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Implementation of a military-derived damage-control resuscitation strategy in a civilian trauma center decreases acute hypoxia in massively transfused patients

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Abstract

BACKGROUND—Recent military experience supports a paradigm shift in shock resuscitation to damage-control resuscitation (DCR), which emphasizes a plasma-rich and crystalloid-poor approach to resuscitation. The effect of DCR on hypoxia after massive transfusion is unknown. We hypothesized that implementation of a military-derived DCR strategy in a civilian setting would lead to decreased acute hypoxia.

METHODS—A DCR strategy was implemented in 2007. We retrospectively reviewed patients receiving trauma surgeon operative intervention and 10 or more units of packed red blood cells (pRBCs) within 24 hours of injury at an adult Level I trauma center from 2001 to 2010. Demographic data, blood requirements, and PaO₂/FIO₂ ratios were analyzed. To evaluate evolving resuscitation strategies, we fit linear trend models to continuous variables and tested their slopes for statistical significance.

RESULTS—Two hundred sixteen patients met the study criteria, with a mean age of 35 ± 1.1 years and Injury Severity Score (ISS) of 31 ± 9.0. Of the patients, 80% were male, and 52% sustained penetrating injuries. Overall mortality was 32%. Overall mean pRBC and fresh frozen plasma (FFP) units infused in 24 hours were 23.2 ± 1.1 and 18.6 ± 1.1, respectively. Trends for patient age, sex, mechanism of injury, ISS, highest positive end-expiratory pressure, and mean total pRBC transfused over 24 hours were not statistically different from zero. An increasing trend in FFP and platelets transfused during the first 24 hours ($p < 0.0001$, $p = 0.04$, respectively) and a decrease in the pRBC/FFP ratio ($p < 0.0001$) were found. The amount of crystalloid infused during the initial 24 hours decreased with time ($p < 0.0001$). The lowest PaO₂/FIO₂ ratio recorded during the initial 24 hours increased during the study period ($p = 0.01$), indicating a statistically significant reduction in hypoxia.

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DISCLOSURE The authors declare no conflicts of interest.

CONCLUSION—A military-derived DCR strategy can be implemented in the civilian setting. DCR led to significant increases in FFP transfusion, decreases in crystalloid use, and acute hypoxia.

Keywords

Damage-control resuscitation; hypoxia; massive transfusion; hemorrhage

Care of casualties during the military conflicts in Iraq and Afghanistan is leading to a paradigm shift in resuscitation strategies for massively bleeding casualties.^{1,2} Recognition that hemorrhage is associated with early onset of trauma-associated coagulopathy³ and potentially worsened by aggressive volume repletion before surgical control of bleeding^{4,5} led to the practice of permissive (or controlled) hypotension, minimization of crystalloid use, and early initiation of fresh frozen plasma (FFP) in a 1:1 ratio with packed red blood cell (pRBC) transfusion. Together, this resuscitation strategy is now known as damage-control resuscitation (DCR). In the military setting, DCR is now considered standard of care.^{6,7} This strategy has been incorporated into clinical practice guidelines⁸ and is supported by the results of multiple studies, indicating that this approach leads to decreased death from hemorrhagic shock in the military trauma environment.

Implementation of DCR for hemorrhagic shock treatment in civilian trauma centers has been controversial.^{9–11} Although initial studies suggest that increased ratios of FFP to pRBCs may be associated with increased survival,^{12,13} some subsequent reports disputed these findings and questioned the optimal ratio of FFP to pRBCs.^{14–17} Additional concerns have been raised about the increased use of FFP during DCR. Plasma transfusion is associated with many known risks, including transfusion reactions, sepsis from bacterial contamination, allergic reactions, and transfusion-related acute lung injury.¹⁸ The use of FFP from female donors is often cited as a possible etiology although restriction of such a donor pool would create inherent difficulties in product availability.¹⁹ Nevertheless, the United Kingdom has made a national effort to limit FFP from female donors.²⁰ Recent studies linking FFP specifically to adult respiratory distress syndrome (ARDS) in patients receiving a massive transfusion (MT) have led to questions of whether the increased use of FFP in DCR might have deleterious effects on oxygenation.^{10,21,22} To attempt to address many of these concerns, a large multicenter, prospective, randomized trial is currently underway.²³

Based on early military data and the experience of several of our deployed surgeons, our institution became an early adopter of DCR in the civilian setting, with the initiation of each component of this strategy in early 2007. The goal of the current study was to determine the effect of implementation of a military-derived DCR strategy on the ratio of blood products used, the amount of crystalloid infused, and respiratory status in civilian operative trauma patients who received a MT. We hypothesized that implementation of such a DCR strategy would not be associated with negative respiratory outcomes, specifically acute hypoxia.

PATIENTS AND METHODS

Study Setting

The University of Cincinnati, University Hospital, is an adult American College of Surgeons-verified Level I trauma center that serves 1.8 million people in southwestern Ohio, northern Kentucky, and southeastern Indiana. The hospital is a 450-bed facility with more than 100 critical care beds, 34 of which are dedicated to injured patients in the surgical intensive care unit (ICU). A unit-specific ventilator weaning protocol for those with acute lung injury was used during the entire study duration. This protocol is guided by the surgical critical care service in conjunction with the trauma team.

Data Collection

This study was approved by the University of Cincinnati Institutional Review Board. We performed a retrospective review of patients entered into the University Hospital trauma database from January 2001 to December 2010, querying for all adult patients who required an operation by a trauma surgeon within 24 hours of admission. The medical records of each patient were reviewed to identify those who had undergone MT, defined as the transfusion of 10 or more units of pRBCs within 24 hours.

Patient records of those who received an MT were reviewed from time of admission in the emergency department through 7 days after injury or until the patient was transferred out of the surgical ICU to the ward or died. Emergency department flow sheets, physician dictations, anesthesia records, operative reports, laboratory results, and ICU nursing records were all reviewed for the collection of a complete data set.

Demographic data including age and sex, injury characteristics, Injury Severity Score (ISS), ICU and hospital length of stay (LOS), and mortality of the cohort were recorded. All blood products transfused (pRBC, FFP, and platelets) and crystalloid infused during the first 24 hours were determined in 6-hour increments. In consultation with the US Air Force Center for Sustainment of Trauma and Readiness Skill at the University of Cincinnati, pulmonary sequelae from resuscitation were specifically investigated. The lowest partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FIO_2) ratio (P/F) during the first 24 hours of care was evaluated to delineate the risk of acute pulmonary deterioration during a time frame in which civilian trauma patients may undergo transport to higher levels of care and during which combat casualties often undergo strategic aeromedical evacuation. The highest positive end-expiratory pressure during 24 hours and ventilator-free days within the span of 30 days were also reviewed.

Data Analysis

Categorical data are presented as proportions and tested for between-period differences using χ^2 methods. Continuous data are presented as means (with SEs) and tested for between-period differences using t tests.

Our primary focus was on the comparison of key variables before and after the implementation of DCR. We tested for differences in two ways. Time of patient intervention

for the model was determined in days from the start of the review period, January 1, 2001. We then used these elapsed times to fit simple linear time trend models to continuous variables for the entire period 2001 to 2010 and tested the trend coefficients for statistical significance. For categorical end points, we fit simple logistic time trend models and tested the estimated odds ratios for statistical significance. Statistically significant trend coefficients and odds ratios indicate overall upward or downward trends over the entire data set. In addition, we divided the cohort into two groups as follows: pre-DCR (2001–2006) and post-DCR (2007–2010). We then tested for differences between these groups by using χ^2 and t tests. All statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Statistical significance was defined as $p < 0.05$.

RESULTS

During the 10-year period, 216 patients met inclusion criteria for the study. Demographic data is presented in Table 1. The mean age of this cohort was 35.2 ± 1.1 years, with a mean ISS of 31.4 ± 9.0 ; 80% of the patients were male. A slight majority (52%) of the cohort sustained penetrating injuries. The mean hospital LOS was 21.0 ± 1.5 days, with an ICU LOS of 14.9 ± 1.2 days. Overall mortality was 32% during the 10-year study period. There was a significant trend of decreasing mortality over time ($p = 0.04$, Table 1). This trend did not persist when mortality was adjusted for ISS ($p = 0.2$). During the 10-year period, age, ISS, percentage of penetrating injuries, sex, ICU LOS, hospital LOS, and ventilator-free days in 30 in this patient population did not change significantly (Table 1). The mean highest positive end-expiratory pressure in the first 24 hours was 8.8 ± 5.1 cm H₂O and did not change significantly during the study period. To evaluate the effects of implementation of the DCR strategy, we then analyzed data in two groups as follows: pre-DCR and post-DCR (Table 2). Trauma surgeons operated on 117 massively transfused patients in the pre-DCR era and 99 in the post-DCR era. No significant differences were found between the groups with respect to age, sex, ISS, rate of penetrating injuries, LOS, ventilator-free days in 30, or mortality (Table 2).

The mean number of pRBCs units transfused to all MT patients was 23.2 ± 1.1 . Despite the change in resuscitation strategy, the number of pRBCs units transfused in the first 24 hours did not change significantly over time ($p = 0.38$, Fig. 1A), indicating that implementation of DCR did not result in increased pRBC use. During the entire period, the number of units of FFP and platelets transfused increased significantly (trend line coefficient, 0.004; $p < 0.0001$; trend line coefficient, 0.0005; $p = 0.02$, respectively; Fig. 1B and C). This contributed to a decrease in the ratio of pRBC to FFP units transfused that was statistically significant (trend line coefficient, -0.0005 ; $p < 0.0001$; Fig. 1D). Analysis of the ratios of pRBCs to FFP by pre-DCR and post-DCR categories showed a significant decrease from $1.9:1 \pm 0.1$ in the pre-DCR era to $1.1:1 \pm 0.04$ in the post-DCR era ($p < 0.0001$).

We analyzed crystalloid use during the first 24 hours of care. The trend of infusion amounts of crystalloid fluid in liters decreased during the 10-year study period (trend coefficient, -0.00279 ; $p < 0.0001$; Fig. 2). Comparative analysis of crystalloid use (mean liters infused) in the pre-DCR versus the post-DCR eras was then performed by 6-hour increments during the first 24 hours of admission. There was a significant decrease in crystalloid use during the

first 6 hours of resuscitation during the post-DCR period (11.6 ± 0.5 vs. 6.2 ± 0.3 , $p < 0.0001$, Table 3). The cumulative use of crystalloid at 12, 18, and 24 hours followed this same pattern (13.9 ± 0.6 vs. 7.7 ± 0.4 , $p < 0.0001$; 15.7 ± 0.7 vs. 9.3 ± 0.4 , $p < 0.0001$; 17.4 ± 0.8 vs. 10.8 ± 0.5 , $p < 0.0001$, respectively).

Because we were concerned about potential adverse acute effects of increased FFP use on pulmonary status, we analyzed these variables in detail. We used the lowest P/F ratio during the first 24 hours of care as a marker for acute hypoxia. During the course of 10 years, a significantly positive P/F ratio slope coefficient was demonstrated, indicating an improvement in patient oxygenation during the period of intervention (slope, 0.02; $p = 0.01$; Fig. 3A). Further analysis demonstrated that the proportion of patients with a P/F ratio greater than 200 mm Hg decreased significantly during the same period (odds ratio [OR], 0.891; 95% confidence interval [CI], 0.803–0.985; $p = 0.03$; Fig. 3B). No difference in the proportion of patients with a P/F of less than 300 mm Hg or in ventilator-free days in 30 was found. Logistic regression models were created that incorporated elapsed time since the beginning of the study period, ISS, and ratios of pRBCs to FFP as well as pRBCs to platelets, and liters of crystalloid to pRBCs. These models failed to demonstrate associations of the ratios with mortality or with the lowest P/F ratio within the first 24 hours.

We then focused our investigation of the linear dependence of the pRBC-to-FFP ratio and crystalloid use with the lowest P/F ratio during the first 24 hours of care. A significant, negative correlation existed between crystalloid use and the lowest P/F ($\rho = -0.21$, $p = 0.004$), whereas no such relationship was found when the pRBC-to-FFP ratio was correlated to the P/F ratio ($\rho = -0.05$, $p = 0.46$). Finally, we performed a logistic regression to determine risk factors for a P/F ratio less than 200 mm Hg during the first 24 hours of care. Crystalloid use in 500-mL increments (OR, 1.024; 95% CI, 1.003–1.046; $p = 0.025$) and a blunt mechanism of injury (OR, 3.053; 95% CI, 1.445–6.45; $p = 0.003$) were significant risk factors for acute hypoxemia, while age, sex, ISS, and the pRBC-to-FFP ratio at 24 hours were not.

DISCUSSION

In the present study, we examined the effect of implementation of a military-derived DCR strategy in the care of massively transfused patients in a civilian Level I trauma center. Our data indicate that this strategy can be implemented rapidly with a resulting pRBC-to-FFP ratio of nearly 1, decreased crystalloid use, and no adverse effect on patient oxygenation.

Several studies have demonstrated that the most severely injured patients are often coagulopathic on admission to the trauma bay.^{3,24–26} Treating the acute coagulopathy of trauma is one of the tenets of DCR.¹ Our results demonstrate that implementing a military-derived DCR strategy led to an increase in FFP and platelet transfusions. However, blood product transfusion is associated with known significant risks.²⁷ One such risk associated with blood and FFP is transfusion-related acute lung injury and ARDS.^{10,28} The use of the standard definition of ARDS as applied to the acute traumatically injured population is controversial and leads to analysis of a diverse cohort with widely disparate clinical courses.²⁹ A number of different factors influence lung function in the massively transfused

trauma patient, including inflammatory mediators, direct injury to the lung, potential fluid overload, and the effects of positive-pressure ventilation.

In this study, we used the lowest P/F ratio seen in patients during the initial 24 hours after injury as an indicator of pulmonary sequelae of an acute resuscitation. This end point was chosen to longitudinally investigate the risk of hypoxemia during a period in which combat casualties are often air evacuated from theater and in which civilian patients are transported. Furthermore, we wanted to examine a parameter that is easily calculated at the bedside and has previously been shown to predict mortality.^{30,31} We found that acute hypoxia as measured by the lowest P/F ratio within an acute period of injury improved significantly during the course of the study. We believe that this improvement is likely related to the significant decrease in crystalloid volume infused in post-DCR patients as well as the efficacy of DCR in treating coagulopathy.

Providing large volumes of blood products rapidly to injured patients is logistically challenging.³² In our institution, overcoming these difficulties was accomplished through coordination and education of surgical, emergency department, transfusion medicine, operating room, and nursing staff. Thawed plasma was made available 24 hours per day not only in the operating rooms but also in the trauma bay of the emergency department. When activated by military-derived transfusion triggers, our MT protocol provides predetermined ratios of pRBC, FFP, and platelets to the provider for infusion.³³ Through this strategy, we noted that the ratio of FFP to pRBCs transfused in these patients increased sharply during the first year of DCR implementation and remained at the goal ratio over time.

A key tenet of military DCR is to minimize crystalloid infusion.¹ In this study, we found that implementation of DCR in our institution was associated with decreased amounts of crystalloid infusion during the first 6 hours. This pattern continued through the initial 24 hours after trauma. The deleterious pulmonary effects of crystalloid infusion are well documented and may include increased leukocyte adhesion and reperfusion injury.³⁴ This has been validated in a clinical study of postoperative general surgery patients in which overresuscitation with crystalloid was shown to be deleterious with increased cardio-pulmonary complications.³⁵ The decreased use of crystalloid in our work may explain the different conclusions our study has drawn in comparison with the studies by others in which an increased risk of ARDS was demonstrated when FFP was given in a high ratio to pRBCs.^{10,36} However, in these works, crystalloid use was unchanged or even greater in the cohort that received a high ratio of FFP to pRBC.^{10,36} A substantial decrease in crystalloid use may be necessary to derive the respiratory benefits of DCR, specifically acute hypoxia, in a way not easily controlled for in regression analysis of retrospective data.

DCR in a military setting has even greater logistical impacts. Currently, the Department of Defense dedicates up to 30% of medical supplies “weight and cube” to the transport of fluids and oxygen. Although the increased use of plasma carries its own additional requirements, the decreasing use of oxygen and crystalloids at all levels of care during the first 24 hours would also be significant.³⁷ Decreased hypoxia in combat casualties may also decrease the need for more advanced mechanical ventilation techniques and the use of

specialized transport teams (such as the Landstuhl Acute Lung Team) and allow potentially for earlier transport of MT patients.³⁸

There are several potential limitations to our study. First, alternative explanations may exist for the improvement of P/F ratios during the 10-year duration of the analysis, including improvements in ventilator management. Within our institution, there were no significant changes in our trauma or ICU practice patterns (other than the institution of DCR) or patient population during the study period. Our institution was an early adopter of protocolized mechanical ventilation techniques for the optimization of oxygenation in patients with acute lung injury and ARDS and followed these protocols during the duration of this study.

By limiting our study to those patients who received an MT and an emergent operative intervention by a trauma surgeon, our goal was to evaluate the “sickest of the sick”—those patients that sustained the double hit of traumatic injury with hemorrhagic shock and an operative intervention. More recently, this same patient subset was used for validating military style MT triggers.³³ Institutionally, the conversion to a MT protocol with balanced plasma and platelet components was met with a great deal of skepticism by nontrauma surgeons. A significant proportion of our trauma surgeon physician group had an active duty experience using DCR. The implementation, education, and process improvement program associated with DCR began within the trauma group and spread institutionally thereafter. Massive transfusions practices incorporating DCR strategies performed in concert with operative interventions with an in-house trauma surgeon serving as a resuscitation consultant constitute more than 95% of MTs during our study period. Nonetheless, our limited study group represents a subset population, and the data collected may, in part, include many factors that limit its applicability to all patients in hemorrhagic shock.

Finally, although our data suggest that mortality decreased over time in our study population, the decrease did not remain statistically significant when corrected for ISS. Unfortunately, our institutional change in ISS scoring during the study period may have led to a decrease in our recent ISS scores.³⁹ This change in scoring may have prevented a difference from being detected when one actually exists. Nonetheless, other studies have demonstrated a mortality benefit to DCR.^{12,22,36,40} Finally, injury patterns determined by Abbreviated Injury Scale (AIS) scores were unable to be evaluated limiting the ability to examine patient subpopulations, specifically head injured patients. Many of these issues are likely to be addressed by ongoing prospective randomized multi-institutional MT trials, and we look forward to the results.

CONCLUSION

Implementation of a military-derived DCR strategy can be accomplished in the setting of a civilian trauma center. DCR led to significant increases in FFP and platelet use and an increased FFP-to-pRBC ratio as well as decreased crystalloid use during the first 24 hours of care during a 10-year interval of analysis. A military-derived DCR strategy did not contribute to an increase in hospital or ICU LOS or a decrease in ventilator-free days and was associated with a decrease in acute hypoxia.

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Figure 1.

Blood product transfusions by MT patient during the initial 24 hours of resuscitation during 10 years. *Vertical dashed line* represents pre-DCR era to the left and post-DCR to the right. *A*, Number of pRBC units transfused per patient during the first 24 hours, trend line with coefficient of 0.00010 ($p = 0.38$ for trend over time). *B*, Number of FFP units transfused per patient during the first 24 hours, trend line coefficient of 0.00443 ($p < 0.0001$ for trend over time). *C*, Number of units of platelets transfused per patient during first 24 hours, trend coefficient of 0.00054 ($p = 0.04$ for trend over time). *D*, Ratio of pRBC s to FFP per patient during the first 24 hours over time, trend coefficient of -0.00046 ($p < 0.0001$ for trend over time). The *asterisk* denotes statistical significance at the 0.05 level or better.

Figure 2.

Crystalloid infusion (in liters) of MT patients during the initial 24 hours of resuscitation over 10 years. *Vertical dashed line* represents pre-DCR era to the left and post-DCR to the right. Trend line with coefficient of -0.00279 ($p < 0.0001$ for trend over time).

Figure 3.

Effect of implementing DCR on acute hypoxia. *A*, The lowest P/F ratio for each patient during the initial 24 hours of resuscitation. *Vertical dashed line* indicates pre-DCR era to the left and post-DCR to the right. Trend line with coefficient of 0.02311 ($p = 0.01$). *B*, Proportion of patients with the lowest P/F ratio of less than 200 during the initial 24 hours of resuscitation by year.

TABLE 1

Comparison of Demographics by Year of MT Patients

Demographics	Total	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p
Sample size	216	18	21	12	22	20	24	35	25	25	14	
Age, y	35.2 ± 1.1	32.2 ± 2.5	37.5 ± 3.3	32.7 ± 3.4	30.4 ± 2.4	36.4 ± 3.9	32.8 ± 2.8	35.7 ± 2.6	39.9 ± 3.8	33.5 ± 3.6	42.3 ± 5.5	NS
Male sex rate, %	80	78	81	92	82	90	83	66	88	76	79	NS
Penetrating injury rate, %	52	50	62	42	36	55	63	49	40	64	57	NS
ISS	31.4 ± 9.0	36.6 ± 4.4	30.0 ± 3.4	42.7 ± 4.0	32.1 ± 3.8	29.8 ± 3.4	30.7 ± 3.0	30.3 ± 2.1	28.1 ± 1.8	27.2 ± 2.2	37.3 ± 5.9	NS
ICU LOS	14.9 ± 1.2	11.0 ± 3.9	14.8 ± 3.9	9.8 ± 3.2	18.0 ± 4.9	16.9 ± 3.1	11.9 ± 3.0	18.7 ± 3.6	14.0 ± 2.9	14.4 ± 2.6	15.3 ± 6.2	NS
Hospital LOS	21.0 ± 1.5	19.2 ± 6.1	21.6 ± 4.3	10.7 ± 3.7	25.8 ± 5.8	20.7 ± 2.6	18.7 ± 5.2	23.9 ± 3.8	20.6 ± 3.2	22.2 ± 4.3	17.3 ± 6.3	NS
Ventilator-free days in 30	20.0 ± 0.6	22.2 ± 2.1	20.1 ± 1.8	22.8 ± 2.4	19.0 ± 1.9	18.1 ± 2.1	21.5 ± 1.8	19.2 ± 1.8	20.3 ± 1.8	19.1 ± 2.0	19.4 ± 2.9	NS
Mortality, %	32	39	48	67	27	20	29	31	20	28	29	0.04*

Continuous variables described, as means ± SE.

NS, not significant.

* Statistically significant ($p < 0.05$) for trend, line analysis versus zero slope.

TABLE 2

Comparison of Patient Demographics by Pre-DCR and Post-DCR Strategy Implementation

Demographics	Pre-DCR (2001–2006), n = 117	Post-DCR (2007–2010), n = 99	<i>p</i>
Age, y	33.7 ± 1.3	36.9 ± 1.8	NS
Male sex rate, %	84	76	NS
Penetrating injury rate, %	52	52	NS
ISS	32.9 ± 1.5	29.6 ± 1.2	NS
ICU LOS	14.1 ± 1.6	16.0 ± 1.8	NS
Hospital LOS	20.2 ± 2.0	21.9 ± 2.1	NS
Ventilator-free days in 30	20.4 ± 0.8	19.5 ± 1.0	NS
Mortality, %	36	27	NS

Continuous variables described, as means ± SE.

NS, not significant.

TABLE 3

Cumulative Mean Crystalloid Use by 6-Hour Increments During the First 24 Hours of Admission by Pre-DCR and Post-DCR Strategy Implementation

Crystalloid Use	Pre-DCR (2001–2006), n = 117	Post-DCR (2007–2010), n = 99	<i>p</i>
Crystalloid 1st 6 h, L	11.6 ± 0.5	6.2 ± 0.3	<0.0001
Crystalloid 1st 12 h, L	13.9 ± 0.6	7.7 ± 0.4	<0.0001
Crystalloid 1st 18 h, L	15.7 ± 0.7	9.3 ± 0.4	<0.0001
Crystalloid 1st 24 h, L	17.4 ± 0.8	10.8 ± 0.5	<0.0001

Continuous variables described as mean ± SE.