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Effects of a restrictive blood transfusion protocol on acute pediatric burn care

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Abstract

Background: Blood transfusion is costly and associated with various medical risks. Studies in critically ill adult and pediatric patients suggest that implementation of more restrictive transfusion protocols based on lower threshold hemoglobin concentrations can be medically and economically

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Declarations

Ethics approval and consent to participate: This retrospective chart and database review was approved by the University of Texas Medical Branch Institutional Review Board and the Shriners Hospitals for Children Office for Clinical Research.

Competing interests: The authors declare that they have no competing interests.

advantageous. The purpose of this study was to evaluate the implications of a hemoglobin threshold change in pediatric burn patients.

Methods: We implemented a change in hemoglobin threshold from 10 to 7 g/dL and compared data from patients before and after this protocol change in a retrospective review. Primary endpoints were hemoglobin concentration at baseline, before transfusion, and after transfusion; amount of blood product administered; and mortality. Secondary endpoints were the incidence of sepsis based on the American Burn Association physiological criteria for sepsis and mean number of septic days per patient. All endpoint analyses were adjusted for relevant clinical covariates via generalized additive models or Cox proportional hazard model. Statistical significance was accepted at $p < 0.05$.

Results: Patient characteristics and baseline hemoglobin concentrations (pre: 13.5 g/dL, post: 13.3 g/dL, $p > 0.05$) were comparable between groups. The group transfused based on the more restrictive hemoglobin threshold had lower hemoglobin concentrations before and after transfusion throughout acute hospitalization, received lower volumes of blood during operations (pre: 1012 mL, post: 824 mL; $p < 0.001$) and on days without surgical procedures (pre: 602 mL, post: 353 mL; $p < 0.001$), and had a lower mortality (pre: 8.0%, post: 3.9%, mortality hazard decline: 0.55 (45%), $p < 0.05$). Both groups had a comparable incidence of physiological sepsis, though the more restrictive threshold group had a lower number of sepsis days per patient.

Conclusions: More restrictive transfusion protocols are safe and efficacious in pediatric burn patients. The associated reduction of transfused blood may lessen medical risks of blood transfusion and lower economic burden.

Study type: retrospective chart review

Level of Evidence: IV

Keywords

blood transfusion; transfusion threshold; pediatric burn injury; intensive care

Background

Transfusion of blood products remains a cornerstone in the successful treatment of anemia in perioperative and critical care settings [1,2]. However, the liberal use of packed red blood cell (pRBC) transfusion has been associated with increased mortality and postoperative morbidity, increasing the receptivity of the critical care community to restrictive transfusion protocols [3–5]. Moreover, blood is a costly and limited resource; in 2013, 13 million units of usable blood were collected and utilized for whole-blood and pRBC transfusions [6]. At an average cost of \$200 or more per unit, almost 3 billion dollars are spent by US hospitals each year on blood alone, without factoring in the additional costs of administering a transfusion [7].

One way to reduce blood product use is to alter the threshold that leads to intervention. The Transfusion Requirements in Critical Care trial [8] and subsequent groundbreaking studies by Hébert et al. [3] and Vincent et al. [4] demonstrated that critically ill patients benefit from a restrictive transfusion strategy (hemoglobin threshold 7 g/dL vs. < 10 g/dL) with

decreased mortality. Further research provided evidence that this restrictive transfusion protocol is associated with fewer cardiac events, re-bleeding episodes, and bacterial infections as well as less pulmonary edema [9–11], while more liberal protocols are linked to an immunosuppressive gene expression pattern, increased infections, and a prolonged hospital stay [12–14]. A randomized prospective trial in severely burned adults indicated the safety of a conservative transfusion protocol as well as a reduction in overall use of blood products in this patient group [15]. While these findings led to widespread adoption of more restrictive protocols, adherence to this practice has been variable, as demonstrated by various prospective and retrospective studies [16–18].

Despite evolving techniques, equipment, and practices over the last decades, excision and grafting procedures after severe burn injury continue to be associated with extensive bleeding and patients frequently require multiple transfusions throughout acute hospitalization [10,12,19]. The large number of transfusions needed, which is unique to burn patients and not seen in other critically ill patients, raises the question of whether lower transfusion thresholds are of benefit to burn patients in general and pediatric burn patients in particular. The purpose of this study was to investigate the adherence of our pediatric burn center to a restrictive transfusion protocol, which was implemented in 2007, and to analyze the clinical and economic consequences by comparing patient cohorts before and after transfusion threshold adjustment.

Methods

Study period and population

The study was reviewed and approved by the University of Texas Medical Branch Institutional Review Board and the Shriners Hospitals for Children Office for Clinical Research. No additional individual patient consent was needed to conduct this review. A retrospective chart and database review of patients admitted to our pediatric burn center during a 20-year period was conducted. All patients under the age of 18 years at the time of admission and admitted between January of 1997 and April of 2017 were considered for this study. We excluded patients who did not have burn injury, as well as those who did have burn injury but did not receive any blood transfusions or had at least one acute burn surgery. Patients were assigned to either the pre-protocol-change group or the post-protocol-change group based on their date of admission. Those admitted January 1, 1997 through December 31, 2003 were considered part of the pre-change group and were transfused based on a hemoglobin threshold of < 10 g/dL. Patients admitted after January 1, 2008 were allocated to the post-change group and were transfused under the more restrictive protocol with a hemoglobin threshold of < 7 g/dL. These dates were determined by examination of the transfusion cutoffs over time with a period of four years allowed for other treatment and epidemiological changes to take effect to prevent contamination of results. Therefore, patients admitted between 2004 and 2008 were excluded from this analysis.

During both time periods, patients were treated according to the standard of burn care at our facility, including resuscitation according to the standardized Galveston formula as previously described as well as early excision and grafting of the burn wound with homo-, auto-, or allograft [20–22]. Transfusions of pRBC during surgical procedures were initiated

at the discretion of the anesthesia team based on actual and estimated blood loss, hemoglobin concentration, and physiological status of the patient. There were no changes in clinical criteria indicating blood transfusion such as hemodynamic variables (blood pressure or heart rate) over the time course of this study. Administration of blood outside of surgical interventions was initiated when measured hemoglobin was below each respective threshold concentration and was directed to a target level above this threshold.

Demographic variables

The following demographic variables were collected from medical records: age, sex, weight, and time post burn. The following injury severity variables were also collected from the medical records: percent total body surface area (TBSA) burned, percent TBSA with 3rd-degree burns, surface area excised during excision and grafting procedures, and incidence of inhalation injury.

Primary and secondary endpoints

The following primary endpoint variables were collected from medical records for statistical analysis: hemoglobin concentration at admission as well as before and after each transfusion (g/dL); volume of pRBC administered on days with surgical procedures (OR) and without operations (non-OR, mL), length of hospitalization, and mortality

The secondary endpoint was the occurrence of sepsis based on the physiological criteria of the American Burn Association (ABA) [23]: heart rate, respiratory rate, temperature, platelet count, glucose, insulin requirements, and stool output. All were retrieved from patient records. Sepsis was defined as meeting at least three of the criteria listed in Table 1 for at least two consecutive days or for one day if the patient expired on the same day. As physiological criteria were used for this definition, no additional documented positive source of infection was used for further modelling.

Statistical analysis

Descriptive summary statistics are presented as means with standard deviations, medians with interquartile ranges, and counts, as appropriate. Totals for each patient spanning the interval from admission to discharge were determined for area grafted and pRBC administered. Differences between pre- and post-change groups were assessed with two sample t-tests for normal variables, non-parametric Wilcoxon Rank Sum test for non-normal variables, and chi-square test for binary variables. The relationships between each outcome and group (pre vs. post) were modeled by generalized additive mixed models (Gaussian family for primary outcomes and binomial for sepsis) including subject as random effect and adjusting for age at burn, sex, percent TBSA burned, percent TBSA with 3rd-degree burns, inhalation injury, time post burn (for hemoglobin concentration and septic status), length of stay, and average body weight during hospital stay (for weight-adjusted total blood administered).

Penalized splines were used to test for significant non-linear relationships between outcomes and time [24]. Interaction between the non-linear effect of time with group was included in the models. Non-linear effects of covariates on the outcomes were also assessed. Bayesian

information criteria and likelihood-ratio tests were used to rule out inclusion of covariates and non-linear relationships. Mortality analysis was performed using a Cox proportional hazard model, adjusting for age, sex, percent TBSA burned, percent TBSA with 3rd-degree burns, inhalation injury, time from burn to admission, and pre- or post-change group [25]. The proportional hazards assumption was verified by scaled Schoenfeld residuals. Statistical analyses were performed using R statistical software (R Core Team, 2015, version 3.3.1, Vienna, Austria). Statistical significance was accepted at $p < 0.05$.

Results

Demographic data and clinical characteristics

A total of 6,715 pediatric patients were admitted between 1997 and 2017. In these patients, mean hemoglobin concentration slowly declined between 2004 and 2008, marking the intermediate period of gradual and incomplete implementation of lower hemoglobin thresholds; patients admitted during this period were excluded from further analysis (Figure 1). A CONSORT flow diagram showing the number of patients initially reviewed for study inclusion and those excluded, along with the reasons for exclusion, is shown in Figure 2. The pre-change group comprised 759 patients and the post-change group 701 patients. Baseline demographic and clinical data are summarized in Table 2. The two groups did not differ regard to age, sex, percent TBSA burned, or percent TBSA with 3rd-degree burns. Length of hospitalization and TBSA grafted were greater in the post- than the pre-change group ($p = 0.007$ and $p < 0.001$, respectively).

Primary endpoints

The initial hemoglobin at admission was 13.5 g/dL in the pre-change group and 13.3 g/dL in the post-change group, with no significant difference between the groups. Daily mean hemoglobin concentrations (Figure 3a) and hemoglobin concentrations before and after each transfusion (Figure 3b) were modelled over time after burn. The models showed that the post-change group had significantly lower hemoglobin concentrations than the pre- group, both before and after pRBC transfusion.

Modelling the total amount of blood transfused per patient (Figure 4) showed that, in the post- group, the amount of blood transfused was reduced on both non-OR days (pre, 602 mL vs. post, 353 mL; $p < 0.001$;) and OR days (pre, 1012 mL vs. post, 824 mL; $p < 0.001$;).

The overall mortality rate was 8.0% (61/759) in the pre-group and 3.9% (27/701) in the post-group; per the Cox proportional hazards model, the hazard of mortality declined by a factor of 0.55 (45%) between the time periods after adjusting for age at burn, percent TBSA burned, inhalation injury, time from burn to admission, and sex ($p = 0.022$).

Secondary endpoints

Physiological sepsis criteria were met at least once during acute burn care in 53.4% of patients in the pre- group and 49.3% of patients in the post- group. The percentage of the acute hospitalization in which patients met sepsis criteria was smaller in the post- than the pre- group (pre, 17.2% vs. post, 13.4%; $p < 0.001$). After adjusting for age, sex, percent

TBSA burned, percent TBSA with 3rd-degree burns, inhalation injury, days post burn, time from burn to admission, and length of stay, we found that the effect of group remained significant ($p < 0.001$). Analysis of the probability of meeting sepsis criteria over time after burn injury revealed that the probability was significantly lower in the post- than pre- group at 5 to 15 days post burn and 20 to 30 days post burn (see Figure, Supplemental Digital Content 1, <http://links.lww.com/TA/B202>).

Missing data There were no missing patient demographics data. For the study period (1997–2017), the sepsis criteria variables and hemoglobin levels were routinely measured and electronically recorded for each patient on a daily basis throughout acute hospitalization period. Transfusion blood volumes were also electronically recorded. The occurrence of missing data in this analysis was rare (<15%) and at random.

Discussion

Here, we show that a conservative transfusion regimen based on a threshold of 7 g/dL hemoglobin can be safely implemented as part of the critical care protocol for severely burned children. We show that this approach is associated with decreased administration of blood products during operations and outside the operating room. Key aspects of acute hospitalization such as probability and duration of sepsis were improved and mortality reduced, while no adverse effects of the more conservative regimen were noted. To date, this is the largest study to show the benefits of conservative blood transfusion in severely burned children.

Several studies in critically ill patients have shown that lowering the hemoglobin threshold for initiating transfusion of blood products decreases the absolute and relative amounts of blood administered [8,18,26–28]. In line with these reports, the volume of blood administered decreased by 25% during debridement and grafting surgeries and by 50% on days without surgical procedures. The smaller relative decrease on operation days could be explained by the fact that the indication for intraoperative blood transfusion is determined not solely by objective hemoglobin measurements, but also by more subjective indications for transfusion such as risk of ongoing hemorrhage and estimation of volume requirements by surgeons and anesthesiologists. This is an important aspect of pediatric burn care and should be considered when designing future studies to further reduce intraoperative transfusion.

In general, reducing the number and volume of blood transfusions has the potential to mitigate risks associated with the administration of blood products. Transmission of both known (i.e., HIV and Hepatitis C virus) and unknown (i.e., Creutzfeld-Jakob prions) pathogens, non-infectious complications (e.g., transfusion-related acute lung injury and allergic, hemolytic, and non-hemolytic transfusion reactions), transfusion-related circulatory overload, and transfusion-related immunomodulation are dependent and proportional to the amount of received transfusions and thus could be reduced [29–32]. While it is reasonable to believe that these risks will be reduced, prospective trials with substantially larger patient cohorts are needed to determine whether these endpoints are affected. Independent of individual patient risk, there is great potential to conserve substantial resources by

implementing a conservative transfusion threshold. Because of exclusion criteria limiting the blood donor pool [33], blood group incomparability, recruiting difficulties, increased regulation, and other factors, the demand for blood products worldwide is persistently higher than the supply. Thus, although the observed reduction in blood product use in this trial is merely associated with the more conservative transfusion threshold, every measure to improve this imbalance is beneficial [34]. Furthermore, substantial financial resources, expressed both in direct and indirect cost of blood transfusion, can be conserved [7].

Infection and sepsis are major contributors to post-burn morbidity and mortality [35]. Some studies in traumatology and burned adults have indicated that the incidence of infection increases following blood transfusion, suggesting that a reduction in transfusion threshold will mitigate this effect [9,12,36]. We implemented ABA criteria for Sepsis [23] to compare the incidence of physiological sepsis between the groups. In agreement with the aforementioned studies, the more conservatively transfused study group had significantly fewer sepsis-positive patient days and a lower probability of sepsis over a substantial portion of the hospitalization; this could be interpreted as an attenuated severity or duration of sepsis in this group. Of note, the ABA criteria are currently being updated based on the model of the Sepsis-3 criteria for non-burned critically ill patients, [37] but these yet-to-be adopted guidelines have not been validated in burn patients at this time. In this study, we modified the ABA criteria, which may have resulted in an underreporting of sepsis: gastric residuals were left out of the model because completeness of the data set could not be assessed retrospectively. Furthermore, patients were marked as sepsis-positive in our model when they displayed the ABA criteria for two consecutive days instead of one. This is a more stringent requirement that allows one to differentiate transient symptoms of burn injury itself from those that persist and are indicative of sepsis. Future research is clearly warranted to confirm actual cases of sepsis from the model predictions.

Here we show that the more conservatively transfused group had lower mortality. This finding is in line with those of several large trials [9,16,30] and has been adjusted for strong possible confounders in a robust statistical model. However, one cannot conclude with absolute certainty that this reduction is completely attributable to the transfusion protocol change. The overall mortality rate during the entire study period is low; it is influenced by multiple clinical parameters and may be driven, in part, by other treatment advancements over time. In particular, crucial improvements in intensive care, such as defensive mechanical ventilation to prevent acute respiratory distress syndrome [38], tight euglycemic control [39] or advances in sepsis management [37] were published well inside the observed time period of this trial and may have contributed to improved survival. Likewise, burn-specific improvements such as further refinement of goal-directed resuscitation, or novel therapeutic agents to modulate the pathophysiological reaction to acute thermal trauma are difficult to quantify and control for in retrospect. Nonetheless, the observed reduction in mortality is at least indicative of the safety of a lower hemoglobin threshold for transfusion in pediatric burn patients.

The implementation of more conservative transfusion protocols can be slow and difficult, as shown by the 4-year transition period with slowly declining average hemoglobin concentrations. This steady decline at our institution was prompted by emerging studies

from other critical care fields, which led to individual and non-standardized protocol changes. An official protocol change was then implemented in 2007 in light of evidence showing the benefits of this approach. We hope that our robust data may serve as a reference for other pediatric burn centers to aid implementation of and adherence to these changes. Of note, the actual target hemoglobin threshold before transfusion of below 7g/dl was not reached on average, despite the fact that no particular group of patients were categorically excluded from the lower transfusion threshold due to the severity of their illness or the anticipated need for repeated operations. This observation is explained by the fact that clinical decisions to transfuse, not triggered by hemoglobin measurements, but for instance by perceived intraoperative blood loss or clinically symptomatic anemia, did occur after and despite the protocol change.

This study has limitations that warrant consideration. First, the single-center retrospective design precludes inferences that can be made in a prospective, randomized, controlled trial in pediatric burn care. However, the large number of study subjects, elaborate and robust statistical modelling, and strict inclusion criteria may at least partially compensate for this. Nonetheless, exclusion of subjects who received neither surgery nor blood products may have introduced collider bias to the study, despite statistical similarities in terms of demographic and clinical data. Second, the ABA criteria for the physiological definition of sepsis had to be modified: a complete data set for gastric residuals could not be obtained and only patients who met the sepsis criteria for two consecutive days were classified as positive. The latter modification was necessary because classification based on the 24-hour period yielded an unrealistically high number of septic days that was not consistent with our prior analyses. Lastly, it was beyond the scope of this study to validate the ABA classification system by confirming or rejecting each incident in which physiological sepsis criteria were met with microbiological proof. This effort is the subject of ongoing prospective research at this institution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Hemoglobin concentrations over time. The generalized additive mixed model adjusted for age at burn, sex, percent TBSA burned, percent TBSA with 3rd-degree burns, inhalation injury, and time post burn. Density of measures is indicated by hatch marks above the x-axis. Red dashed lines mark the transition period in which the transfusion threshold of < 10 g/dL was changed to ≤ 7 g/dL; this period was excluded from the pre- vs. post- analyses.

Figure 2.
CONSORT flow diagram. pRBC: packed red blood cells.

Figure 3.

Effect of hemoglobin threshold adjustment on mean hemoglobin concentrations; a: Hemoglobin concentrations during acute hospitalization before and after the protocol change. The generalized additive mixed model adjusted for age at burn, sex, percent TBSA burned, percent TBSA with 3rd-degree burns, inhalation injury, and time post burn. b: Hemoglobin concentrations before and after transfusion in the pre- and post- groups.

Figure 4. Volume of packed red blood cells transfused per patient and day. The generalized additive mixed model adjusted for age, sex, percent TBSA burned, inhalation injury, weight, and length of hospitalization.

Table 1:

Determinants of incidence and patient days of sepsis; modified after ABA criteria [22]

Parameter	ABA Sepsis Criteria
Temperature	> 39°C or < 36.5°C
Heart rate	> 110 bpm
Respiratory rate	> 25 breaths/min (spontaneous ventilation) > 12 L/min (mechanical ventilation)
Thrombocyte concentration	< 100,000 platelets/ μ L
Blood glucose	> 200 mg/dL > 7 IU of i.v. insulin/h > 25% increase in insulin requirement/24 h
Feeding	uncontrollable diarrhea > 36 mL/kg/d

Patients were classified as positive for sepsis if at least three criteria were met for at least two consecutive days or for one day if the patient expired on the same day.

bpm: beats per minute; IU: international units.

Table 2:

Patient characteristics

Patient Characteristics	Pre-Protocol Change	Post-Protocol Change	p Value
	1997–2004 (n = 759)	2008–2017 (n = 701)	
Age	7 ± 5	7 ± 6	0.788
Sex (M/F)	469/290	453/248	0.293
TBSA burned (%)	45 ± 21	43 ± 17	0.225
TBSA 3rd degree burned (%)	31 ± 25	28 ± 22	0.406
Burn to admission (days)	12 ± 48	8 ± 37	0.007
Length of hospitalization (days)	24 ± 25	27 ± 26	< 0.0001
TBSA excised and grafted (cm ²)	7072 ± 9230	8487 ± 11013	< 0.0001
Total pRBC administered (mL)	2282 ± 3393	2278 ± 3672	0.673
Patients meeting sepsis criteria during acute hospitalization	405 (53.4)	346 (49.3)	0.12
Sepsis days/days of hospitalization (%)	17.2	13.4	< 0.0001
Mortality	61 (8)	27 (3.9)	0.022

Data reported as mean ± SD or n (%) unless otherwise noted. TBSA: total body surface area; pRBC: packed red blood cells.