Restrictive Transfusion Strategy Is More Effective in Massive Burns: Results of the TRIBE Multicenter Prospective Randomized Trial

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ABSTRACT Objectives: Studies suggest that a restrictive transfusion strategy is safe in burns, yet the efficacy of a restrictive transfusion policy in massive burn injury is uncertain. Our objective: compare outcomes between massive burn (≥60% total body surface area (TBSA) burn) and major (20–59% TBSA) burn using a restrictive or a liberal blood transfusion strategy. Methods: Patients with burns ≥20% were block randomized by age and TBSA to a restrictive (transfuse hemoglobin <7 g/dL) or liberal (transfuse hemoglobin <10 g/dL) strategy throughout hospitalization. Data collected included demographics, infections, transfusions, and outcomes. Results: Three hundred and forty-five patients received 7,054 units blood, 2,886 in massive and 4,168 in restrictive. Patients were similar in age, TBSA, and inhalation injury. The restrictive group received less blood (45.57 ± 47.63 vs. 77.16 ± 55.0, $p < 0.03$ massive; 11.0 ± 16.70 vs. 16.78 ± 17.39, $p < 0.001$) major). In massive burn, the restrictive group had fewer ventilator days ($p <$ 0.05). Median ICU days and LOS were lower in the restrictive group; wound healing, mortality, and infection did not differ. No significant outcome differences occurred in the major (20–59%) group ($p > 0.05$). Conclusions:: A restrictive transfusion strategy may be beneficial in massive burns in reducing ventilator days, ICU days and blood utilization, but does not decrease infection, mortality, hospital LOS or wound healing.

INTRODUCTION

Red blood cell (RBC) transfusion is an essential therapy in surgical conditions that entail blood loss, including burns and trauma, yet the optimal use of RBC after burn and trauma is not clearly defined in massive blood loss situations. Blood transfusion has salutary effects, including increasing oxygen delivery and carrying capacity, blood volume, and potentially wound healing which could prove advantageous in patients with major wounds, including burns.[1,2] However, these benefits must be balanced against the risk of transfusion reaction, transfusion-related acute lung injury (TRALI), immunosuppression, blood-borne diseases, and transfusion associated cardiac overload (TACO).[3] Previous studies have reported equivalent outcomes between a restrictive (transfuse if hemoglobin <7 g/dL) and a liberal policy (transfuse if hemoglobin <10 g/dL) in critical illness and in stable non-bleeding patients.[4–7]

The generalizability of these findings of these trials to burn patients, however, is problematic. Therefore, we completed the Transfusion Requirement in Burn Care Evaluation (TRIBE) study, a multicenter randomized prospective trial of blood transfusion in major burn injury.[8] This trial randomized patients with burns ≥20% total body surface area

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(TBSA) to either a liberal or restrictive transfusion policy. More than 7,000 units of RBCs were transfused in 347 patients; hence, each patient received far more blood products than reported in other analyses. Despite this intensive transfusion experience, there was no difference in any outcome measure, including bloodstream infection, length of stay, duration of mechanical ventilation, multiple organ dysfunction score, survival, or wound healing.

However, the response to major (20–59% TBSA) differs markedly from a massive (≥60% TBSA) burn injury. The hypermetabolic response is amplified, with massive burn (MASS) patients having higher caloric requirements, loss of lean body mass, increased number of operations, more transfusions, longer duration of mechanical ventilation, more dressing changes, and increased mortality compared to major (MAJ) burn patients.[9–12] Concomitantly, massive burn patients also have exponentially higher resource utilization, including medications, transfusions, and dressings. Wound healing, strength, and endurance are the lynchpins for survival in massive burns. A higher hemoglobin may increase endurance and wound healing in the massive burn patient. In a previous study of burn transfusion practice, burn surgeons reported that they target a higher hemoglobin in massive burn injury ostensibly to improve wound healing as well as strength maintenance and recovery.[13] Hence, understanding the impact of RBC transfusion on outcomes, including wound healing, and resource utilization in massive burns is essential.

The limited number of massive burns treated at any single center is prohibitive in determining the impact of a restrictive vs. liberal transfusion policy. However, the TRIBE study, which contains numerous patients with massive burns, provides a data source to address this question. Our objective, therefore, was to compare resource utilization and outcomes between patients from the TRIBE cohort with massive burn injury (≥60% total body surface area (TBSA) burn) and major (20–59% TBSA) burn injury using a restrictive or a liberal blood transfusion strategy. We hypothesized that the massive burn group would have greater benefit from a restrictive transfusion strategy.

METHODS

As previously reported, the TRIBE trial was registered (Clintrials.gov identifier NCT01079247) and approved by the University of California Davis Human Subjects Review Board (Protocol #200816457), the Department of Defense Human Research Protection Official (Log# A-15003), and the Human Subjects Review Board of each site.[8] Adults with burns ≥20% TBSA were randomized to receive RBC transfusions to maintain a hemoglobin level approximately 10–11 g/dL (liberal group) or a hemoglobin level approximately 7–8 g/dL (restrictive group).

Major burn (MAJ) was defined as burn injury 20–59% TBSA; massive burn (MASS) was defined as ≥60% TBSA. The demographic, injury, treatment, resource utilization, and outcome data collected in the TRIBE study were used in the analyses. The outcome measures for this study included resource utilization (number of RBC transfusions, duration of mechanical ventilation, Intensive Care Unit (ICU) days) and outcomes (survival, number of infections, and wound healing).

Statistical analyses

Continuous variables were compared between treatment groups within each burn size group using Wilcoxon rank sum tests as most variables deviated from normality; medians [25th percentile, 75th percentile] are reported. For dichotomous variables, Fisher' exact tests were used to compare proportions between treatment groups. analyses were conducted in R Statistical Computing Software, version 3.2.3. All tests were two-sided with a significance level of 0.05.

RESULTS

Patient and Transfusion Characteristics

A total of 345 patients received a total of 7,054 units RBC, 2,886 units in the massive group and 4,168 in the major group. (46 MASS, 299 MAJ, Table I) Overall, the MASS group burn size was more than twice that of the MAJ group

TABLE I. Demographics and Injury Characteristics. Summary statistics of Patient Characteristics

	Massive Burns (TBSA≥60%)			Major Burn (TBSA 20–59%)		
	Liberal (*n* = 25)	Restrictive (*n* = 21)	*p*	Liberal (*n* = 152)	Restrictive (*n* = 147)	*p*
Age	33 [28, 51]	32 [25, 46]	0.31	42 [31, 55]	42 [29, 58]	0.46
Gender (% male)	92	76.2%	0.22	76.3	80.3	0.48
TBSA	76 [68, 82]	72 [63, 75]	0.11	30 [24, 40]	30 [24, 36]	0.58
Full thickness	64 [28, 80]	61 [40, 68]	0.34	18 [3, 30]	18 [5, 28]	0.95
Partial thickness	5 [0, 40]	7 [0, 32]	0.99	13 [2, 23]	12 [1, 23]	0.68
Inhalation Injury (%)	32	42.9	0.55	19.1	21.8	0.57
APACHE Score	25 [21, 27]	26 [22, 28]	0.75	17 [11, 24]	16 [12, 21]	0.56
Admit MOD	7 [5, 9]	8 [6, 9]	0.11	4 [1, 6]	4 [1, 6]	0.66

Data expressed as medians [25th, 75th quantiles] or percentage (*n*) of selected variables for each treatment group.

(74 vs 30% TBSA) and had larger full thickness burn size, incidence of inhalation injury, Acute Physiology and Chronic Health Evaluation (APACHE) score, and admission Multiple Organ Dysfunction (MOD) score. However, there was no difference between restrictive and liberal transfusion strategy subgroups within the MASS group or within the MAJ group in age, TBSA burn, and inhalation injury.

Resource Utilization

Overall, the MASS group had almost triple the hospital length of stay, double the ICU days, 10 times the ventilator days, 3 times as many operations, and 4 times the number of RBC transfusions compared to the MAJ group. (Table II) The differences were most pronounced between the liberal arms of the MASS and MAJ groups.

Within the MASS group, the number of ventilator days was significantly lower in the restrictive arm (29 vs. 50 days, $p < 0.03$); for the MAJ groups there was no difference in ventilator days (4 vs. 4 days, $p = 0.22$) between restrictive and liberal strategies. Although not statistically significant, median ICU days and hospital length of stay (LOS) in the MASS group were considerably lower in the restrictive group relative to the liberal group (Table II). In contrast, ICU days and LOS were similar in the two transfusion groups in the MAJ group (Table II), Not surprisingly, the number of RBC transfusions differed significantly between restrictive and liberal groups in both MASS (45.57 ± 47.63 vs. 77.16 ± 55 units, respectively) and MAJ (11.0 ± 16.70 vs. 16.78 ± 17.39 units, respectively).

Outcome Measures

Overall, the MASS group had a higher mortality, worse MOD scores (more organ dysfunction), four times the wound healing time, and increased incidence of infection (bloodstream, urinary tract, wound, and pneumonia). (Tables II and III) However, when comparing the restrictive and liberal groups within the MASS or within the MAJ there was no difference in mortality, MOD score, wound healing, or infection.

DISCUSSION

The findings of this study comparing the outcomes of restrictive and liberal transfusion policies in two different burn

TABLE II. Resource Utilization

	Massive Burns (TBSA≥60%)			Major Burn (TBSA 20–59%)		
	Liberal ($n = 25$)	Restrictive ($n = 21$)	p	Liberal ($n = 152$)	Restrictive ($n = 147$)	p
LOS	98 [63, 146]	68 [24, 106]	0.18	27 [19, 44]	30 [21, 54]	0.18
Ventilator day	50 [23, 82]	29 [10, 40]	0.03	4 [0, 14]	4 [0, 22]	0.22
ICU days	87 [49, 119]	45 [17, 86]	0.09	18 [6, 30]	20 [11, 38]	0.1
Wound healing (days)	70 [50, 118]	81 [50, 140]	0.81	22 [13, 35]	22 [14, 33]	0.74
Operation #	7 [5, 16]	6 [2, 13]	0.5	2 [1, 4]	2 [1, 4]	0.35
Worst MOD	10 [8, 13]	11 [10, 13]	0.53	6 [3, 9]	7 [4, 10]	0.22
Mortality (%)	28	28.6	1	8.6	11.6	0.44
Surgery (%)	100	100		92.8	93.2	1
RBC Transf. Count	66 [36, 123]	38 [19, 58]	0.03	13 [5, 23]	6 [2, 13]	<0.001

Data expressed as medians [25th, 75th quantiles] or percentage (n) of selected variables for each treatment group.

TABLE III. Summaries of Infections for Each Treatment Group

	Massive Burns (TBSA≥60%)			Major Burn (TBSA 20–59%)		
	Liberal ($n = 25$)	Restrictive ($n = 21$)	p	Liberal ($n = 152$)	Restrictive ($n = 147$)	p
BSI (%)	64	57.1	NS	17.1	19	NS
Number BSI	1 [0, 2]	1 [0, 2]	NS	0 [0, 0]	0 [0, 0]	NS
BSI (#/1,000 patient days)	12.77	10.91	NS	8.35	6.66	NS
UTI (%)	32	33.3	NS	10.5	11.6	NS
Number of UTI	0 [0, 1]	0 [0, 1]	NS	0 [0, 0]	0 [0, 0]	NS
UTI (#/1,000 patient days)	5.18	5.46	NS	3.08	3.24	NS
Pneumonia (%)	68	42.9	NS	21.1	27.2	NS
Number Pneumonia	1 [0, 2]	0 [0, 1]	NS	0 [0, 0]	0 [0, 1]	NS
Pneumonia (#/1,000 pt day)	13.12	11.33	NS	0	8.54	NS
Wound (%)	36	33.3	NS	7.9	8.8	NS
Number wound infections	0 [0, 1]	0 [0, 1]	NS	0 [0, 0]	0 [0, 0]	NS
Wound (#/1,000 pt days)	6.21	5.46	NS	2.54	3.07	NS

Data expressed as medians [25th, 75th quantiles] or percentage (n) of selected variables for each treatment group. BSI, bloodstream infection; UTI, urinary tract infection.

types, massive vs. major burns, found that a restrictive policy may benefit patients with massive burns by decreasing duration of ventilation at the same time limiting the number of overall blood transfusions. This suggests that a restrictive strategy may be more effective in more critically ill patients. This study also argues against the common practice of targeting a higher hemoglobin in patients with massive burn injury, as this may lead to an increased incidence of pulmonary dysfunction without adversely impacting wound healing. Although not statistically significant, the median differences between MASS and MAJ are thought-provoking, as the median differences are notable. This could be due, in part, to small sample size and variability in these variables, but could also be an important indicator of potential benefit for a restrictive policy in massive burns.

This study is unique in that it characterizes the impact of a therapeutic intervention in two distinct patient subgroups defined by severity. While it can be argued that the two groups (massive and major burns) are fundamentally different, our findings emphasize a fundamental issue: intervention studies with heterogeneous patient populations must be designed and analyzed appropriately to avoid confounding; i.e., using a stratified block randomization and statistical adjustment. Overall, this analysis confirms the findings of studies in critically ill patients; namely, that a restrictive strategy may be beneficial to critically ill patients.[4–7] It may also explain why studies in other populations have different findings, and raises caution for universal application of a restrictive policy in unstudied populations.[14,15] This study also demonstrates that the pathophysiologic response to burn injury is not linear or uniform. The massive group had much greater resource needs, yet had worse outcomes than the major group. The hypermetabolic response is likely not uniformly increased by burn size; other factors likely play an important role. RBC transfusion has been associated with decreased in-hospital muscle strength in critically ill patients requiring mechanical ventilation, which could potentially explain these findings.[16] Unfortunately, the study was not funded to examine inflammatory markers associated with transfusion. Hence, the influence of transfusion on those markers cannot be reported.

Another consideration in the use of a restrictive transfusion is its potential impact on cost and quality of care. The cost savings of a restrictive strategy are far more pronounced in the MASS group. For example, the median number of transfusions in MASS was decreased from 77 to 45 units of blood. Given the cost/unit of blood of $1,600–2400/unit, the cost savings/patient would range from $51,000–$76,800.[17] In the USA alone this would result in a savings of millions of dollars yearly. Importantly, our study suggests that the quality of care, as reflected in ICU and hospital length of stay, days on mechanical ventilation, wound healing, and infections were not different between groups.

A strength of the design of the TRIBE multi-institutional randomized trial is that it allows for comparison of possible potential differential treatment effects across patient subgroups such as those defined by burn severity. This could not feasibly be done with single institution studies. Even so, this study was not powered to formally detect differences in patient subgroups based on factors such as inhalation injury given the relatively small sample size. However, measures such as the number of transfusions received per patient in the massive group far exceeds any previous studies of transfusion. As such, the potential effects of transfusion would be demonstrated in this group.

CONCLUSIONS

This analysis of data from a randomized prospective transfusion trial is the first to compare patient characteristics, resource utilization, and outcomes in massive burns among 18 different burn centers in a relatively short time frame. The volume of blood transfused, particularly in the massive group, far exceeds any reported in the literature. Application of a restrictive transfusion policy decreased the need for mechanical ventilation in massive burn patients without impacting infection rate, wound healing, or survival.

PREVIOUS PRESENTATIONS

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