Original Investigation | PACIFIC COAST SURGICAL ASSOCIATION

Changing Patterns of In-Hospital Deaths Following Implementation of Damage Control Resuscitation Practices in US Forward Military Treatment Facilities

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IMPORTANCE Analysis of combat deaths provides invaluable epidemiologic and quality-improvement data for trauma centers and is particularly important under rapidly evolving battlefield conditions.

OBJECTIVE To analyze the evolution of injury patterns, early care, and resuscitation among patients who subsequently died in the hospital, before and after implementation of damage control resuscitation (DCR) policies.

DESIGN, SETTING, AND PARTICIPANTS In a review of the Joint Theater Trauma Registry (2002-2011) of US forward combat hospitals, cohorts of patients with vital signs at presentation and subsequent in-hospital death were grouped into 2 time periods: pre-DCR (before 2006) and DCR (2006-2011).

MAIN OUTCOMES AND MEASURES Injury types and Injury Severity Scores (ISSs), timing and location of death, and initial (24-hour) and total volume of blood products and fluid administered.

RESULTS Of 57 179 soldiers admitted to a forward combat hospital, 2565 (4.5%) subsequently died in the hospital. The majority of patients (74%) were severely injured (ISS > 15), and 80% died within 24 hours of admission. Damage control resuscitation policies were widely implemented by 2006 and resulted in a decrease in mean 24-hour crystalloid infusion volume (6.1-3.2 L) and increased fresh frozen plasma use (3.2-10.1 U) (both $P < .05$) in this population. The mean packed red blood cells to fresh frozen plasma ratio changed from 2.6:1 during the pre-DCR period to 1.4:1 during the DCR period ($P < .01$). There was a significant increase in mean ISS between cohorts (pre-DCR ISS = 23 vs DCR ISS = 27; $P < .05$) and a marked shift in injury patterns favoring more severe head trauma in the DCR cohort.

CONCLUSIONS AND RELEVANCE There has been a significant shift in resuscitation practices in forward combat hospitals indicating widespread military adoption of DCR. Patients who died in a hospital during the DCR period were more likely to be severely injured and have a severe brain injury, consistent with a decrease in deaths among potentially salvageable patients.

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Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) are the first prolonged conflicts the United States has been involved in since the Vietnam War. Throughout history, medical and surgical advances have often emerged from the high-intensity experiences of treating a high volume of battlefield casualties. One of the hallmarks of the current operations in Iraq and Afghanistan has been the prospective capture of data on all patients presenting to US forward military treatment facilities (MTFs). Much of the data has now been consolidated in the Joint Theater Trauma Registry (JTTR), a large military database created to improve the care and outcomes of soldiers.[1] This registry has been validated as an important tool in the assessment of casualty care[2-4] and has been used to analyze a wide range of trauma topics, including care for extremity wounds,[5] airborne critical care,[6,7] administration of recombinant factor VII,[8] and treatment of infectious diseases.[9,10]

Arguably the most important advancement in combat trauma care has been the widespread adoption of damage control resuscitation (DCR). The basic principles of DCR include the early administration of blood products in a balanced ratio, aggressive correction of coagulopathy, and the minimization of crystalloid fluids.[11,12] Ever since these resuscitation strategies have been widely adopted in civilian hospitals, there has been a noticeable shift toward reducing the volume of both crystalloid and blood products administered and associated improvements in survival.[13-16] In the combat setting, the use of DCR has been credited with improvements in survival among severely injured patients, particularly for those requiring a massive transfusion.[17-20] However, there remains significant debate about the efficacy and application of DCR that will require prospective controlled studies to resolve.

Critical analysis of outcomes, and particularly adverse outcomes, is one of the cornerstones of quality and process improvement for trauma centers and systems. Data related to deaths from traumatic injuries, and particularly data on deaths that were potentially preventable, have been instrumental in improving the delivery of care at all levels. Early military studies of battlefield deaths from OIF and OEF[21,22] demonstrated that up to 30% of soldiers died of potentially survivable injuries, and these data were used, for example, to initiate the widespread distribution of tourniquets and advanced hemostatic dressings. However, these studies[21,22] mainly examined prehospital care and were limited to US service members only. A subsequent study[23] published in 2009 focused on deaths at the hospital level but was limited to a single facility in Baghdad, Iraq, and only covered a 1-year period. The purpose of our study was to analyze all in-hospital deaths at US forward medical facilities during a decade of sustained combat operations. In addition to describing the epidemiology and temporal patterns seen over this period, we sought to analyze any change in injury type/severity or trends associated with the widespread adoption of DCR policies. We hypothesized that an independent survival benefit of DCR should also be reflected by a corresponding change in the epidemiology of in-hospital trauma deaths.

Methods

Data for our study were obtained from the JTTR, which is maintained by the Joint Theater Trauma System under the US Army Institute of Surgical Research, Fort Sam Houston, Texas. Established in 2003, the JTTR is the largest and most comprehensive database of wartime wounded and injured patients ever assembled. This prospectively collected trauma registry includes data from all patients evaluated and cared for at forward US MTFs during combat operations in Iraq (OIF) and Afghanistan (OEF), and, as of August 2013, it contains more than 77 000 patients' medical records. Our study protocol was reviewed and approved by the institutional review boards at Madigan Army Medical Center in Tacoma, Washington, and the Joint Theater Trauma System. The aggregate data were de-identified.

The JTTR was queried to identify all OIF and OEF deaths that occurred at MTFs from 2002 to 2011. Only those who presented to an MTF with recorded vital signs (blood pressure and heart rate) and subsequently died were included in our study, and in accordance with standard combat mortality definitions, these patients were considered to have "died of wounds" (DOW). All patients arriving without vital signs were considered dead on arrival (DOA). Primary data included basic demographics, prehospital assessments and interventions, presenting vital signs and laboratory values, emergency department and operative interventions, initial (24-hour) and total blood products and fluid administered, injuries and diagnoses, Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS), and time from admission to death (in days). Severe injury in each body region was defined as an AIS score of 3 or higher, and severely injured patients were defined as those with an ISS of higher than 15.

To provide both numerator and denominator data for comparison of DOW rates and other population-based ratio data, the total number of patients captured in the JTTR per year was obtained. In addition, summary data documenting the overall and theater-specific (OIF vs OEF) numbers and percentages of patients defined as killed in action (KIA) and the case-fatality rate (CFR) were obtained from review of the monthly the Joint Theater Trauma System Theater Director Reports. These reports provide summary data from the JTTR and continuously track the cumulative rolling monthly averages for the KIA rate and the CFR. The KIA rate reflects the percentage of deaths prior to reaching an MTF among all significantly wounded patients, and the CFR represents all deaths as a percentage of all wounded patients.[24] Thus, the KIA rate is primarily a reflection of the lethality of injuries and the effectiveness of prehospital care, whereas the CFR reflects the overall lethality in a battlefield environment.

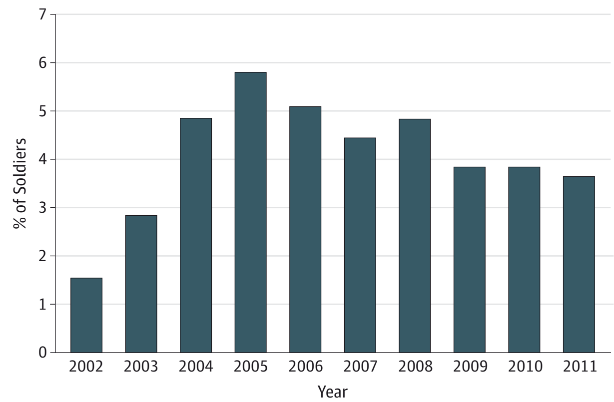
Descriptive statistics for the entire patient cohort were analyzed, and trends for key study variables over time were analyzed by grouping them into calendar years based on the date of injury. The widespread implementation of DCR policies and a DCR-based massive transfusion clinical practice guideline were implemented over the latter half of 2005. Based on this, patients were divided into 2 primary groups by the date of in-

Table 1. Demographics and Clinical Characteristics of All Patients Who Died of Wounds

Characteristic	Value
Patients, No.	2565
Sex, No.	
Male	2341
Female	224
Mean age, y	24.8
Mean ISS	25.2
Severely injured (ISS > 15), No.	1899
Mean RTS	4.99
Mean TRISS probability of survival	0.68
Severe injury (AIS score >3), No.	
Any	1670
Head	908
Chest	251
Abdomen	225
Extremities	161
Mean time from admission to death, d	2.1
Post-ED destination, No.	
Morgue	555
Operating room	888
Intensive care unit	483
Medical/surgical unit	91
Other	6
Mean volume administered in 24 h	
Crystalloid, L	3.6
Colloid, mL	830
PRBCs, U	11
FFP, U	9.8
Mean PRBC:FFP ratio	1.5
Massive transfusion (>10 U/24 h), No.	359

Abbreviations: AIS, Abbreviated Injury Scale; ED, emergency department; FFP, fresh frozen plasma; ISS, Injury Severity Score; PRBC, packed red blood cell; RTS, Revised Trauma Score; TRISS, Trauma Score and Injury Severity Score.

Figure 1. Died of Wounds Rates Over Time



jury and whether this date fell into the pre-DCR (before January 2006) or DCR (2006-2011) time period. The specific categories of data that were compared by year and between the 2 study groups included the initial (24-hour) and the total volume of fluids and blood products administered for the hospital admission. In addition, the ISS and AIS scores, based on body region (head/neck, face, thorax, abdomen, extremities, and external/skin), were analyzed. The Revised Trauma Score was calculated for each patient, as previously described.[25] In addition, the probability of survival for each patient was calculated using the TRISS (Trauma Score and Injury Severity Score) method.[26] The Revised Trauma Score and the probability of survival were calculated using the ICDPIC version 3.0 module in Stata version 12.1 (StataCorp). A statistical comparison of the continuous data was performed with the *t* test or the Mann-Whitney *U* test, and the categorical data were analyzed using the χ^2 test. All statistical analyses were performed using SPSS version 21 (IBM Corporation) with statistical significance set at $P < .05$.

Results

From 2002 to early 2011, a total of 57 179 soldiers were admitted to an MTF for a trauma-related injury, and these admissions were recorded in the JTTR. Of these 57 179 soldiers, 2565 subsequently died in theater MTFs, for an overall DOW rate of 4.5% (**Table 1**; **Figure 1**). Of these 2565 soldiers, 902 died during the pre-DCR period, and 1663 died during the DCR period. The majority of those killed in either time period (80% of all deaths) died less than 24 hours after injury (ie, early deaths), and this percentage of early deaths increased significantly from the pre-DCR period (77%) to the DCR period (80%) ($P = .02$). The percentage of intermediate deaths (1-7 days after injury) was unchanged (13% for both periods; $P = .95$), whereas the percentage of late deaths (>7 days after injury) decreased from 10% during the pre-DCR period to 6% during the DCR period ($P \le .01$). Throughout the entire study period, 74% of soldiers who DOW had an ISS of higher than 15, qualifying them as severely injured. Comparing the pre-DCR and DCR periods (**Table 2**), we found that both the mean ISS and the percentage of patients with severe injury increased significantly (from a mean ISS of 22.5 to 26.7 and from 63.5% to 79.7%, respectively; $P < .05$). Similarly, the mean Revised Trauma Score was significantly lower (indicating more severe injury) for the DCR cohort (4.76) than for the pre-DCR cohort (5.67) ($P < .001$). The mean probability of survival based on the TRISS method was 77% for the pre-DCR cohort and 64% for the DCR cohort ($P < .001$). Severe injuries to specific body regions (defined as a regional AIS score of >3) were identified in 65% of all patients. The mean AIS score for the head/neck region increased significantly from 3.9 during the pre-DCR period to 4.3 during the DCR period ($P < .01$), whereas the mean score for all other body systems did not change. In addition, the percentage of patients with severe head injuries increased significantly from 57% during the pre-DCR period to 73% during the DCR period ($P < .05$), whereas the percentage of those with severe facial, chest, abdominal, extremity, and external injuries did not change (**Figure 2**; Table 2). To examine whether the

Table 2. Demographics and Injury Data for Pre-DCR and DCR Study Cohorts

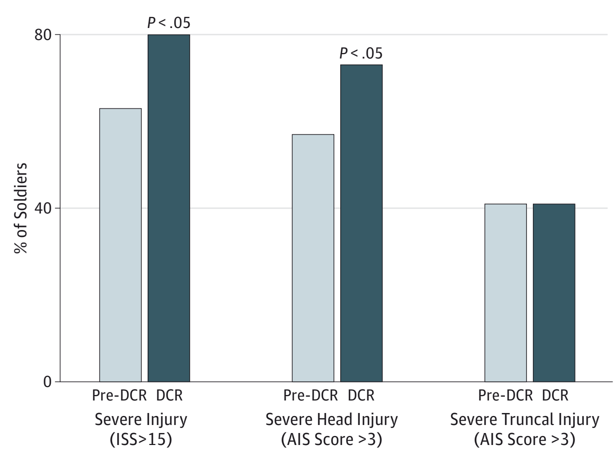
Data	Pre-DCR	DCR	*P* Value
Years	2001-2005	2006-2011	
Patients, No.	902	1663	
Deaths, %			
Early (0-24 h)	77	80	.02
Intermediate (1-7 d)	13	13	.95
Late (>7 d)	13	6	<.01
Mean ISS	22.5	26.7	.03
ISS > 15, %	63.5	79.7	<.01
Any AIS score >3, %	55.6	69.9	<.01
AIS score, %			
Head	3.9	4.3	<.01
Face	1.71	1.78	.39
Chest	3.26	3.19	.67
Abdomen	2.93	3.09	.24
Extremities	2.82	2.95	.57
External (skin)	2.07	2.11	.81
Revised Trauma Score, %	5.67	4.76	<.01
TRISS probability of survival, %	0.77	0.64	<.01

Abbreviations: AIS, Abbreviated Injury Scale; DCR, damage control resuscitation; ISS, Injury Severity Score; TRISS, Trauma Score and Injury Severity Score.

significant increase in injury severity among soldiers who subsequently died in the hospital was simply a reflection of increasing injury severity among all wounded patients, overall trends from all injured patients in the JTTR were examined. As demonstrated in **Figure 3**, there was no significant increase in injury severity (by mean ISS) among all injured patients during this time period. Consistent with previous reports, there were significant decreases seen in the percentage of KIA cases and in the CFR.

When examining fluid and blood product use, we found that there was a notable decrease in the amount of crystalloid given in the first 24 hours, from 6.1 L during the pre-DCR period to 3.2 L during the DCR period ($P < .05$). Colloid volume was not significantly changed (from 695 mL during the pre-DCR period to 857 mL during the DCR period), and there was also no difference in the use of cryopreciptate (from 8.6 U during the pre-DCR period to 7.8 U during the DCR period; $P = .79$) or platelets (from 3.1 U during the pre-DCR period to 3.8 U; $P = .61$) between the 2 study periods. The initial administration of both packed red blood cells (PRBCs) and fresh frozen plasma (FFP) increased significantly between the 2 time periods (the mean volume of PRBCs increased from 8.4 U during the pre-DCR period to 11.4 U during the DCR period, and the mean volume of FFP increased from 3.2 U during the pre-DCR period to 10.1 U during the DCR period) (both $P < .05$). Platelets given during these 2 time periods were not significantly changed (from 3.1 to 3.8 U), although very few patients received early platelets in the pre-DCR period. There was a marked change in the blood product ratio administered in the first 24 hours between the 2 time periods. The mean PRBC:FFP ratio changed from 2.6:1 during the pre-DCR period to 1.4:1 during the DCR period ($P < .01$) (**Figure 4**; **Table 3**). The ratio of cryoprecipitate to PRBCs (from 1.03:1 to 0.7:1) and the ratio of platelets to PRBCs (from 0.37:1 to 0.33:1) showed no significant differences between the 2 time periods.

Figure 2. Percentages of Soldiers With Severe Injury, Stratified by Study Cohort and Type of Injury

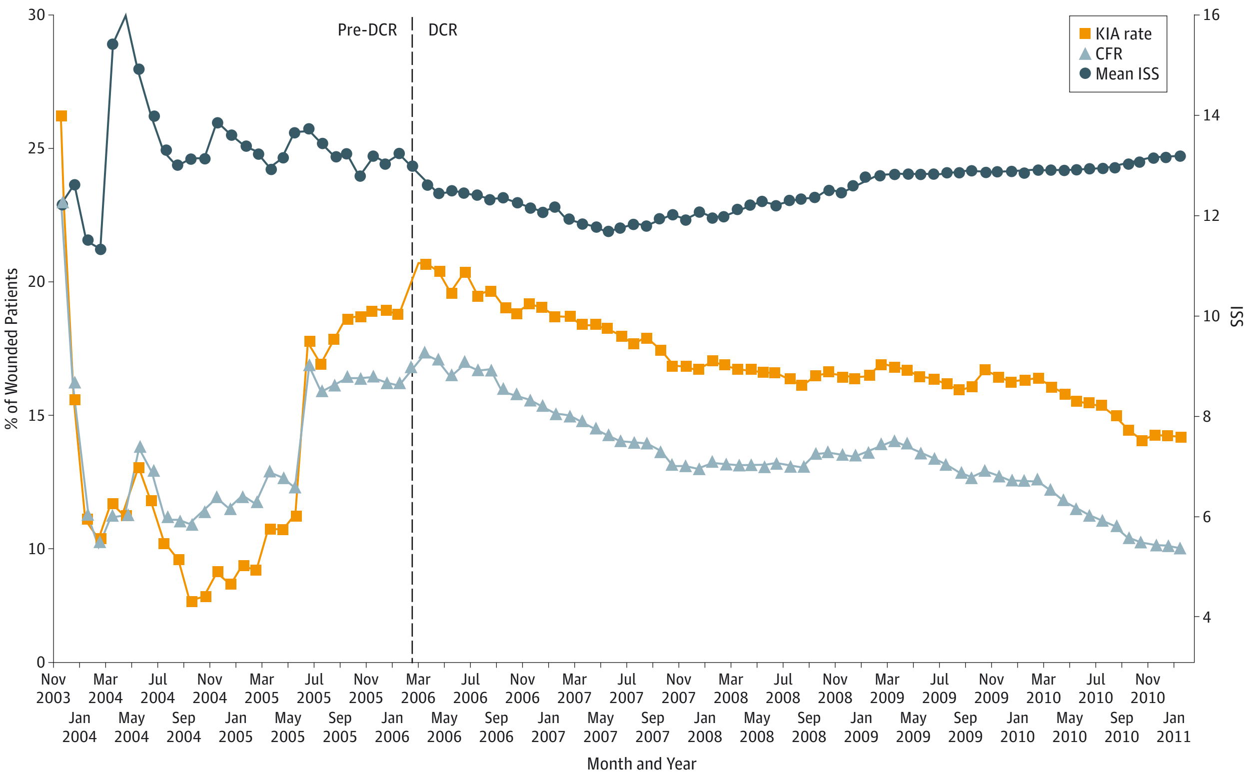


Statistical significance was determined by use of the χ^2 test. AIS indicates Abbreviated Injury Scale; DCR, damage control resuscitation; and ISS, Injury Severity Score

Discussion

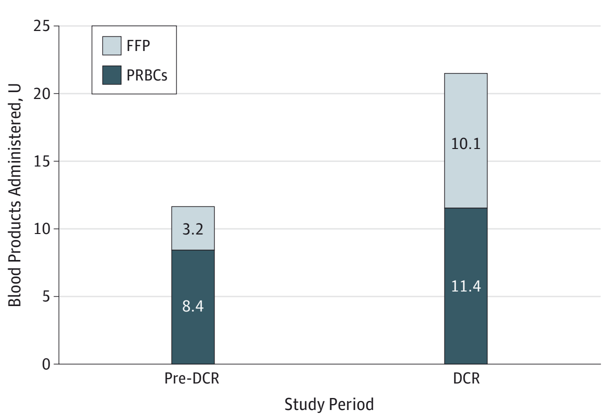
Combat fatalities are an unfortunate but inevitable consequence of war. The high volume and the increased severity of injured patients seen during combat operations throughout history has resulted in major advancements in trauma care. The recent conflicts in Iraq and Afghanistan have been no exception, with real-time data collection and timely analyses providing information that has been used to implement immediate improvements in care. Despite the progress in frontline battlefield care and the implementation of improved military-wide processes,[27,28] as many as 87% of

Figure 3. Cumulative Monthly Rolling Averages for Killed in Action (KIA) Rate, Case-Fatality Rate (CFR), and Mean Injury Severity Score (ISS) for All Wounded Patients



Data were obtained from the Joint Theater Trauma System Directors Report 2013. The dashed line indicates the time point used to divide the study population into those who were treated before the implementation of damage control resuscitation (DCR) policies and those who were treated after.

Figure 4. Total Volume of Blood Products Administered in the First 24 Hours



DCR indicates damage control resuscitation; FFP, fresh frozen plasma; and PRBCs, packed red blood cells.

battlefield deaths still occur in the pre-MTF setting.[29] This is nearly unchanged from the oft-cited 90% prehospital mortality rate of previous conflicts.[30,31] However, even though the proportion of deaths that occur in the pre-MTF phase of care remains high, there has been a significant improvement in overall survival during the last 70 years. Case fatality rates have decreased to approximately 10% in OIF and OEF,[32] a significant decrease from the 30% seen during World War II and the 24% seen during the Vietnam and Persian Gulf conflicts.[33]

Although overall battlefield mortality is now at a historic low, the number of in-hospital deaths has increased significantly but has received relatively little focused analysis. This historically high DOW rate is likely a reflection of improved prehospital care and decreased transport times, resulting in more severely injured patients surviving to reach a medical facility. Although this data set did not provide accurate times from injury to admission, there has been a well-described continuous improvement in transport times, with the average transport time decreasing from approximately 2 hours in the early years of OEF and OIF to approximately 45 minutes in more recent years. The analysis of in-hospital deaths has long been a key component of process- and quality-improvement efforts in civilian trauma centers, and it has been associated with decreased morbidity and mortality. We believe that analysis of this patient population is of equal or even greater importance in the combat setting and can provide invaluable data for evidence-based decision making. In addition, we felt that dynamic analysis of this patient population for significant changes over time would be important for both epidemiologic and clinical reasons.

In the prehospital combat setting, Eastridge et al[29] have shown that 24.3% of deaths were due to potentially survivable injuries, with hemorrhage accounting for the vast majority. As such, much of the military-relevant trauma research has focused on decreasing bleeding in the early postinjury period, with tourniquets[34-36] and hemostatic dressings[37,38] receiving special attention. While the body of literature on pre-MTF deaths continues to grow, there is relatively little data regarding in-hospital combat deaths. However, given that only 24% of pre-MTF combat deaths are due to potentially survivable injuries[29] and that 51% of in-hospital deaths were due to wounds that were labeled as potentially survivable,[39] it would seem prudent to shift more focus on those patients who DOW after presentation. Of the aforementioned patients, potentially survivable wounds were predominantly due to hemorrhage (80%), whereas nonsurvivable wounds were most often due to head injuries (83%). Other studies support these findings, confirming that head injury and hemorrhage are the most significant causes of in-hospital mortality,[23,40] with most deaths occurring shortly after admission.[23,41] Thus, there appears to be a significant potential for salvage in up to 50% of patients who die of wounds at an MTF.

Head injuries have been identified as one of the most significant causes of death in all combat environments. Our data support this finding and show that head injuries are associated with the highest mean AIS score in DOW patients, have demonstrated an increase in average severity, and represent an increasing percentage of the DOW population. This also implies that head injuries contribute disproportionately to the increase in overall injury severity that we observed in this data set. This injury pattern can be attributed to 2 unique features of our current conflicts: the evolution of enemy armaments and the widespread implementation of improved body armor. The use of improvised explosive devices has also increased dramatically during these conflicts[42,43] and is evidenced by a significantly increased percentage of blast injuries.[44,45] The increased incidence and severity of these blast injuries, combined with the increased use of protective gear that shields the torso, has caused damage to be shunted away from the trunk and toward the head and extremities.[46-48] This is consistent with the data presented by many other researchers.[44,49-53] Focused efforts for both the prevention and treatment of major head/brain injury warrant significant attention from combat trauma researchers, and our results indicate that this is becoming an increasingly important cause of in-hospital mortality.[45,54-58] Significant initiatives aimed at prevention or minimization of traumatic brain injuries, including improved personal protective equipment, vehicles, and wearable helmet blast sensors, have been implemented, but further research efforts are indicated.[46,59,60]

Severe hemorrhage has clearly been identified as the most common cause of preventable battlefield death. However, only about one-third of hemorrhagic deaths are from wounds amenable to a tourniquet, whereas two-thirds are attributed to junctional (axilla/groin) or truncal hemorrhage. Among this patient population, the manner and method of resuscitation and correction of coagulopathy have been essential to improving outcomes. Emerging from the early years of our current conflicts,[12,21] the foundation of DCR practice rests on the theory that the coagulopathy of trauma is worsened when the physiologic balance of whole blood is disrupted.[61,62] Several studies[17-20,63-66] have shown improvements in early and overall survival and functional outcomes when DCR practices are applied in the wartime setting. Similarly, civilian studies[13-15,67] have suggested survival benefits for trauma patients, particularly those who receive a massive transfusion. It should be noted that although DCR strategies are generally accepted as beneficial,[68] several studies have shown no mortality benefit,[69,70] whereas others have challenged whether the 1:1 ratio of PRBCs to plasma is truly optimal.[71] Furthermore, no true randomized controlled trials have evaluated DCR strategies, and many of the available observational studies are significantly limited by observer and time bias.[72] Even with these problems, the amount of literature favoring the early transfusion of balanced blood products has led to widespread adoption of these resuscitative techniques in both the military and civilian settings[69,73] and has powered the general belief that DCR is one of the most important medical breakthroughs of our current conflicts.

Table 3. Data on Fluids and Blood Products Administered in 24 Hours for the 2 Study Cohorts

Fluids or Blood Products	Mean Value: Pre-DCR	Mean Value: DCR	*P* Value
Volume			
Crystalloid, L	6.1	3.2	<.01
Colloid, mL	695	857	.32
PRBCs, U	8.4	11.4	.01
FFP, U	3.2	10.1	.01
Platelets, U	3.1	3.8	.60
Cryoprecipitate, U	8.6	7.8	.79
Whole blood, U	4.1	6.8	.27
PRBC:FFP ratio	2.6:1	1.4:1	<.01

Abbreviations: DCR, damage control resuscitation; FFP, fresh frozen plasma; ISS, Injury Severity Score; PRBCs, packed red blood cells.

Our data confirm findings from other studies showing that the military has actively implemented DCR policies, particularly among the most severely injured patients. We found that the average resuscitation ratio of red blood cell products to FFP decreased significantly between the 2 time periods and approached the "gold standard" of a 1:1 resuscitation ratio in the later years of our study. This reflects both the implementation of DCR protocols and the widespread acceptance of the concept of DCR among military trauma surgeons. Although our analysis primarily focused on red blood cells and FFP, we also noted that select patients received additional products, including cryoprecipitate and platelets, but that there was no significant difference between the 2 time periods with respect to these products. Several previous series[74,75] have demonstrated a potential survival benefit associated with the use of cryoprecipitate or platelets when given in balanced ratios to red blood cells. However, it is difficult to sort out the independent contribution of these products to improved outcomes because they are highly associated with FFP administration and may just represent another surrogate for a balanced product resuscitation.

Along with the change in the resuscitation approach, we noted a significant change in the epidemiology of the DOW population in terms of injury severity and patterns of injury. The overall ISS increased significantly between the 2 study periods, and the anatomic distribution demonstrated an increase in wounds, such as severe brain injury, that typically have been classified as "nonsurvivable." These findings are additionally confirmed by the comparison of the calculated Revised Trauma Score and TRISS survival probabilities between cohorts, with both demonstrating a greater injury burden and a significantly lower probability of survival in the DCR cohort. We believe that this represents a logical second-order effect of improved early care and resuscitation (namely, that there is improved salvage of less severely injured patients and a decreased number of deaths among those with potentially survivable injuries). In addition to representing an interesting epidemiologic phenomenon and confirmation of improved survival data, this has important implications for the utility and focus of combat death analysis. One could argue that this indicates that analysis of in-hospital deaths may represent an area of diminishing returns because the proportion of patients with truly nonsurvivable injuries increases while the opportunities for improvement correspondingly decrease. It could also support the assertion that a shift to other areas of potential improvement or patient salvage is indicated, such as deployed neurotrauma critical care and head-injury preventative measures. Finally, such data may be important for the design and selection of outcome measures in future studies of this patient population.

Our study has several limitations that are important to discuss. The data used for this analysis come from a combat trauma registry and may be subject to data entry and coding errors. The analysis was done retrospectively and, therefore, is subject to inherent limitations and potential bias or confounding. The potential for observer bias, misclassification, interobserver variability, confounding variables, and differing clinical judgment may have affected the treatment of patients in our study. Although data were included on anatomic areas of injury and injury scores, there was no reliable data on the exact cause of death or the exact timing from injury to death (or transport times). Our study also compares 2 groups in a before-and-after design over an 8-year period, and there were undoubtedly multiple systemic factors that evolved and improved during this time that could have contributed to the outcome measures. We primarily analyzed the ratio of FFP to PRBCs, and there may have been interactions with other products such as cryoprecipitate or platelets that are not accounted for. Finally, only in-hospital deaths were analyzed, and the classification and treatment of prehospital deaths and survivors cannot be inferred.

Conclusions

There has been a significant shift in resuscitation practices in forward combat hospitals, indicating the widespread military adoption of DCR. Patients who died in the hospital during the DCR period were more likely to have been severely injured and to have had severe brain injury, consistent with a decrease in the number of deaths among potentially salvageable patients. Our study provides a valuable adjunct to the currently available DCR literature in that it removes survivor bias and confirms that severely injured patients who DOW are receiving more balanced transfusion ratios and less crystalloid. The widely reported reductions in mortality associated with the adoption of DCR policies appears to also be reflected by an epidemiologic shift in in-hospital deaths toward increased overall injury severity and an increased percentage of soldiers with nonhemorrhagic causes of death, such as severe brain injury.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Langan, Eckert.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
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