digestive, oncologic, thoracic, vascular, or solid organ transplant surgeries; (2) postoperative period following coronary artery bypass grafting, valve replacement, or cardiac transplantation; (3) sepsis or septic shock, including mainly patients presenting with community-acquired pneumonia, sepsis from surgical

or urological causes, acute pancreatitis (Balthazar classification, grade "E"), or infective endocarditis; (4) coronary artery disease, including acute myocardial infarction, angina pectoris, or congestive heart failure; (5) other medical diagnosis, including patients presenting with re-exacerbation of chronic obstructive pulmonary disease and asthma, metabolic disturbances, medical intoxications, acute pulmonary embolisms, or acute hepatic failure.

Each NTAP was matched by investigators (SRLN and MJS) with a TAP, based on the fulfillment of all of the following five criteria of presenting with the same: (1) nadir hemoglobin level recorded throughout the ICU stay and pre-transfusion hemoglobin level (±5 g/l); (2) admission diagnostic group; (3) severity of illness at admission, as assessed by APACHE II score (±5); (4) severity of illness at the moment of matching, as assessed by SOFA score (±2); (5) age (±5 years). In cases where two or more matched TAPs were found, the subject with the same gender and the closest date to the NTAP admission date was chosen.

In addition to the matching variables, a set of clinical and laboratory baseline variables (Table 1) were gathered. After hospital discharge, all patients underwent a 2-year follow-up period by consulting the hospital database for patients' clinical status or by phoning the patients or their relatives when it was not recorded.

The primary outcome measure was clinical outcome, including mortality and morbidity. Crude mortality rates in the ICU, during the hospital stay, and after 1 and 2 years of follow-up were considered. Morbidity based on the rate of hypoxemia, nosocomial infectious diseases, acute renal failure, ischemic cerebral accidents, and cardiac events was assessed. The length of ICU stay and the rate of readmission to the ICU were also considered. Readmission to the ICU was defined as admission occurring within 24 h from discharge. All these outcome variables were selected because they have been shown to correlate with both anemia and RBCT in a number of previous studies [1–4]. Only leukoreduced packed red cell units were given to all TAPs.

Definitions

Information about baseline comorbidities was obtained from the electronic records of the hospital, which are coded according to C.I.E.9. New onset (i.e., not present upon patient's admission to the ICU) of the following events was recorded: (1) *cardiac event*, which includes myocardial infarction, angina pectoris, and congestive heart failure (chest radiograph interpreted as a new congestive heart failure in combination with compatible echocardiography and treatment with diuretics, angiotensin-converting enzyme inhibitors, and/or parenteral administration of vasoactive amines); (2) *cerebral stroke,* defined as persistent or transient ischemic neurologic events; (3) *nosocomial infection and septic shock,* including ventilator-associated nosocomial pneumonia, catheter-related bloodstream infection, primary bacteremia, sepsis, and septic shock, according to the definitions described elsewhere [9]; (4) *hypoxemia*, defined as a peripheral hemoglobin saturation, as assessed by pulse oximetry, of less than 90 % with a facial mask; (5) *acute kidney injury,* defined according to the RIFLE criteria [18].

All of these outcome variables were recorded for the whole ICU stay, independently of whether a specific outcome preceded the RBCT or not. Subsequently, the analysis was repeated only for those events that occurred after RBCT (Tables 1, 2, 3).

Statistical analysis

Sample size The null hypothesis that the proportion of 1 of the discordant paired results is equal to 0.50 was assessed by using McNemar's test. In accordance with McNemar's test of equality of paired proportions, a sample size of 200 pairs was needed to detect a difference in proportions of 0.10, with a 90 % power and a 0.05 two-sided significance level, when the proportion of discordant paired results is expected to be 0.20. Discordant paired results in excess of 20 % should be sufficient to conclude that the groups are not equivalent [19].

Analysis of variables Most variables were non-normally distributed, so the data are reported as median [interquartile range (IQR) 25–75 %] and percentages. Continuous variables were compared using Wilcoxon's test. Dichotomous variables were analyzed by McNemar's test. All statistical analyses were performed using a licensed computer software package [SPSS (Statistical Package for the Social Sciences) 18, SPSS, Inc., Chicago, IL], and a p value of less than 0.05 was considered significant.

Results

A flow chart of the matching process, including the reasons for patients' exclusion, is depicted in Fig. 1. We obtained 214 pairs of patients who fulfilled the five matching criteria. No TAP matches were found for 81 NTAPs who were excluded from the study. No significant differences were observed between successfully matched and non-matched anemic patients (data not shown).

Baseline characteristics of both groups (NTAPs and TAPs) are shown in Table 1. In particular, all conditions that may be worsened by anemia (previous history of ischemic cardiomyopathy, respiratory insufficiency, and scorings of severity, as assessed by APACHE II at admission and SOFA at the time of matching, were homogeneously distributed between the two groups (Table 1). Moreover, the pH and base excess values,

Table 1 Matching, baseline and outcome variables for non-transfused and transfused anemic patients

Variables	Non-transfused anemic patients $N = 214$	Transfused anemic patients $N = 214$	P value
Matching variables			
Nadir hemoglobin level (g/l)[a]	83 [80, 87]	83.3 [80, 88]	NS
APACHE II (at admission)	14 [10, 18]	13.6 [9, 18]	NS
SOFA	2 [1, 4]	2 [1, 5]	NS
Age (years)	64 [52, 72]	62 [51, 72]	NS
Diagnostic group at admission at ICU			
General surgery	91 (42.5)	91 (42.5)	
Cardiac surgery	44 (20.6)	44 (20.6)	
Medical	38 (17.8)	38 (17.8)	
Sepsis/septic shock	22 (10.3)	22 (10.3)	
CAD or CHF[b]	19 (8.9)	19 (8.9)	
Other variables at the time of matching			
pH[c]	7.34 [7.31, 7.38]	7.34 [7.30, 7.38]	NS
Base excess[c]	0 [−3, 2.9]	0 [−2.9, 2]	NS
Patients receiving RBCT before the ICU admission	16 (7.5)	10 (4.6)	NS
Patients receiving RBCT after discharge from the ICU	14 (6.5)	16 (7.4)	NS
Baseline variables at admission			
Hemoglobin level (g/l)	98 [85, 105]	96 [86, 106]	NS
Mechanical ventilation	158 (73.8)	159 (74.2)	NS
Gender (male)	125 (58.4)	132 (61.6)	NS
Diabetes mellitus	52 (24.2)	67 (31.3)	NS
Obesity	28 (13.0)	26 (12.1)	NS
Coronary artery disease	79 (36.9)	69 (32.2)	NS
Arterial hypertension	106 (49.5)	94 (43.9)	NS
COPD[d]	31 (14.4)	28 (13.0)	NS
Chronic renal failure	26 (12.1)	23 (10.7)	NS
Dyslipidemia	53 (24.7)	68 (31.7)	NS
Cancer	61 (28.5)	57 (26.6)	NS
Outcome variables			
ICU mortality	22 (10.2)	30 (14.0)	NS
Hospital mortality	28 (13.0)	45 (21.0)	<0.05
1-year follow-up mortality	52 (24.2)	56 (26.1)	NS
2-year follow-up mortality	61 (28)	62 (29)	NS
Cardiologic event	17 (7.9)	14 (6.5)	NS
After RBCT[e] ($N = 206$)	15 (7.2)	12 (5.8)	NS
Cerebral stroke	2 (0.9)	3 (1.4)	NS
After RBCT[e] ($N = 215$)	2 (0.9)	3 (1.3)	NS
Acute kidney injury	38 (17.7)	56 (26.1)	<0.05
After RBCT[e] ($N = 209$)	35 (16.7)	52 (24.8)	<0.05
Nosocomial infections	14 (6.5)	34 (15.9)	<0.05
After RBCT[e] ($N = 208$)	14 (6.7)	27 (12.9)	<0.05
Septic shock or sepsis	24 (11.2)	30 (14)	NS
After RBCT[e] ($N = 192$)	22 (11.4)	23 (11.9)	NS
Hypoxemia	32 (14.9)	33 (15.4)	NS
After RBCT[e] ($N = 198$)	29 (14.6)	20 (10.1)	NS
ICU re-admission	4 (1.9)	16 (7.4)	<0.05
Length ICU stay (days)	4 [3, 7]	5 [3, 9]	<0.05

[a] The lower hemoglobin level over the intensive care unit (ICU) stay in non-transfused anemic patients or the pre-transfusion hemoglobin in anemic transfused patients

[b] *CAD* coronary artery disease, *CHF* congestive heart failure

[c] The worst values obtained within a 12-h period before RBCT

[d] *COPD* chronic obstructive pulmonary disease

[e] Only paired-matched patients ($N =$) in whom the outcome variable occurred after red blood cell transfusion (RBCT) were considered. Quantitative variables are expressed as a median [interquartile range]. Qualitative variables are expressed as a incidence (percentage)

measured within a 12-h period before RBCT, were similar in both groups (Table 1).

TAPs were given two [1, 3] units of leukoreduced packed red blood cells, and most of them were transfused on the 2nd [1, 4] day of their ICU stay. For NTAPs, hemoglobin levels reach a nadir on the 4th day [3, 5] of their ICU stay. Interestingly, both groups showed an almost identical nadir hemoglobin level on the 2nd day of evolution [NTAP 84.1 (80, 89) g/l vs. TAP 83.3 (80, 88) g/l], when most TPAs received RBCT.

Table 2 Matching, baseline and outcome variables for non-transfused and transfused anemic patients with pre-transfusion hemoglobin level ≤80 g/l (see caption for Table 1 for details)

Variables	Non-transfused anemic patients $N = 68$	Transfused anemic patients $N = 68$	P value
Matching variables			
Nadir hemoglobin level (g/dl)[a]	77 [73, 80]	77.2 [73, 90]	NS
APACHE II	14 [9, 20]	14 [9, 19]	NS
SOFA	3 [2, 5]	3 [1, 5]	
Age (years)	64 [49, 72]	63 [52, 74]	NS
Diagnostic group at admission at ICU			
General surgery	31 (45.6)	31 (45.6)	
Cardiac surgery	9 (13.2)	9 (13.2)	
Medical	14 (20.6)	14 (20.6)	
Sepsis/septic Shock	10 (14.7)	10 (14.7)	
ACD or CHF[b]	4 (5.9)	4 (5.9)	
Other variables at the time of matching			
pH[c]	7.33 [7.28, 7.37]	7.36 [7.30, 7.38]	NS
Base excess[c]	−1 [−4, 0.7]	0 [−2.4, 2.5]	NS
Patients receiving RBCT before the ICU admission.	6 (8.8)	4 (5.8)	NS
Patients receiving RBCT after discharge from the ICU	8 (11.7)	7 (10.2)	NS
Baseline variables at admission			
Hemoglobin level (g/l)	93.8 [83, 107]	93.2 [83, 104]	NS
Mechanical ventilation	48 (70.5)	50 (73.5)	NS
Gender (male)	43 (63.2)	44 (64.7)	NS
Diabetes mellitus	15 (22.0)	20 (29.4)	NS
Obesity	10 (15.6)	12 (17.6)	NS
Coronary artery disease	19 (27.9)	21 (30.8)	NS
Arterial hypertension	28 (41.1)	29 (42.6)	NS
COPD[d]	12 (17.6)	9 (13.2)	NS
Chronic renal failure	7 (10.2)	9 (13.2)	NS
Dyslipidemia	14 (20.5)	18 (26.4)	NS
Cancer	18 (26.4)	22 (32.3)	NS
Outcome variables			
ICU mortality	9 (13.2)	11 (16.1)	NS
Hospital mortality	11 (16.1)	15 (22.0)	NS
1-year follow-up mortality	19 (27.9)	20 (29.4)	NS
2-year follow-up mortality	23 (33.8)	24 (35.2)	NS
Cardiologic event	5 (7.3)	3 (4.4)	NS
After RBCT[e] ($N = 68$)	5 (7.3)	3 (4.4)	NS
Cerebral stroke	0 (0)	2 (2.9)	NS
After RBCT[e] ($N = 64$)	0 (0)	1 (1.5)	NS
Acute kidney injury	16 (23.5)	18 (26.4)	NS
After RBCT[e] ($N = 61$)	14 (23)	19 (31.1)	NS
Nosocomial infections	1 (1.4)	9 (13.2)	<0.05
After RBCT[e] ($N = 68$)	1 (1.4)	9 (13.2)	<0.05
Septic shock or sepsis	12 (17.6)	13 (19.1)	NS
After RBCT[e] ($N = 64$)	11 (17.1)	9 (14.0)	NS
Hypoxemia	11 (16.1)	13 (19.1)	NS
After RBCT[e] ($N = 63$)	10 (15.8)	9 (14.2)	NS
ICU re-admission	2 (2.9)	6 (8.8)	NS
Length ICU stay (days)	5 [3, 7]	6 [4, 12]	<0.05

Most patients (317/428; 74.2 %) were admitted to the ICU on mechanical ventilation (Table 1). A total of 182 (42.5 %) of patients were admitted following general, non-cardiac surgery, and 88 [20.6 %] following cardiac surgery. Non-surgical patients composed the remaining 36.9 % (158/428) of ICU admissions.

Crude mortality was evaluated over different follow-up periods. When compared with NTAPS, in-hospital mortality was higher in TAPs, although this difference was no longer significant during the follow-up (Table 1). Similarly, TAPs also had higher rates of nosocomial infections and new onset of acute kidney injury, both over the entire length of ICU stay and when considering only the period after RBCT (Table 1). Finally, the length of the ICU stay and the rate of readmission were also higher in TAPs.

Given that the NTAPs with more severe anemia (Hb ≤ 80 g/l) might have worse clinical results than the matched TAPs, the whole analysis was repeated for these subgroups of patients (68 pairs), but the results were not significantly different from those obtained with the global sample (Table 2).

Table 3 Matching, baseline and outcome variables for non-transfused and transfused anemic patients presenting with cardiac disease (see caption of Table 1 for details)

Variables	Non-transfused anemic patients $N = 63$	Transfused anemic patients $N = 63$	P value
Matching variables			
Nadir hemoglobin level (g/dl)[a]	85 [83, 89]	86 [82, 89]	NS
APACHE II	12 [8, 16]	12 [9, 15]	NS
SOFA	3 [2, 5]	3 [2, 6]	NS
Age (years)	66 [58, 73]	66 [58, 74]	NS
Other variables at the time of matching			
pH[c]	7.34 [7.28, 7.38]	7.35 [7.30, 7.37]	NS
Base excess[c]	0.5 [−3, 0.6]	0 [−2.3, 2.5]	NS
Patients receiving RBCT before the ICU admission.	7 (11.1)	6 (9)	NS
Patients receiving RBCT after discharge from the ICU	8 (12.6)	8 (12.6)	NS
Other baseline variables at admission			
Hemoglobin level (g/l)	98 [90, 104]	94 [88, 104]	NS
Mechanical ventilation	59 (93.6)	55 (87.3)	NS
Gender (male)	32 (50.7)	34 (54)	NS
Diabetes mellitus	17 (26.9)	24 (38)	NS
Obesity	11 (17.4)	8 (12.7)	NS
Arterial hypertension	37 (58.7)	36 (57.1)	NS
COPD[d]	8 (12.7)	4 (6.3)	NS
Chronic renal failure	8 (12.6)	6 (9.5)	NS
Dyslipidemia	22 (34.9)	31 (49.2)	NS
Cancer	5 (7.9)	4 (6.3)	NS
Outcome variables			
ICU mortality	2 (3.2)	8 (12.7)	<0.05
Hospital mortality	5 (7.9)	10 (15.9)	NS
1-year follow-up mortality	9 (14.2)	10 (15.9)	NS
2-year follow-up mortality	9 (14.2)	10 (15.9)	NS
Cardiologic event	5 (7.9)	3 (4.8)	NS
After RBCT[e] ($N = 62$)	5 (8.1)	3 (4.8)	NS
Cerebral stroke	1 (1.6)	1 (1.6)	NS
After RBCT[e] ($N = 63$)	1 (1.6)	1 (1.6)	NS
Acute kidney injury	10 (15.9)	16 (25.4)	NS
After RBCT[e] ($N = 58$)	10 (17.2)	12 (20.6)	NS
Nosocomial infections	1 (1.6)	3 (4.8)	NS
After RBCT[e] ($N = 61$)	1 (1.6)	1 (1.6)	NS
Septic shock or sepsis	1 (1.6)	2 (3.2)	NS
After RBCT[e] ($N = 62$)	1 (1.6)	1 (1.6)	NS
Hypoxemia	10 (15.9)	9 (14.2)	NS
After RBCT[e] ($N = 59$)	9 (15.3)	6 (10.1)	NS
ICU re-admission	1 (1.5)	2 (4.4)	NS
Length ICU stay (days)	4 [3, 5]	4 [3, 6]	NS

To rule out the possibility that having heart illness influences the results in the NTAPs, data from TAPs and NTAPs who were admitted to the ICU with diagnoses of coronary artery disease or after cardiac surgery (63 pairs) were separately analyzed. Once again, the results were not significantly different from those obtained with the global sample (Table 3).

Discussion

We compared the clinical outcomes of two populations of non-bleeding, moderately anemic critically ill patients fulfilling five matching criteria, which included two severity scores, nadir hemoglobin level, admitting diagnosis, and age. The first group consisted of patients exposed to anemia risks throughout their ICU stay (NTAPs). The second group comprised transfused patients who were, at least theoretically, less exposed to anemia risks, but exposed to RBCT risks (TAPs). Our results suggest that for non-bleeding, moderately anemic critically ill patients, RBCT does not confer any advantage in terms of reduced mortality and morbidity. Moreover, TAPs had poorer clinical outcomes than matched NTAPs, thus suggesting the potential adverse effects of RBCT.

Current clinical guidelines suggest that transfusion decisions should be influenced by data suggestive of tissue hypoxia and not solely by a pre-fixed cutoff hemoglobin value [3, 4]. Data on tissue hypoxia can be obtained from hemodynamic parameters, pulse oxymetry, lactate, and mixed venous oxygen saturation. In everyday practice, the vast majority of intensivists rarely measure

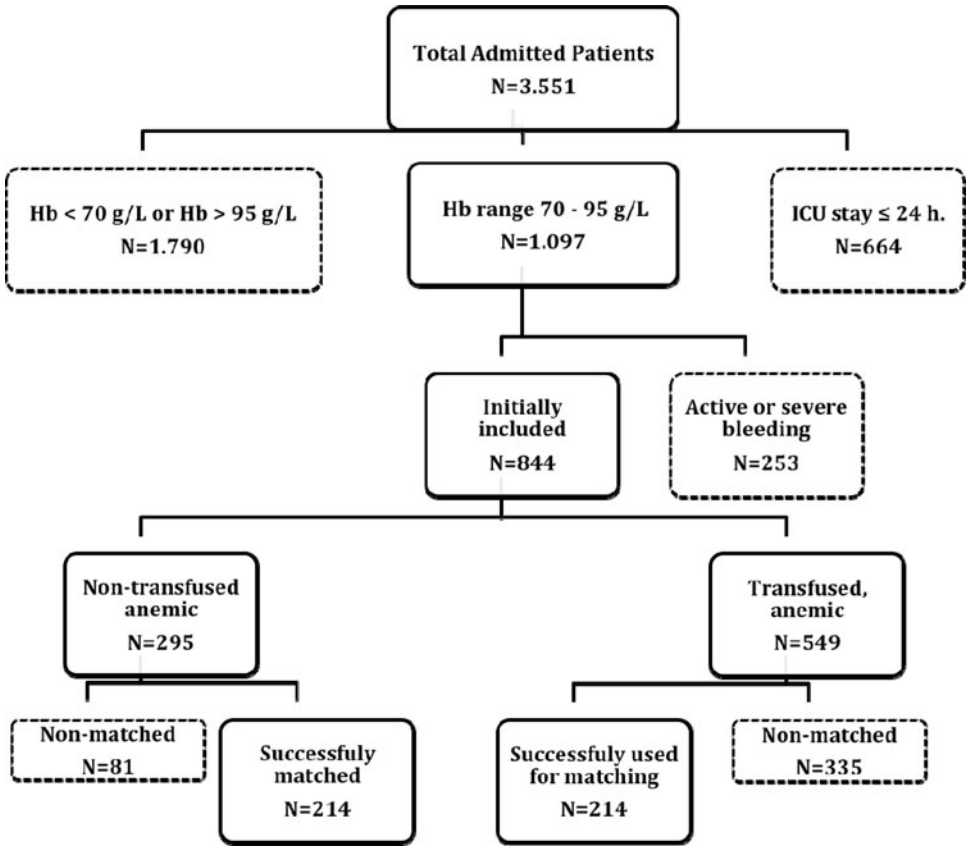

Fig. 1 Flow diagram of the matching process. A total of 214 pairs of moderately anemic patients were successfully matched. *N* number of patients

these variables prior to prescribing a RBCT, and prospective observational surveys on blood use at the ICU reveal that 'a low hemoglobin level' is by far the most commonly reported reason for RBCT [1–4, 20].

However, the critical hemoglobin level that is considered harmful for patients and triggers RBCT varies widely among hospitals, disciplines, and physicians, leading to a great variability in RBCT practice [12–15]. Recently, an international multidisciplinary panel of experts reviewed the appropriateness of RBCTs in moderately anemic, non-bleeding patients and rated most indications (90 %) as inappropriate or uncertain [21], thus confirming our recent observations [14].

In addition, a hemoglobin level increment, as opposed to an oxygen utilization improvement, is generally regarded as RBCTsuccess. It is obvious that RBCTs may be life-saving in the context of acute anemia or severe bleeding [6–8], but there is little evidence of a benefit for non-bleeding medical or surgical patients with moderate anemia (Hb $>$ 70 g/l) [1, 2, 15, 17], who actually receive a high percentage of all RBCTs [11, 17, 22, 23]. In fact, the available evidence suggests that the benefits of RBCT in these patient populations do not outweigh the risks [16, 17, 24].

We assessed the effects of anemia and RBCT in patients from five diagnostic groups. Classically, cardiac function has been thought to dictate the patient's ability to tolerate anemia. However, a recent RCT documented that octogenarian patients who had either a history of or risk factors for cardiovascular disease, and whose hemoglobin level was below 100 g/dl after hip-fracture surgery, did not benefit from RBCT [23]. In cardiac surgery, recent guidelines suggest that postoperative RBCT is reasonable in most patients whose hemoglobin level is less than 70 g/l [8]. RBCT in low-risk cardiac surgery patients without complications may lead to increased rates of postoperative complications [3, 13, 14, 22]. Our data seem to corroborate these conclusions, as significantly longer length of ICU stay and higher rates of nosocomial infections, acute renal failure, and readmission to the ICU were observed in TAPs when compared with paired NTAPs (Table 1). The reasons why RBCT does not benefit these patients remain largely elusive, although they might include a decrease in cardiac output because of the increase in blood viscosity, the absence of acute anemia or severe bleeding, supply-independent oxygen consumption [25], and reduced ability of stored RBCs to upload oxygen [26].

The concept of blood transfusion is continuously evolving, from being part of the solution to being part of the problem. Two observational, multicenter studies, which included patients admitted to 198 European ICUs and were conducted 6 years apart, showed that the

percentage of transfused patients was close to 35 % and did not vary greatly over the time [1, 27]. These data strongly suggest that the well-documented association between RBCT and poorer clinical outcomes has not significantly influenced transfusion practices. Therefore, appropriate training, education, and awareness are needed to improve decisions on RBCT, thus limiting the exposure to RBCT and RBCT-related risks.

Finally, it is worth noting that our study has limitations and strengths. Among its several limitations, the possible selection bias that may have occurred when comparing TAP versus NTAP could be the most important one. The need for RBCT might have selected a group of individuals at greater risk for adverse outcomes, and TAP could have been perceived as being sicker than NTAPS. Although TAP and NTAP presented the same nadir hemoglobin level at different days over their evolution (2nd vs. 4th day, respectively), the time course of daily hemoglobin concentrations was similar (at admission and the 2nd day) in both groups. These data are in agreement with a study including non-bleeding ICU patients that clearly showed that hemoglobin levels typically decline by >5 g/l/day during the first 2 days of the ICU stay [28]. However, as we compared two carefully matched populations of moderately anemic, non-bleeding patients, the risk for selection bias was greatly diminished, although not completely excluded. In this regard, it is important to stress that enormous variability in intra- and inter-center transfusion practices exits [12–15]. It is therefore conceivable that in our study this variability, rather than patient's severity (as assessed by APACHE and SOFA scores), was responsible for giving RBCT or not to patients with similar clinical characteristics.

Among the strengths, both the study design and the study population should be quoted. Matching ensured that both groups were similar in terms of severity, admission diagnosis, and nadir hemoglobin, which are the most important confounding variables. Moreover, this research focused on non-bleeding, moderately anemic patients, a critically ill population that consumes a significant percentage of all transfusion resources without clear evidence of benefit. But, above all, our patient management database (GESTUCI) enabled us for documenting a temporal relation between RBCT and clinical outcome.

Conclusions

The results of this study suggest that using RBCT to increase Hb concentration in an attempt to improve tissue oxygen delivery in critically ill patients with moderate anemia is not associated with a clear clinical benefit and could result in adverse effects. Therefore, our data add to the evidence provided by the TRICC trial [29] and seem to further support the use of restrictive transfusion protocols in critically ill patients, including those with cardiovascular diseases.

Further research is needed to determine the role of RBCT in non-bleeding, moderately anemic patients. Meanwhile, prescribing RBCT to this patient population to merely increase hemoglobin levels should be strongly discouraged.

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