Safety and Feasibility of Ultra-Restrictive Transfusion Protocol as a Blood-Preservation Strategy During Shortage Crises

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ABSTRACT

BACKGROUND: We hypothesized that implementation of new ultra-restrictive transfusion protocol in adult surgical intensive care units (SICU) was safe and feasible during pandemic-associated shortage crises.

METHODS: Retrospective analysis two months pre- and post-implementation of ultra-restrictive transfusion protocol in March 2020 with hemoglobin cutoff of 6 g/dL (6.5 g/dL if ≥ 65 years old) for patients without COVID, active bleeding, or myocardial ischemia.

RESULTS: We identified 16/93 and 27/168 patients PRE and POST meeting standard transfusion threshold (7 g/dL); within POST, 12 patients met ultra-restrictive cutoffs. There was no significant difference between PRE and POST in the rate of mortality, ischemic complications, or the number of transfusions per patient, however, the overall incidence of transfusion was lower in the POST group (7.1 vs 17.2%, p = 0.02). Patients received a mean (SD) of 4(3.8) and 2.4(1.5) PRBC transfusions pre- and post-implementation. Odds ratio of mortality in POST group was 0.62 (95%CI: 0.08-5.12) adjusted for age, sex, and SOFA score.

CONCLUSIONS: Implementation of an ultra-restrictive transfusion protocol was feasible and effective as a blood-preservation strategy.

KEYWORDS: COVID-19; transfusion; crisis; pandemic; blood products

BACKGROUND

The COVID-19 pandemic presented innumerable, well-documented challenges to healthcare systems including the cancellation of elective surgeries,[1] delayed diagnosis and treatment of patients with malignancy,[2] disruptions in the management of time-sensitive emergencies including myocardial infarction and stroke,[3] and disruptions in the delivery of routine and emergency psychiatric care.[4] With a dramatic rise in hospital admissions secondary to COVID-19 pneumonia and acute respiratory distress syndrome, there was a significant reduction in supply of medical equipment and medications.[5-7] During the first wave of COVID-19 in March 2020, the majority of public health attention and efforts were rightly focused on containment as well as the triage and treatment of patients with active infection. However, we anticipated that other patients with critical illness would also suffer secondary to the increased consumption of scarce resources, including blood products.

Hesitancy among the general population to donate blood early in the pandemic resulted in a significant and sharp decline in the number of donations and available blood products in hospitals across the nation.[8-11] In March 2020, the American Red Cross reported receiving 86,000 fewer blood donations "due to an unprecedented number of blood drive cancellations" and media reports of critical shortages in cities including New York City alarmed intensivists around the world.[12,13] In Rhode Island, a similar increase in mobile blood drive cancellations was attributed to individuals' fear of being in public spaces amid the evolving pandemic.[14] The Rhode Island Blood Center reported that the widespread cancellation of mobile drives resulted in a 50% decrease in the pre-pandemic supply of blood donors and that maintenance of an adequate blood supply would require 100% occupancy of expanded appointment times by individual donors at donation centers.[15] This shortage threatened patients who could require emergency transfusion for traumatic or obstetric hemorrhage as well as those requiring routine blood transfusions for chronic hematologic and oncologic diseases.

Recognizing the importance of maintaining an adequate stockpile of blood products, we joined our colleagues across the country in exploring ways to preserve blood products.[16,17]

In addition to attempting to increase the available supply through hospital-based blood drives, we aimed to curtail the demand by reducing over-utilization of red cell transfusion in the inpatient setting among patients with anemia of critical illness. In March 2020, we implemented an ultra-restrictive protocol by reducing the hemoglobin threshold for transfusion in the surgical intensive care units (SICU) in the setting of a declared state of emergency. We thus aimed to examine the safety and feasibility of the protocol for patients as well as its efficacy in preserving blood products through a proof-of-concept study. We hypothesized that the adoption of an ultra-restrictive transfusion protocol in surgical intensive care units is safe and feasible compared with standard transfusion practices and is effective as a blood-preservation strategy during times of critical shortage.

METHODS

Effective March 20, 2020, our division implemented an ultra-restrictive transfusion protocol by decreasing the transfusion threshold in our SICUs compared to our standard practice threshold of 7 g/dL. We established a new threshold of 6 g/dL for patients younger than 65 years old and 6.5 g/dL for those 65 years old or older. Patients were transfused with 1 unit of PRBC when they met the cutoff. The ultra-restrictive protocol excluded patients who tested positive for SARS-CoV-2, had active bleeding, or who had signs of ongoing myocardial ischemia based on anginal symptoms or electrocardiographic changes. The protocol was adopted along with other measures of an overall blood-preservation strategy including the recommendation to limit routine daily blood draws in accordance with best practices in critical care. Though patients with active hemorrhage were excluded from this analysis of the impact of the ultra-restrictive threshold, an additional aspect of our overall strategy was to review the indications for massive transfusion protocol activation on a case-by-case basis. If activation of the massive transfusion protocol was deemed futile, then blood product resuscitation was planned to be withheld. Fortunately, however, this portion of the protocol remained purely hypothetical and there were no cases where massive transfusion was withheld due to the blood shortage. All physicians providing patient care in the SICU during the study period were notified of the immediate implementation of the ultra-restrictive protocol beginning on March 20th, 2020. The protocol remained continuously active for the duration of the study period.

After constructing the study concept, we obtained an Institutional Review Board approval prior to collecting the data (Lifespan IRB#1610422). The ultra-restrictive protocol was developed urgently in response to impending blood shortage crises facing our intensive care units, and clinical implementation of the protocol preceded the formulation of this associated research hypothesis. Thus, the informed consent requirement was waived for the retrospective review of prospectively collected clinical data. We then proceeded to perform a single-center, retrospective cohort study of all adult patients admitted to surgical intensive care units at Rhode Island Hospital two months before (PRE) and after (POST) implementation of the new protocol. Thus, our sample included critically ill patients admitted to either the general surgical or trauma intensive care unit who received both operative as well as nonoperative management. Though elective surgeries were paused during the majority of the post-implementation study period, there was no difference in surgical practice between groups with respect to intraoperative blood-preservation strategies nor the decision to proceed with urgent or emergency surgery among patients admitted to the intensive care unit.

Our primary outcome was in-hospital mortality. Secondary outcomes included the incidence of packed red blood cells (PRBC) transfusion in our SICUs, the number of transfusions per patient, and the development of ischemic complications, defined as the occurrence of clinically significant acute myocardial, cerebral, mesenteric, or limb ischemia. We used multiple logistic regression to adjust our mortality outcome for age, sex, and Sequential Organ Failure Assessment (SOFA) score to capture patients' overall level of critical illness and organ dysfunction. We also performed a pre-specified analysis of patients who were transfused according to the standard protocol within the PRE group compared with those in the POST group who would have qualified for transfusion based on the standard threshold (7 g/dL) but did not meet the new ultra-restrictive criteria for transfusion. Categorical data were analyzed using Chi-square and reported as frequencies and percentages. Parametric continuous variables were analyzed using Student's t-test. Nonparametric continuous data were analyzed using Wilcoxon-Rank Sum test. These are presented as medians or averages with interquartile range (IQR) or percent as appropriate. All statistical analyses were computed using a commercial statistical software (Stata/SE 14, StataCorp 2015, College Station, TX, USA) and were conducted with a significance level of 0.05.

RESULTS

Our study cohort included 261 patients, of whom 93 were admitted to an SICU before implementation of the protocol (PRE) and 168 were admitted thereafter (POST). Within the PRE group, 16 patients (17.2%) experienced a hemoglobin drop below 7 g/dl and received red cell transfusion per standard protocol. Within the POST group, 27 patients (16.1%) had a hemoglobin drop beneath the standard transfusion threshold. Of these, 12 patients (44.4%) met the ultra-restrictive cutoffs and subsequently received transfusion according to the new protocol. Overall, the percentage of SICU patients who received PRBC transfusion was significantly lower in the POST group (7.1% versus 17.2%, $p = 0.02$), (**Figure 1**).

Among those who met the transfusion cutoff, we observed no statistically significant differences between the two groups with respect to age, sex, medical comorbidities, and SOFA score (**Table 1**). Similarly, there was no significant difference in the ICU length of stay or time-to-transfusion between those pre- and post-implementation of the ultra-restrictive protocol. For the primary outcome, there was no statistically significant difference in the rate of in-hospital mortality between transfused patients within the PRE and POST groups (31.3 vs 25.0%, $p = 1$). Likewise, we observed no significant difference in the rate of ischemic complications (12.5 vs 33.3%, $p = 0.35$) or the number of PRBC units transfused per patient (4.0 vs 2.4, $p = 0.21$) between transfused patients within the PRE and POST groups, respectively. On multiple logistic regression adjusting for age, sex, and SOFA score, the odds ratio for in-hospital mortality within the POST group was 0.62 (95% CI: 0.08 to 5.12).

Figure 1. Flow chart of our cohort of patients Pre- and Post-Protocol of ultra-restrictive transfusion.

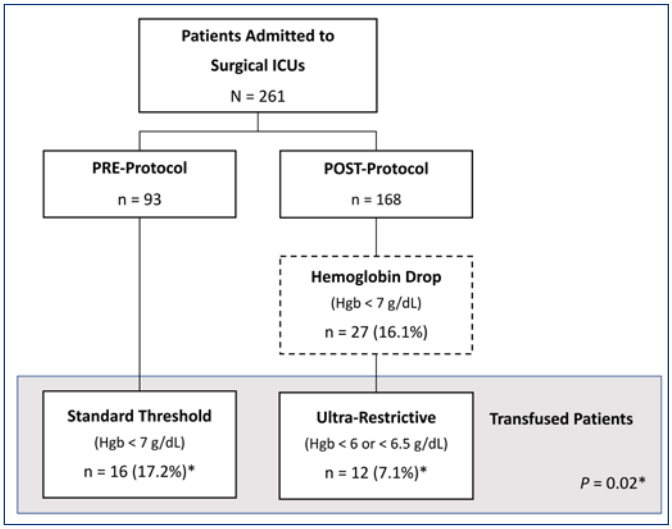

ABB: Hgb: hemoglobin.

Table 1. Comparison of characteristics and outcomes of patients who met transfusion cutoffs Pre- and Post-implementation of ultra-restrictive protocol.

	PRE (n=16)	POST (n=12)	*P* value
Age (years), mean (SD)	64 (14)	69 (18)	0.41
Age ≥ 65 years, n (%)	7 (43.8)	9 (75.0)	0.20
Sex (male), n (%)	8 (50.0)	8 (66.7)	0.46
Trauma admission, n (%)	9 (56.3)	9 (75.0)	0.43
Past Medical History, n (%)			
Liver disease	2 (13.3)	1 (8.3)	1
Chronic kidney disease	3 (18.8)	4 (33.3)	0.42
Hypertension	11 (68.8)	8 (66.7)	1
Coronary artery disease	2 (12.5)	1 (8.3)	1
Atrial Fibrillation	2 (12.5)	3 (25.0)	0.62
Congestive heart failure	2 (12.5)	0 (0)	0.49
Stroke	0 (0)	2 (16.7)	0.18
Chronic anemia	0 (0)	2 (16.7)	0.18
SOFA score, median [IQR]	3 [1, 4]	5 [2, 8]	0.26
ICU LOS (days), median [IQR]	7 [5, 18]	6 [5, 13]	0.67
Hospital LOS (days), median [IQR]	13 [8, 26]	13 [10, 20]	1
In-hospital mortality, n (%)	5 (31.3)	3 (25.0)	1
Ischemic complications, n (%)	2 (12.5)	4 (33.3)	0.35
PRBC transfusions per patient (units), mean (SD)	4.0 (3.8)	2.4 (1.5)	0.21
Time-to-transfusion (days), median [IQR]	2 [1, 4.5]	2.5 [2, 6]	0.27

ABB: ICU: Intensive care unit. LOS: Length of stay. SOFA: Sequential Organ Failure Assessment. PRBC: Packed red blood cells.

Within the POST group, there were 15 patients who were eligible for transfusion based on the standard threshold after experiencing a hemoglobin drop below 7 g/dL but failed to ultimately meet the ultra-restrictive cutoffs implemented during the shortage crisis. Compared with patients transfused according to the standard protocol in the PRE group, these patients were significantly younger (49 vs 63 years old, $p = 0.02$). However, we observed no statistically significant difference in the proportion of patients greater than 65 years old. Though there were no statistically significant differences in other baseline characteristics between these groups (**Table 2**), the "standard-eligible" yet non-transfused patients within the POST group were observed to have a lower rate of trauma and a higher rate of chronic anemia. For outcomes, we observed no significant differences in the rates of in-hospital mortality (13.3 vs 31.3%, $p = 0.39$) or ischemic complications (20.0 vs 12.5%, $p = 0.65$) between the non-transfused patients with hemoglobin drop below 7 g/dL in the POST group and patients transfused for hemoglobin drop below 7 g/dL within the PRE group, respectively. On multiple regression controlling for age, sex, and SOFA score, the adjusted odds for in-hospital mortality among these standard-eligible, non-transfused patients compared to the PRE group was 0.37 (95%CI: 0.05 to 2.95).

Table 2. Comparison of characteristics and outcomes of between patients with hemoglobin drop below 7 g/dL Pre-protocol and those in Post-protocol group with hemoglobin below 7 but did not meet the new ultra-restrictive transfusion cutoff.

	PRE (n=16)	POST (n=15)	*P* value
Age (years), mean (SD)	63 (14)	49 (17)	0.02
Age ≥ 65 years, n (%)	7 (43.8)	3 (20.0)	0.30
Sex (male), n (%)	8 (50.0)	12 (80.0)	0.14
Trauma admission, n (%)	9 (56.3)	4 (26.7)	0.15
Past Medical History, n (%)			
Liver disease	2 (13.3)	1 (6.7)	1
Chronic kidney disease	3 (18.8)	1 (6.7)	0.6
Hypertension	11 (68.8)	6 (40)	0.16
Coronary artery disease	2 (12.5)	2 (13.3)	1
Atrial Fibrillation	2 (12.5)	0 (0)	0.48
Congestive heart failure	2 (12.5)	2 (13.3)	1
Stroke	0 (0)	2 (13.3)	0.23
Chronic anemia	0 (0)	3 (20.0)	0.1
SOFA score, median [IQR]	3 [1, 4]	5 [2, 6]	0.25
ICU LOS (days), median [IQR]	6 [5, 18]	7 [5, 14]	1
Hospital LOS (days), median [IQR]	13 [8, 26]	16 [7, 31]	0.58
In-hospital mortality, n (%)	5 (31.3)	2 (13.3)	0.39
Ischemic complications, n (%)	2 (12.5)	3 (20.0)	0.65

ABB: ICU: Intensive care unit. LOS: Length of stay. SOFA: Sequential Organ Failure Assessment. PRBC: Packed red blood cells.

As noted, we did not observe a statistically significant difference in the mean (SD) number of PRBC units transfused *per patient* between the PRE and POST groups (4.0 (3.8) vs 2.4 (1.5), $p = 0.21$). Importantly, however, implementation of the ultra-restrictive protocol resulted in 15 of 27 eligible patients with hemoglobin drop below 7 g/dL not receiving any red cell transfusions. Considering the number of units transfused per patient prior to the implementation of the ultra-restrictive protocol, we estimated that 60 to 100 units of PRBCs were preserved during the two months of the protocol, reflecting a 55 to 73% reduction in PRBC utilization in our SICUs.

DISCUSSION

In our small, pragmatic, proof-of-concept study of the safety, feasibility, and efficacy of an ultra-restrictive transfusion protocol as a blood-preservation strategy during a pandemic-associated shortage crisis, we found that implementation of a new hemoglobin threshold of 6 g/dL (6.5 g/dL if ≥ 65 years old) for transfusion was feasible and effective in reducing the number of patients undergoing transfusion and overall PRBC utilization when compared with standard practice. Though we failed to observe significant differences in the rates of in-hospital mortality or ischemic complications, our small sample size and low statistical power limit our ability to meaningfully assess the safety of these ultra-restrictive thresholds outside of blood shortage crises.

The potential for critical blood shortage during crises – both natural and man-made – has been previously recognized and observed.[18,19] Disaster experts have attempts to simulate blood-shortage scenarios and model potential interventions to mitigate the imbalance between supply and demand.[20,21] Importantly, however, most models were developed to simulate the effects of short-term disasters, such as a terrorist attack or a natural disaster. These models focused on preemptively boosting hospitals' supply to meet the short-term demand of massive transfusion needs.[22] Often, during such crises, there is actually increased motivation among the public to donate blood. During the COVID-19 pandemic, however, the imbalance also resulted from a sustained and significant decrease in blood supply due to public fear of COVID-19 transmission surrounding blood donation.[8-11,14] At our center, we observed that the demand for blood products remained relatively stable to slightly increased. Considering the limited shelve life of PRBCs, contingency plans to boost supply are not sustainable solutions during extended periods of blood shortage, establishing the need for long-term interventions.[23,24] Investigators in Melbourne, Australia have reported a simulation model for prolonged disasters.[25] Though their model was limited in duration to 21 days, they found that restricting PRBC transfusion resulted in a 28.5% reduction in utilization among patients with nonurgent indications. Our experience showed a higher potential reduction in PRBC utilization (55% to 73%) compared to our routine transfusion practices in the ICU, which comprise the majority of nonurgent transfusions in the inpatient setting. A validation of the actual reduction potential using mathematical modeling, applying our approach, should be performed to accurately predict the potential reduction in a large healthcare system.

Anemia among critically ill patients is common and multifactorial.[26,27] Our results also provide preliminary evidence that suggests that ultra-restrictive transfusion protocols may be safe compared to standard practice in the ICU. Since the landmark TRICC trial in 1999, restrictive transfusion practices were found to be safe and effective compared to liberal practices.[28] This was later confirmed to also be a safe strategy among specific ICU populations, including patients with septic shock and following cardiac surgery.[29-31] Restrictive strategies were associated with decreased exposure to allogenic blood transfusions without an impact on mortality or morbidity.[32] Considering the strong evidence, it became a standard practice to limit nonurgent blood transfusion in the ICU for patients by establishing a hemoglobin threshold of 7 g/dL, although the true threshold for critical anemia remains unknown. Evidence from patients with anemia who refuse blood transfusion demonstrate that an increased mortality rate is observed below a hemoglobin cutoff of 5 g/dL.[33] However, evidence for establishing a hemoglobin threshold for transfusion below 7 g/dL among any patients remains sparse. One study reported using a hematocrit of 20% compared with 25% as an on-pump intraoperative transfusion threshold during coronary artery bypass grafting, thus limiting the generalizability of results to patients not undergoing cardiopulmonary bypass.[34] Additionally, one study implemented a restrictive transfusion protocol with a hemoglobin threshold of 6.4 g/dL among low-risk orthopedic surgery patients under the age of 50 undergoing elective total hip or knee arthroplasty.[35,36] However, their results were pooled across low- (< 50 years old), intermediate- (50 to 70 years old), and high-risk patients (70 years old) with separate transfusion thresholds of 6.4, 7.2, and 8.9 g/dL for each subgroup, respectively. Thus, in the absence of any evidence for transfusion thresholds below 7 g/dL among the critically ill, our ultra-restrictive threshold was determined by consensus agreement within our division. In order to establish a blood-preservation effect while remaining conservative and promoting patient safety, our protocol lowered the threshold to 6.0 g/dL for patients under the age of 65 and 6.5 g/dL for patients ≥ 65 years old. Though this small, single-center evaluation was under-powered to assess the difference in mortality and ischemic complications between groups, our results establish a need to further evaluate our current transfusion practices and consider whether similar ultra-restrictive thresholds may offer benefit, even outside of blood shortage crises. Of course, such validation would require multi-center, prospective evaluation of clinical outcomes

as well as consideration of oxygen delivery and end-organ ischemia seen with lower hemoglobin levels.

Our study is not without significant limitations. First, this protocol was intended to remain active for a brief time during the COVID-19 pandemic during the highest period of resource demand at our institution. As a result, the number of patients who met the ultra-restrictive transfusion cutoff was small, resulting in low to very low statistical power to assess the primary and secondary outcomes. Though the ultra-restrictive protocol has been intermittently reactivated for use during additional periods of critical blood shortage following this study period, we chose to limit the timeframe for our analysis to increase the direct comparability of patient groups in the first days of the pandemic when the greatest strain was seen across the healthcare system. Therefore, the findings that implementation of the new protocol was not associated with increased mortality or ischemic complications must be interpreted cautiously and only for the purpose of hypothesis generation. Additionally, we only included patients that were admitted to either the general surgical or trauma intensive care unit, which further limits the generalizability of our results to other critically ill populations. As a result, we cannot recommend widespread implementation of this protocol at institutions with predominantly non-surgical patients and different admitting diagnoses without further study and adequate validation. Importantly, though our multiple regression model was controlled for age, sex, and SOFA score, the presence of other confounding variables or effect modifiers including baseline hemoglobin cannot be excluded. Furthermore, we did not include an analysis of institution-wide utilization of blood products at our institution. Therefore, we cannot conclude definitively that the reduction in blood product utilization among our intensive care units directly resulted in the improved availability of blood products for other patients in the hospital. Despite these limitations, the results of our study highlight the potential of our transfusion protocol as a blood-preservation strategy during subsequent pandemic-associated shortages and other similar disasters where triage decisions must be made.

CONCLUSION

Our small, pragmatic, proof-of-concept study demonstrated that the implementation an ultra-restrictive transfusion protocol as a blood-preservation strategy during a pandemic-associated shortage crisis was feasible and effective in reducing blood product utilization within the surgical intensive care units at our institution. Though we failed to observe a significant increase in the rate of adverse events, further validation is required to assess the safety of this strategy outside for other patient populations and outside of states of emergency. If our results are validated, an ultra-restrictive transfusion protocol may represent a viable strategy during future shortage crises.

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