Submitted April 2020; Accepted October 2020

ORIGINAL ARTICLE

Physiological nonutility of red blood cell transfusion in acute hypoxaemic respiratory failure

B. Gupta, D. Jamieson, R. Sonti

Medstar Georgetown University Hospital, Division of Pulmonary, Critical Care and Sleep Medicine, Washington DC, USA

Correspondence

R. Sonti - rajiv.sonti@gunet.georgetown.edu

Keywords - **RBC transfusion, TRALI, hypoxaemic respiratory failure, critical care**

Abstract

Purpose: Transfusing red blood cells (RBCs) in non-bleeding critically ill patients once the haemoglobin meets a certain threshold is the standard of care, despite the lack of robust data suggesting improved outcomes with this practice. Our aim was to critically examine if there are discernible physiological benefits to RBC transfusion in patients with respiratory failure, individuals who are susceptible to transfusion-related adverse events.

Materials and methods: This is a single-centre, cross-sectional study including mechanically ventilated adults who were not bleeding and underwent an isolated RBC transfusion for a haemoglobin level of <7 g/dl identified on a routine blood draw. We recorded vital signs and variables related to organ function (gas exchange, laboratory data and severity of illness) in the six hours pre- and post-transfusion that might plausibly benefit from the transfusion.

Results: Seventy-four patients met the inclusion criteria. There were no improvements in vital signs, laboratory data, vasopressor requirements and overall illness severity after RBC transfusion. Gas exchange as measured by the PaO2/FiO2 ratio, however, worsened (pre-transfusion 233±106, post-transfusion 199±92; p=0.01), an association which held after multivariate adjustment in the two time periods.

Conclusions: We found no change in common physiological parameters after RBC transfusion in patients intubated for hypoxaemic respiratory failure. In fact, the PaO_2/FiO_2 ratio worsened slightly. This might be related to an adverse effect of the transfusion, perhaps mediated by a volume effect or direct lung injury. These data provide preliminary rationale of the nonutility of RBC transfusion based purely on an arbitrary haemoglobin threshold in this patient population.

Introduction

Transfusion of red blood cells (RBCs) is common practice in non-bleeding critically ill patients, despite the surprising sparsity of supportive evidence. In the intensive care unit (ICU), 44% of patients receive an RBC transfusion, 76% of which are not for acute blood loss.[1] There is undoubtedly a sound physiological rationale for RBC transfusion: it increases arterial oxygen content and, in turn, its delivery to organs.[2] The translation of this principle toward improved clinical outcomes, however, has not been definitively shown in individuals who are not bleeding.[3,4] In fact, much of the literature in this area suggests equivalent or improved outcomes by restricting RBC use. In 1999, a landmark trial demonstrated a strong trend toward decreased in-hospital mortality in ICU patients by restricting RBC transfusions,[5] thereby establishing the paradigm for transfusing at a haemoglobin level of 7 g/dl among euvolaemic ICU patients. This was later supported by similar findings in sepsis and other disease states.[6,7]

The clinical benefit of lower haemoglobin targets may be related to the many known downsides to RBC transfusion, including volume loading,[8] the development of lung injury,[9] and a general mild immunosuppressive effect.[10] Independent of specific adverse effects, transfused RBCs are less effective than native ones at oxygen delivery due to physiological changes accrued during procurement and storage (termed 'RBC storage lesion').[11] Examples are substantially reduced levels of 2,3-diphosphoglycerate as well as RBC membrane damage, which impair tissue oxygen unloading and disrupt microvascular flow, respectively.[11,12] Additionally, restrictive transfusion is likely well tolerated due to the many adaptive responses to anaemia: favourable alterations in blood flow patterns[13] along with increased stroke volume,[14] and oxygen extraction maintain tissue oxygenation.

Other than a universal haemoglobin cut-off, clinicians generally do not consider the baseline haemoglobin level, the severity of the clinical course, or the individual specific risk of transfusion in deciding to transfuse. This is because biomarkers (other than the haemoglobin level) to guide transfusion decisions have not been well established.[6] Therefore, our aim was to critically examine if there are discernible macro-physiological benefits to RBC transfusion in ICU patients with hypoxaemic respiratory failure, a group who may be particularly prone to adverse transfusion-related events.[9] We evaluated respiratory and circulatory function in a way commonly used by clinicians (vital signs, ventilator parameters, basic laboratory data, vasoactive drug doses), rather than more obscure biomarkers of oxygen delivery or tissue perfusion in order to provide practical information for clinicians.

Material and methods

Patients

This is a cross-sectional study from the medical intensive care unit (ICU) at Medstar Georgetown University Hospital, USA, from July 2018 to January 2020. All admitted patients are included into a prospectively maintained registry in which past medical history, admitting diagnosis and variables pertinent to their ICU course are recorded. We included patients who required invasive mechanical ventilation for acute hypoxaemic respiratory failure and received an RBC transfusion on the basis of a complete blood count test, drawn in routine fashion in the morning, showing the haemoglobin value to be ≤7.0 g/ dl. This represents the standard of care. We only considered each individual's first RBC transfusion after intubation.

Excluded were patients who experienced overt bleeding during their ICU stay (of any severity), suffered from a myocardial infarction, underwent surgery during the hospitalisation, had a primary bone marrow disorder or inherited anaemia syndrome (such as sickle-cell disease), received multiple simultaneous blood products or for whom arterial blood gas data were not available during the study period. Laboratory data and documentation were extensively reviewed to ensure these transfusions were not performed as a result of bleeding.

Data

We recorded patient level variables plausibly affected by the receipt of an RBC transfusion in the six hours before and after patients were transfused. These included vital signs (heart rate, mean arterial pressure, respiratory rate, oxygen saturation, fluid balance and presence or absence of fever); indices of organ function (lactate, creatinine, vasopressor doses); ventilator and arterial blood gas data (FiO_2, PEEP, pH, pCO_2, PaO_2 / FiO_2 ratio) along with severity of illness as estimated by the Sequential Organ Failure Assessment (SOFA score).[15] Our institution generally sequentially uses norepinephrine, vasopressin (in a non-titratable fashion) followed by phenylephrine (rather than epinephrine) as a third vasopressor.

Vital signs, fluid balance and vasopressor doses are measured hourly, so we recorded mean values in each six-hour period (before and after). Similarly, we recorded mean values of laboratory or arterial blood gas data if multiple measurements were made during the study period. We settled on a six-hour timeframe to balance two competing principles: a period long enough to capture any potential impact of the RBC transfusion on common physiological parameters, but short enough that observed changes could reasonably be attributed to the RBC transfusion as much as possible, isolated from progression of the underlying disease or other interventions. For the SOFA score, however, we used the worst values of each component in the 12 hours before and after transfusion since certain components of the score are measured infrequently enough such that calculating it over a six-hour time period was impractical.

Analysis

Summary statistics describe the frequency and mean or median of each categorical and continuous variable, respectively. Patients act as their own control: the intervention is the RBC transfusion, the 'control' period is the six hours beforehand and 'study' period the six hours afterwards. Therefore, we conducted a matched pair analysis. McNemar's test was used for paired categorical data; a paired t-test and the Wilcoxon signed-rank test were used for parametric and nonparametric continuous data, respectively. We formally tested for normality with the Shapiro-Wilk method.

To account for the dynamic nature of critically ill ICU patients, we adjusted statistically significant relationships for changes in severity of illness (SOFA score) along with other relevant covariates between time periods. To do so, we used the difference between the two measurements as the dependent variable in a linear regression model (with the difference in covariates in both time periods as independent variables). Given this is a hypothesis generating clinical inquiry rather than a pilot experimental trial, we elected not to control for familywise error rate associated with multiple comparisons. The analysis was performed with JMP15 Pro (SAS Institute, Cary, NC, USA). The study was approved by the Institutional Review Board of Medstar Georgetown University Hospital.

Results

Cohort characteristics

Seventy-four patients met the inclusion criteria *(table 1)*. The causes of hypoxaemic respiratory failure in these individuals (as determined by the admitting intensivist) were: pneumonia (58, 78.3%), pulmonary oedema (6, 8.1%) and other/equivocal (10, 13.5%), including pulmonary embolism and acute pulmonary

Table 1. Baseline characteristics

	N=74
Age (years); mean ± SD	62.8±14.2
Female, n (%)	31 (42)
BMI; median (IQR)	28 (24-33)
Morbid obesity (BMI >40); n (%)	10 (14)
Comorbidities, n (%):	
Cirrhosis	18 (24.3)
Chronic kidney disease	12 (16)
Oxygen dependent lung disease	6 (8.1)
Cancer:	
- Solid	14 (18.9)
- Haematological	2 (2.7)
Systolic heart failure	4 (5.4)
Organ transplant	4 (5.4)
HIV/AIDS	2 (2.7)
SOFA Score (on ICU admission); median (IQR)	7 (5-9)
PaO2 / FiO2 ratio immediately post-intubation; mean ± SD	242±110
Days between intubation and RBC transfusion; median (IQR)	2 (1-6)
Haemoglobin level (g/dl); mean ± SD:	
Pre-transfusion	6.7±0.4
Post-transfusion	7.8±0.8

infiltrates of undetermined cause. Fifty-seven (77%) were weaned from mechanical ventilation, 10 (13.5%) underwent tracheostomy prior to discharge to long-term acute care, and seven (9.5%) were transitioned to comfort measures. Fourteen (18.9%) needed renal replacement therapy, 47 (63.5%) required sustained vasopressor use (>3 hours), and 12 (16.2%) required paralysis for hypoxaemia at some point during their stay. The median ICU length of stay was nine days (IQR 5-13).

Transfusions

The RBC transfusion occurred a median of two days after intubation (IQR 1-6). While the number of RBC transfusions during the ICU stay had a median of three (1-4) per patient, all data were collected for only the first transfusion after intubation.

Organ function before and after RBC transfusion

There was no improvement in vital signs, indices of organ function, vasopressor requirement and overall illness severity after RBC transfusion (*table 2*). PaO_2/FiO_2 ratio, however, worsened after transfusion (pre-transfusion 233±106, post-transfusion 199±92; p=0.01) despite no change in FiO2 or PEEP during these time periods (*table 2*). We generated a linear model of the change in PaO_2/FiO_2 ratio post-transfusion using variables plausibly related to an improvement or worsening in oxygenation in the two time periods (FiO_2, PEEP, fluid balance, SOFA score). The relationship held with multivariate adjustment: unadjusted difference -24±52; adjusted difference -21±57 (p=0.01). None of the included covariates contributed significantly to predicting PaO_2/FiO_2 ratio post-RBC transfusion. Notably, the SOFA score (of which PaO_2/FiO_2 ratio is a component) was unchanged post-transfusion.

Analysis based on the presenting diagnosis is limited by small numbers of patients without pneumonia. However, in those 16 individuals, there remains a trend toward worsening PaO_2/FiO_2 ratio (adjusted difference -32±35, p=0.10) with no other statistically significant relationship. For those with pneumonia (n=58), the adjusted difference in PaO_2/FiO_2 ratio was -23±54, p=0.02).

Discussion

In clinical practice, the decision to transfuse a non-bleeding patient is based on a haemoglobin threshold (usually 7 g/dl) and the 'success' of that intervention is measured by the improvement in the haemoglobin level. Generally, other physiologic biomarkers related to anemia besides haemoglobin are not tracked before and after transfusion. We analysed continuously monitored physiological parameters in a cohort of non-bleeding ICU patients with respiratory failure and found no changes in the several hours after RBC transfusion, except the PaO_2/FiO_2 ratio which worsened slightly.

The transfusions performed in these individuals met the current standard of care,[16] and ostensibly the purpose was to improve tissue oxygen uptake (VO_2). Transfusion increases VO_2 if oxygen delivery (DO_2) is inadequate: termed VO_2/DO_2 dependency[17] or 'pathological coupling.' In health, the critical haemoglobin level at which this occurs with preserved cardiac output is ~4 g/dl.[2] Granted, this is likely not the case in critically ill individuals. But, we presume that if the transfusions in our studied population mitigated VO_2/DO_2 dependency (whose mean pre-transfusion haemoglobin was 6.7 g/dl) there would have been an appreciable change in haemodynamics or commonly tracked measures of organ function, none of which were observed. Regardless, improvement in haemoglobin as the sole indicator of the success of RBC transfusion is inconsistent with the scrutiny applied toward other ICU interventions. For example, after administering antibiotics or changing ventilator settings, several patient-level parameters are closely tracked by clinicians. These include variables related to the macro-physiological impact on the patient (e.g. vital signs and laboratory indices of organ function) for which the original intervention would be re-considered if favourable changes were not observed. Biomarkers that are more specific than haemoglobin in indicating

Table 2. Patient features pre- and post-transfusion

	Pre-transfusion	Post-transfusion	P
Vital signs			
HR; mean ±SD	84±17	85±17	0.91
MAP (mmHg), median (IQR)	73 (67-81)	75 (65-82)	0.09
Respiratory rate, mean ±SD	21±5	22±6	0.15
Urine output (ml/h), median (IQR)	38 (7-80)	30 (3-70)	0.29
Net fluid balance (ml/h), median (IQR)	4 (-39-35)	10 (-38-46)	0.08
Fever (presence), n (%)	12 (16)	10 (14)	0.35
Ventilator / respiratory parameters			
pH, mean ±SD	7.38±0.07	7.40±0.07	0.20
PCO2, mean ±SD	38 (35-45)	37 (33-41)	0.14
FiO2, median (IQR)	60 (50-70)	60 (50-70)	0.29
PEEP (cm H20), median (IQR)	10 (8-12)	10 (8-12)	0.47
PaO2 / FiO2 ratio, mean ±SD	233±106	199±92	0.01
Laboratory data			
Creatinine (mg/dl), mean ±SD	1.8 (1-2.5)	1.8 (0.9-3)	0.61
Lactate (mg/dl), mean ±SD	1.6 (0.8-2.9)	1.6 (1-2.1)	0.59
Other			
SOFA score, median (IQR)	8 (5-12)	8 (5-13)	0.38
Norepinephrine (µg/min), mean ±SD	6±9	5±7	0.81
Phenylephrine (µg/min), mean ±SD	20±44	23±53	0.68
Vasopressin (y/n) [n (%)]	13 (18)	14 (19)	0.36

Showing mean values in the 6 hours before and after red blood cell transfusion, with the exception of SOFA score which was calculated in the 12 hours pre- and post-transfusion period

clinically relevant anaemia have been examined, but mostly in surgical populations with capacity for haemodynamic monitoring via pulmonary artery catheters. For example, one study of cardiovascular surgical patients found pre-transfusion haemoglobin *unrelated* to the ultimate change in VO_2 after RBC transfusion, while pre-transfusion oxygen extraction (O_2ER) index (as measured with the mixed venous and arterial oxygen saturation) was.[18] This finding was corroborated by another study of a population of anaemic individuals undergoing cardiac surgery, in which O_2ER was 'stressed' (greater than 30%) in only 44% of patients who were transfused, leading to a post-transfusion O_2ER that was unchanged.[19] In a medical ICU population such as ours, further study is needed to determine what variables (whether central venous oxygenation, invasive or noninvasive measures of cardiac output or estimates of peripheral tissue oxygenation) in addition to haemoglobin should be followed before and after transfusion, over what time period, which patients are poised to respond to transfusion, and what the precise definition of a 'positive' response is.

We observed the post-transfusion PaO_2/FiO_2 ratio to worsen slightly. Since this was the only statistically significant relationship, it may be artefactual due to multiple comparisons. Additionally, the clinical impact is uncertain, given that the SOFA score (which requires PaO_2/FiO_2 ratio for its calculation) and other metrics of circulatory function were unchanged. However, RBC transfusions are a known risk factor for the development of lung injury mediated via both volume overload and inflammation,[8] particularly in critically ill mechanically ventilated individuals.[9] In fact, in the landmark trial establishing the ICU paradigm of 'restrictive' transfusions, patients randomised to the 'liberal' arm (haemoglobin target of 10) were more likely to develop ARDS.[1,20] Specific risk factors for transfusion-related acute lung injury (TRALI) remain uncertain and are likely an interplay of patient-level features, therapeutics (including the type of resuscitative fluid used) and the blood itself.[21-23]

Several caveats are worth mentioning. For one, the time period studied was only six hours. Given the dynamic nature of ICU patients, we settled on this time frame to isolate the impact of the RBC transfusion from other interventions and the natural history of the patient's clinical course. This misses potential long-term benefits of the transfusion; however, previous studies have generally suggested a neutral or detrimental effect[5-7] in non-bleeding individuals. Secondly, haemodynamic or direct microcirculatory monitoring to provide data about changes in venous oxygen saturation, cardiac output or tissue oxygenation was lacking; but, this reflects the modern care of most medical ICU patients. Additionally, our goal was to measure respiratory and circulatory parameters normally tracked by clinicians in the care of critically ill patients, not surrogate markers of unclear macro-physiological significance. Lastly, our population is limited to those intubated for respiratory failure derived from one institution, and findings would need to be corroborated.

Conclusions

Adherence to guideline-suggested transfusion practices in non-bleeding individuals intubated for hypoxaemic respiratory failure has little to no short-term easily identifiable physiological impact. We believe this provides preliminary rationale for trialling further restriction or individualisation of RBC transfusions.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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