The evolution of pediatric transfusion practice during combat operations 2001-2013

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BACKGROUND: Hemostatic resuscitation principles have significantly changed adult trauma resuscitation over the past decade. Practice patterns in pediatric resuscitation likely have changed as well; however, this evolution has not been quantified. We evaluated pediatric resuscitation practices over time within a combat trauma system.

METHODS: The Department of Defense Trauma Registry was queried from 2001 to 2013 for pediatric patients (<18 years). Patients with burns, drowning, and missing injury severity score were excluded. Volumes of crystalloid, packed red blood cells (PRBC), whole blood, plasma, and platelets (PLT) given in the first 24 hours were calculated per kilogram body weight. Tranexamic acid use was also determined. Patients were divided into Early (2001–2005) and Late (2006–2013) cohorts, and subgroups of transfused (TX+) and massively transfused (MT+) patients were created. Intensive care unit and hospital length of stay and 24-hour and in-hospital mortality rates were compared.

RESULTS: A total of 4,358 patients met inclusion criteria. Comparing Early versus Late, injuries from explosions, isolated or predominant head injuries, and injury severity score all increased. The proportion of TX+ patients also increased significantly (13.6% vs 37.4%, $p < 0.001$) as did the number of MT+ patients (2.1% vs 15.5%, $p < 0.001$). Transfusion of high plasma:RBC and PLT:RBC ratios increased in both the TX+ and MT+ subgroups, although overall, PLT and whole blood use was low. After adjusting for differences between groups, the odds of death was no different Early versus Late but decreased significantly in the MT+ patients with time as a continuous variable.

CONCLUSION: Transfusion practice in pediatric combat casualty care shifted toward a more hemostatic approach over time. All-cause mortality was low and remained stable overall and even decreased in MT+ patients despite more injuries due to explosions, more head injuries, and greater injury severity. However, further study is required to determine the optimal resuscitation practices in critically injured children. (*J Trauma Acute Care Surg.* 2018;84: S69–S76. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Epidemiologic study, level IV.

KEY WORDS: Pediatric trauma; transfusion; damage control resuscitation; combat injury.

Resuscitation practices in adult combat casualties changed significantly over the course of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).[1] Analysis of early transfusion data demonstrated that increased empiric use of plasma (PLAS), platelets (PLT), and whole blood (WB) significantly improved survival in severely injured, bleeding casualties.[1–3] Internal dissemination of these results, command briefings with military medical and nonmedical leadership, and publication of a resuscitation clinical practice guideline (CPG), which promoted these hemostatic resuscitation principles that occurred in late 2004 and continued through 2005.[4]

From these efforts, the concept now widely known as damage control resuscitation (DCR) emerged.[5–7] This resuscitation approach seeks to replace shed blood with WB or components that resemble as closely as possible what has been lost[8,9] while also minimizing crystalloid and colloid infusions, which dilute clotting factors and worsen acidosis.[9,10] This approach has significantly improved survival in both severely injured combat casualties and civilians, and consequently, DCR is now a fixture in both military and civilian CPGs.[11–13]

During these same combat operations, pediatric combat casualties and humanitarian patients represented nearly 6% of admissions and 11% of hospital bed days.[14] However, resuscitation practices in these pediatric patients and the degree to which DCR principles were applied during this time remain unknown. In this study, we sought to characterize the practice patterns of pediatric trauma resuscitation over the course of OIF and OEF

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and to evaluate the hypothesis that hemostatic resuscitation increased significantly over time in this population.

METHODS

This study was initiated under a protocol reviewed and approved by the San Antonio Military Medical Center Institutional Review Board. We queried the Department of Defense Trauma Registry (DoDTR) for all injured patients younger than 18 years admitted to US combat support hospitals in Iraq and Afghanistan from 2001 to 2013. This included direct admissions to Level/Role III care as well as transfers in from other US and coalition facilities.[14,15] Based on the dissemination of research results throughout the DoD and at national meetings in 2004 and 2005[15,16] and publication of the first DCR CPG in December 2004,[11] we defined the period of 2001-2005 as Early and 2006-2013 as Late.

For this analysis, we focused on traumatized patients requiring admission. Thus, we a priori excluded those with isolated burns, drowning, and other nontrauma mechanisms within the registry as well as those with missing injury severity score (ISS) data. We also prospectively planned a subset analysis exclusively on those patients who were transfused any blood product (TX+) as well as those who received a massive transfusion (MT+). We defined MT as 40 mL/kg or more total blood products given within the first 24 hours of injury.[17]

Study demographics included age, weight, sex, and injury mechanism. Missing weights were imputed using mean recorded weights for each age and sex grouping (in 1-year increments) as previously described.[17] Measures of injury severity including GCS (Glasgow Coma Scale), Abbreviated Injury Scale (AIS) for each body region and ISS were also retrieved. Patients with severe traumatic brain injury (TBI) were classified as having a severe isolated head injury (defined as a head AIS ≥ 3 with no other injuries) or a predominant head injury (head AIS of 2 or more over the next highest AIS).[18] Physiologic and laboratory data collected on admission to Level/Role III care were evaluated, including temperature, hematocrit, base deficit, platelet count, and international normalized ratio (INR). Base deficit-INR-GCS (BIG) scores were calculated in patients with all constituent values recorded.[19] Age-adjusted tachycardia and hypotension were identified using published heart rate and blood pressure norms.[20] Coagulopathy was defined as an admission INR ≥ 1.5. The primary end points for this analysis were 24-hour and in-hospital mortality rates. Hospital length of stay and intensive care unit length of stay were also evaluated.

Resuscitation data included the 24-hour volumes for crystalloid and the number of units of WB, packed red blood cells (PRBC), PLAS, PLT, and cryoprecipitate (CRYO). The volume of blood products administered was converted from units to milliliters by using standard volumes of in-theater blood products (WB, 450 mL; PRBC, PLAS, and PLT, 250 mL; and CRYO, 90 mL or 150 mL) and then divided by the patient's weight in kilograms. Platelet units were aphaeresis units, which represent the equivalent of approximately six pooled donor units. Tranexamic acid (TXA; currently considered off-label for trauma) administration was also retrieved.

For ratio calculations, WB volumes were added to both the numerator (PLAS or PLT) and denominator (red blood cells (RBC)) after the method of Pidcoke et al.[1] Patients were grouped by product ratios for PLAS and PLT to RBC using target ratios of 1:1:2 and 1:1:1.[11,12] Four blood product ratio combinations for PLAS and PLT relative to RBC were evaluated using the method of Pidcoke et al.[1] using both 1:1:2 and 1:1:1 cutoffs: LO/LO, HI/LO, LO/HI, HI/HI.

Chi-square and Mann-Whitney *U* tests were used as appropriate with results presented as frequency (percent) and median [25%–75% interquartile range]. Effects over time were assessed using the Kruskal-Wallis H test. Multivariable logistic regression with backward elimination was performed to determine factors independently associated with death in this population reported as odds ratio (OR) [95% confidence interval (CI)]. Covariates for this model were selected by comparing demographics, injury mechanism and severity, and treatment variables between survivors and nonsurvivors. Those with a $p < 0.1$ were identified for inclusion in the model. The effect of blood product ratio combinations on mortality was also evaluated using logistic regression reported as OR and 95% CI. $p < 0.05$ was considered statistically significant for all comparisons. Statistical analysis was performed with SPSS Version 23 (IBM Analytics, Armonk, NY).

RESULTS

Between 2001 and 2013, 4,990 patients younger than 18 years were included in the DoDTR. From this cohort, 632 were excluded, leaving 4,358 for analysis. Of these, 1,068 (24.5%) were managed from 2001 to 2005 (Early), while 3,290 were managed from 2006 to 2013 (Late) (Figure, Supplemental Digital Content 1, http://links.lww.com/TA/B100). Patients in the Late group were somewhat younger and smaller as compared to those in the Early group (Table 1). The injury demographics also changed with an increase in explosive mechanisms and more patients with isolated or predominant head injuries in the Late group. On admission, patients had a high rate of tachycardia, were relatively anemic, and had a high rate of coagulopathy on admission. Finally, injury severity was high in all years and increased over time (Table 1).

Over the entire study period, 1,377 patients (31.6%) received a blood product during the course of their management (TX+), and 531 (12.2%) received a massive transfusion (MT+). The proportion of both TX+ and MT+ patients increased over time (Table 1, Fig. 1), and TX+ patients in the Late group were smaller and more severely injured. Trends in specific resuscitation practice included an overall decrease in crystalloid with a concomitant increase in all blood product components including PRBC, PLAS, PLT, and CRYO (Table 2, Fig. 2). Twenty-four-hour total resuscitation volume remained stable throughout the study period in the TX+ group, but total resuscitation volume decreased significantly in the MT+ group (Table 2, Fig. 2). The proportion of patients achieving a 1:2 ratio of PLAS:RBC and PLT:RBC increased significantly in both the TX+ and MT+ subgroups (Table 2). The proportion of those achieving a 1:1 ratio also increased significantly for both PLAS:RBC and PLT:RBC in the TX+ group and PLT:RBC in the MT+ group (Table 2). Analysis of ratio combinations indicated a significant shift toward the HI/LO and HI/HI groups over time (Table 2); however, regression analysis did not demonstrate any survival benefit in any of the HI groups relative to LO/LO. Although PLAS use increased significantly and remained high after 2006, PLT use was generally low throughout the course of the study with

TABLE 1. Patients' Demographics and Outcomes

		ALL 01-13	Early 01-05	Late 06-13		TX+ Early	TX + Late		MT + Early	MT+ Late	
	n	n = 4,358	n = 1,068	n = 3,290	*p*	n = 145	n = 1,232	*p*	n = 22	n = 509	*p*
Age, y		9 [6–13]	10 [6–13]	9 [6–13]	0.001	12 [7–14]	10 [6–13]	0.138	8 [5–12]	9 [5–11]	0.531
Weight, kg	2,230	30 [20–40]	31 [21–41]	28 [20–39]	<0.001	36 [20–46]	30 [20–40]	0.023	24 [14–36]	26 [19–36]	0.353
Female sex		955 (21.9)	227 (21.3)	728 (22.1)	0.549	27 (18.6)	289 (23.5)	0.190	5 (22.7)	133 (26.1)	0.722
Conflict					<0.001			0.019			0.002
OEF		2,610 (59.9)	543 (50.8)	2,067 (62.8)		78 (53.8)	785 (63.7)		7 (31.8)	327 (64.2)	
OIF		1,748 (40.1)	525 (49.2)	1,223 (37.2)		67 (46.2)	447 (36.3)		15 (68.2)	182 (35.8)	
Mechanism					<0.001						
Blunt		1,092 (25.1)	346 (32.4)	746 (22.7)		20 (13.8)	179 (14.5)		2 (9.1)	53 (10.4)	
Explosion		1,921 (44.1)	361 (33.8)	1,560 (47.4)		70 (48.3)	656 (53.2)		12 (54.5)	305 (59.9)	
Penetrating		1,345 (30.9)	361 (33.8)	984 (29.9)		55 (37.9)	397 (32.2)		8 (36.4)	151 (29.7)	
Isolated head		282 (6.5)	52 (4.9)	230 (7.0)	0.014	6 (4.1)	91 (7.4)	0.148	1 (4.5)	35 (6.9)	0.670
Predominant head		427 (9.8)	81 (7.6)	346 (10.5)	0.005	15 (10.3)	152 (12.3)	0.487	0 (0)	54 (10.6)	0.107
ISS		9 [4–17]	9 [4–14]	10 [5–17]	<0.001	11 [10–18]	16 [10–24]	0.002	16 [10–22]	17 [11–26]	0.485
ED temperature, °C	3,506	36.9 [36.4–37.5]	36.9 [36.4–37.5]	36.9 [36.4–37.4]	0.460	36.8 [36.1–37.7]	36.8 [36.2–37.4]	0.737	36.4 [36.1–37.3]	36.6 [36.0–37.3]	0.881
ED pulse	4,158	118 [110–139]	115 [98–131]	119 [100–140]	<0.001	128 [105–145]	128 [108–150]	0.247	130 [121–150]	136 [116–160]	0.740
Tachycardia, age-adj		1,574 (37.9)	336 (33.8)	1,238 (39.1)	0.003	72 (54.1)	638 (53.6)	0.909	13 (61.9)	305 (62.0)	0.994
ED SBP	4,047	116 [103–128]	115 [103–127]	116 [103–128]	0.079	109 [94–123]	110 [95–125]	0.730	110 [85–125]	103 [85–119]	0.532
Hypotension, age-adj		196 (4.8)	47 (4.9)	149 (4.8)	0.888	14 (10.9)	120 (10.3)	0.827	5 (25.0)	90 (18.8)	0.488
GCS	3,749	15 [8–15]	15 [13–15]	15 [7–15]	<0.001	15 [8–15]	13 [3–15]	<0.001	15 [7–15]	10 [3–15]	0.017
HCT	3,022	34 [29–37]	33 [28–38]	34 [29–38]	0.021	28 [23–34]	31 [26–36]	0.001	29 [26–32]	30 [26–35]	0.021
PLT	2,847	313 [233–393]	322 [239–397]	311 [233–393]	0.455	316 [216–402]	285 [196–380]	0.143	223 [144–393]	266 [169–377]	0.625
INR	2,236	1.2 [1–1.4]	1.3 [1.1-1.5]	1.2 [1.0-1.4]	<0.001	1.4 [1.2-1.6]	1.3 [1.1-1.7]	0.188	2.2 [1.3-2.8]	1.4 [1.2-2.0]	0.087
Coagulopathy	2,236	526 (23.5)	34 (28.8)	492 (23.2)	0.164	17 (37.0)	327 (37.6)	0.932	6 (60.0)	158 (48.9)	0.490
pH	2,651	7.32 [7.25–7.38]	7.33 [7.24–7.39]	7.32 [7.25–7.38]	0.855	7.31 [7.19–7.36]	7.27 [7.20–7.34]	0.279	7.20 [7.05–7.28]	7.23 [7.13–7.31]	0.601
Base deficit	2,638	4 [2–7]	5 [3–8]	4 [2–7]	0.023	7 [4–11]	6 [4–10]	0.307	9 [6–16]	8 [5–12]	0.621
BIG score	1,910	9.25 [5.25–17.5]	10.5 [6.75–19.1]	9 [5.25–17.5]	0.228	17.25 [11–23.5]	14.75 [9–21.5]	0.481	17.5 [17.25–26.25]	19 [11.5–24.75]	0.826
TX+		1,377 (31.6)	145 (13.6)	1,232 (37.4)	<0.001	—	—	—	—	—	—
MT+		531 (12.2)	22 (2.1)	509 (15.5)	<0.001	22 (15.2)	509 (41.3)	<0.001	—	—	—
TXA		98 (2.2)	7 (0.7)	91 (2.8)	<0.001	2 (1.4)	73 (5.9)	0.023	1 (4.5)	59 (11.6)	0.307
ICU LOS		1 [0–3]	1 [0–4]	1 [0–3]	<0.001	3 [1, 7]	3 [1, 5]	0.464	4 [2, 15]	4 [2, 7]	0.441
Hospital LOS		3 [1–7]	4 [2–9]	3 [1–7]	<0.001	6 [3, 12]	6 [3, 11]	0.394	6 [3, 21]	7 [3, 13]	0.704
Died <24 hrs		160 (3.7)	21 (2.0)	139 (4.2)	0.001	2 (1.4)	65 (5.3)	0.039	1 (4.5)	34 (6.7)	0.693
Died in hospital		323 (7.4)	61 (5.7)	262 (8.0)	0.015	14 (9.7)	162 (13.1)	0.233	3 (13.6)	90 (17.7)	0.625

Results are presented as median [IQR] or as n (%).
HCT, hematocrit; ICU, intensive care unit; LOS, length of stay; SBP, systolic blood pressure; TX+, transfused patients.

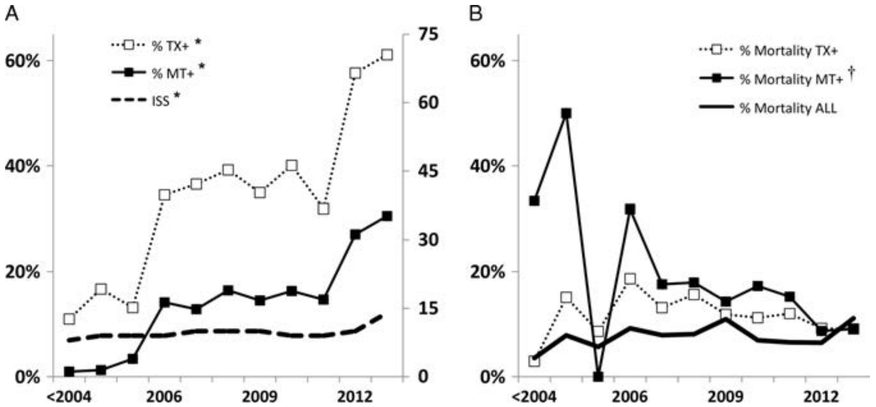

Figure 1. Trends in transfusion over time. (*A*) Percent of the entire patient population receiving any blood product transfusion (TX+) or a massive transfusion (MT+, ≥ 40 mL/kg all blood products) over the entire study period along with median ISS (*dashed line*). (*B*) Percent mortality in the overall group (solid line) as well as the TX+ and MT+ subgroups. $^{*}p < 0.001$; $^{\dagger}p = 0.038$ by Kruskal-Wallis H test.

notable increases in PLT use only occurring in the MT+ group in 2011 and 2012 (Fig. 2B, D). Furthermore, use of WB was uncommon (2% TX+ and 4% MT+). Transfusion practices varied significantly over time by conflict as well with OIF dominating the Early period and OEF dominating in the Late period (Table 1, Fig. 3).

Tranexamic acid was used infrequently as well; however, its use increased significantly overall and in the TX+ subgroup (Table 1). Although TXA was used primarily in the TX+ and MT+ patients, there were a total of 23 patients who received TXA but were not transfused.

Patients in the Late group had shorter intensive care unit and hospital stays (Table 1). When considering time as a categorical variable (Early vs Late), after adjusting for significant differences between survivors and nonsurvivors (Table, Supplemental Digital Content 2, http://links.lww.com/TA/B101), no significant findings in mortality at 24 hours or in-hospital emerged. Conversely, with time as a continuous variable, mortality significantly decreased in the MT+ subgroup on both univariable (Fig. 1B; $p = 0.038$) and multivariable analysis (OR, 0.739; 95% CI, 0.575–0.950; $p = 0.018$). BIG scores were calculated for 1,910 of 4,358 patients (43.8%) and were 9.25 [5.25–17.5] in the total cohort, 14.75 [9–21.5] in TX+, and 19 [11.5–24.75] in MT+. This gave an observed: expected (O/E) mortality ratio of 0.95 [0.21–2.07], 1.36 [0.45–4.02], and 0.92 [0.42–3.5], respectively. These scores did not change significantly over the study period (Table 1).

On multivariable logistic regression, independent predictors of mortality at 24 hours and hospital discharge included female sex, isolated head injury, ISS, age-adjusted tachycardia, presence of coagulopathy, and increasing base deficit (Table 3). Greater crystalloid volumes were associated with *decreased* mortality (24 hours and hospital), while greater blood product volumes were associated with *increased* mortality (hospital). As previously noted, management in the Early versus Late time period was not independently associated with mortality.

DISCUSSION

The purpose of this study was to describe resuscitation practices in pediatric trauma patients during combat operations in Iraq and Afghanistan, specifically with regard to the application of DCR principles and the effect of their use on patient outcomes. From this analysis, it seems that the DCR principles of balanced blood product resuscitation, decreased crystalloid use, and the select use of hemostatic adjuncts such as TXA were applied with increased frequency over time. Furthermore, the proportion of patients who were transfused and who received a massive transfusion increased markedly. Over the course of OIF and OEF, the incidence of injuries from explosive mechanisms, the incidence of TBI, and injury severity increased among pediatric patients. Notwithstanding, mortality at 24 hours and hospital discharge was no different in the Late period after controlling for significant differences between groups and improved significantly in the MT+ group over the entire study period. Furthermore, in those who were transfused or received a massive transfusion, a high ratio of PLAS:RBC and PLT:RBC was achieved more often in the Late period.

Over the course of combat operations in Iraq and Afghanistan, thousands of host nation children were managed in US combat facilities for combat injuries, burns, and a range of other medical and surgical conditions.[14,21–24] One recent analysis of 7,505 pediatric admissions (<18 years old) during combat operations found that pediatric inpatient care represented, on average, nearly 6% of all admissions and 11% of inpatient bed days.[14] These patients remained in the hospital longer than all other groups including adult local nationals. Furthermore, these young patients also had a higher mortality than all other groups at 8.5% with age younger than 8 years and female sex representing independent risk factors for death. Thus, going forward, planning for pediatric medical care with regard to pediatric supplies, pediatric predeployment training, and pediatric practice guidelines represents the minimum standard for medical readiness. From the present study, it is also clear that frequent high-volume pediatric resuscitations should also be anticipated in a combat environment.

Historically, very little has been written on the subject of large-volume resuscitation in children. The principal exception is in the area of pediatric burns.[25] In 1999, Barrett et al. reported a case series of 20 consecutive severely burned pediatric patients (mean age, 6.4; mean total body surface area burned, 80%) who were managed with 1:1 PLAS to PRBC and minimal crystalloid

TABLE 2. Treatments and Outcomes in the Transfusion and Massive Transfusion Subgroups

	Early 01-05	Late 06-13	
TX+	**n = 145**	**n = 1,232**	***p***
Crystalloid, mL/kg	93 [52, 134]	65 [34, 104]	<0.001
PRBC, mL/kg	14 [10, 23]	18 [10, 38]	0.003
WB, mL/kg	0 [0, 0]	0 [0, 0]	0.551
PLAS, mL/kg	0 [0, 0]	13 [0, 29]	<0.001
PLT, mL/kg	0 [0, 0]	0 [0, 0]	<0.001
CRYO, mL/kg	0 [0, 0]	0 [0, 0]	<0.001
Total blood products, mL/kg	17 [10, 26]	33 [16, 67]	<0.001
Total fluids, mL/kg	112 [66, 164]	107 [67, 171]	0.933
Hi ratio PLAS:RBC, ≥1:2	25 (17.2)	783 (63.6)	<0.001
Hi ratio PLT:RBC, ≥1:2	4 (2.8)	224 (18.2)	<0.001
Hi ratio PLAS:RBC, ≥1:1	16 (11.0)	560 (45.5)	<0.001
Hi ratio PLT:RBC, ≥1:1	3 (2.1)	168 (13.6)	<0.001
MT+	**n = 22**	**n = 509**	
Crystalloid, mL/kg	136 [100, 209]	78 [42, 126]	<0.001
PRBC, mL/kg	46 [25, 60]	42 [29, 60]	0.939
WB, mL/kg	0 [0, 0]	0 [0, 0]	0.963
PLAS, mL/kg	24 [0, 33]	33 [21, 50]	0.004
PLT, mL/kg	0 [0, 0]	0 [0, 10]	0.010
CRYO, mL/kg	0 [0, 0]	0 [0, 0]	0.011
Total blood products, mL/kg	63 [50, 87]	78 [53, 125]	0.049
Total fluids, mL/kg	234 [171, 298]	177 [127, 248]	0.029
HI ratio PLAS:RBC, ≥1:2	14 (63.6)	434 (85.3)	0.007
HI ratio PLT:RBC, ≥1:2	3 (13.6)	198 (38.9)	0.016
HI ratio PLAS:RBC, ≥1:1	7 (31.8)	263 (51.7)	0.075
HI ratio PLT:RBC, ≥1:1	2 (9.1)	145 (28.5)	0.046
Ratio groups (1:1:2)*-LO,LO	7 (31.8)	58 (11.4)	0.009
HI,LO	12 (54.5)	254 (49.9)	
LO,HI	1 (4.5)	17 (3.3)	
HI,HI	2 (9.1)	180 (35.4)	
Ratio groups (1:1:1)*-LO/LO	14 (63.6)	181 (35.6)	0.050
HI/LO	6 (27.3)	184 (36.1)	
LO/HI	1 (4.5)	65 (12.8)	
HI/HI	1 (4.5)	79 (15.5)	

Results are presented as median [IQR] or as n (%).

*Ratio groups are annotated as PLAS,PLT relative to PRBC using two different cutoffs for classification as a HI ratio (1:1:2 and 1:1:1).

ICU, intensive care unit; LOS, length of stay.

during burn excision. These patients received on average nearly 200-mL/kg blood products and only 45-mL/kg crystalloid during burn wound excision. Postoperatively, only one patient had a bleeding complication in the setting of preoperative acute renal failure and all survived. These remarkable results predated the concept of DCR, which has since been widely applied to adult trauma resuscitation[13] and has also been revalidated as a beneficial approach in pediatric burns.[26]

There are now several small retrospective studies on pediatric blood product resuscitation in civilian trauma patients, and the recent study by Nosanov et al.[27] provides some context for interpreting the results of our study. In this report from the LA County + USC Medical Center, 6,675 pediatric patients (age ≤ 18) were admitted over a 7-year period. During this time, 82 died within 24 hours and were excluded, 403 (6.0%) were transfused, and of these, 105 (1.6% overall and 26.1% of transfused) received an MT defined as blood product transfusion of 50% or greater of estimated blood volume (approximately 35 mL/kg in school-age children). Slightly higher rates of both transfusion and MT were reported in a recent retrospective study by Livingston et al.[28] of 435 severely injured pediatric trauma patients (age <18 years, ISS >12) in which 79 were transfused (18%) and of these, 13 (3% overall and 16% of transfused) received an MT (>40-mL/kg PRBC). By comparison, we report 4,358 injured children over 11 years of whom 1,377 (31.6%) were transfused some type of blood product and of these, 531 (12.2% overall and 38.6% of transfused) received an MT (≥40 mL/kg total blood products). Thus, the frequency of both transfusion and massive transfusion was far greater in our experience than in these civilian reports. We also included those who died within 24 hours (n = 160) as part of this comprehensive descriptive analysis.

Of the 105 massively transfused patients who survived over 24 hours reported by Nosanov et al., 92 (87.6%) also received PLAS and 57 (54.3%) received PLT, which allowed further assessment of patients according to the transfused blood product ratio. In this study, blood product ratios did not seem to have any effect on mortality likely because all deaths after 24 hours (n = 19, 18.1%) were in patients with head injuries. By comparison, in our study, 495 MT+ patients (93%) received plasma while only 199 (37.5%) received PLT and only 23 (4.3%) received WB. The lower use of PLT in our patients was likely due to inconsistent availability of apheresis platelets throughout these combat operations. Future efforts should focus on making PLT transfusions more consistently available and in promoting PLT and WB use more routinely for severely injured pediatric patients. However, like Nosanov et al., we ultimately found there was no independent association between high PLAS:PLT:RBC ratios and patient survival within the limits of the DoDTR data set.

There are very striking similarities between our findings and the adult DCR experience in Iraq and Afghanistan as reported by Pidcoke et al.[1] These include significant rates of coagulopathy among transfused patients (37.6% vs 32.6%), increases in RBC, PLAS, and PLT transfusions over time, increased relative use of PLAS with a major upswing from 2005 to 2006, an overall decrease in crystalloid use, and a significant increase in TXA use near the end of combat operations. Furthermore, there were similar trends upward in MT. Thus, it is quite clear that adult resuscitation practices were being applied to pediatric patients as well.

The mortality rates we report in the subset of TX+ patients (12.8%) and MT+ patients (17.5%) also compare favorably to those reported by Pidcoke et al. (15.6% and 18.5%, respectively),[1] and we found that mortality in the MT+ subgroup decreased over the entire study period. In addition, the O/E mortality using BIG scores indicated survival within the expected range for all groups. However, on closer inspection of our findings, we believe there are several areas for improvement. First, the independent association between crystalloid volumes, blood product volumes, and mortality bears mention. The association between low crystalloid volumes and increased mortality is likely due to inherent survivor bias (i.e., patients died before they were able to receive significant volumes of crystalloid), as this association did not persist when early deaths were excluded.

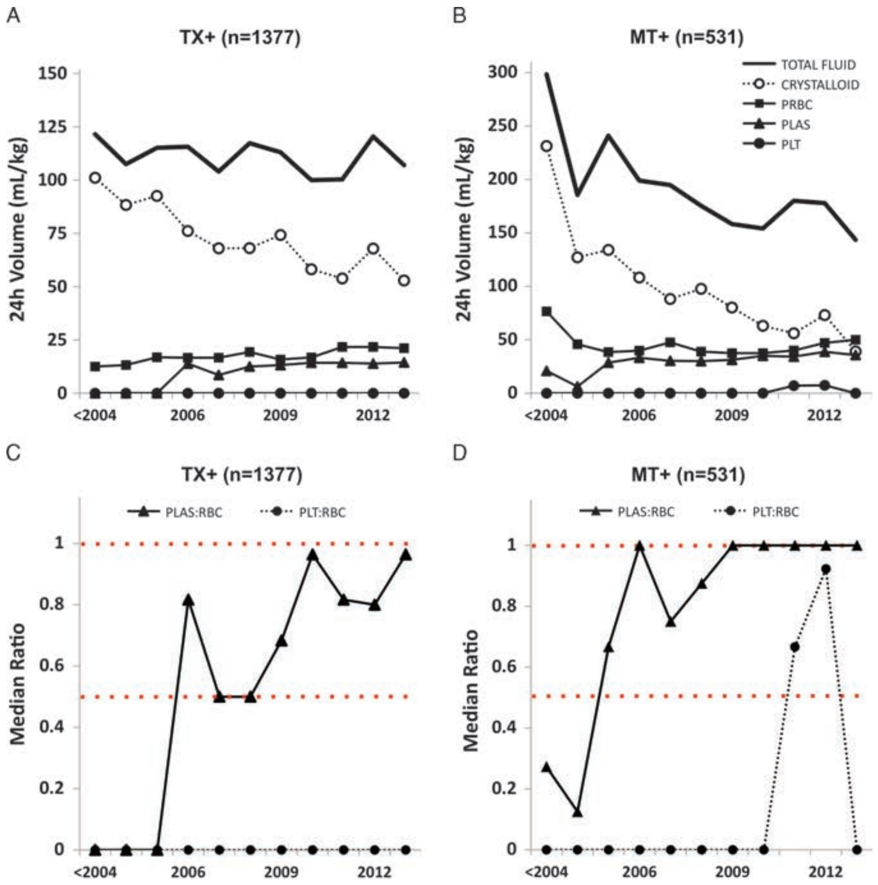

Figure 2. Twenty-four-hour volumes of crystalloid, PRBC, PLAS, and PLT in the TX+ and MT+ subgroups (*A*, *B*, respectively) of those who were transfused (*A*) and who received a massive transfusion (*B*; note the difference in *y*-axis scale). Median ratios of PLAS:RBC and PLT:RBC as well as mortality in the TX+ and MT+ subgroups (*C*, *D*, respectively). *Horizontal dashed lines* represent the target ratios of 1:2 (TQIP) and 1:1 (Joint Trauma System CPG).

However, the blood product association did persist upon excluding early deaths, suggesting late mortality due to over-resuscitation, multiorgan failure, or other causes potentially related to the resuscitation. Second, a number of children with no documented head injury expired without receiving a transfusion, including 45 children with documented vitals on admission and 11 with coagulopathy. Although this finding could be due to inaccurate data entry, it warrants further exploration. Finally, the infrequent use of both PLT and WB was surprising and represents an area for future improvement.

Although this analysis represents the largest reported experience of pediatric trauma resuscitation to date, several limitations must be noted. First, the granularity of the DoDTR does not lend itself to capturing the time-sensitive, dynamic

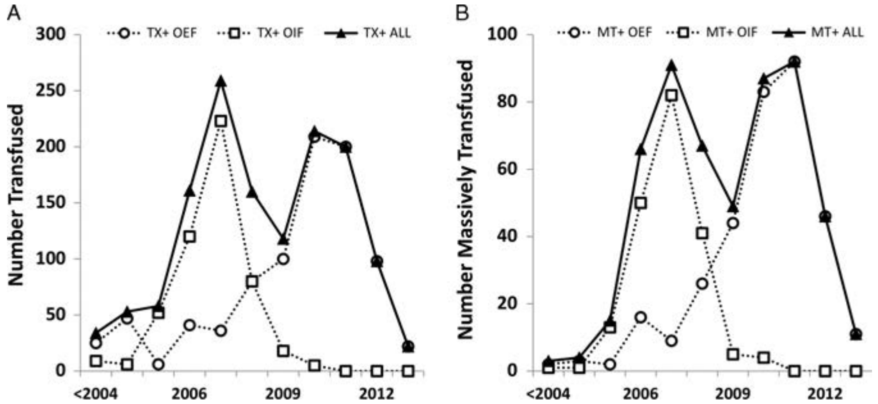

Figure 3. Number of transfused and massively transfused patients (*A*, *B*, respectively) over time divided by military operation. OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom.

TABLE 3. Multivariable Logistic Regression

24-Hour Mortality	**OR**	**95% CI**	***p***
Female sex	2.156	[0.961, 4.731]	0.062
Isolated head	7.611	[3.208, 18.058]	<0.001
ISS	1.063	[1.034, 1.093]	<0.001
Tachycardia (age-adj)	2.728	[1.207, 6.166]	0.016
Coagulopathy	4.844	[2.103, 11.155]	<0.001
Base deficit	1.086	[1.021, 1.155]	0.008
Total crystalloid	0.977	[0.966, 0.988]	<0.001
Hospital Mortality	**OR**	**95% CI**	***p***
Female sex	2.232	[1.271, 3.919]	0.005
Isolated head	5.329	[2.711, 10.475]	<0.001
ISS	1.101	[1.074, 1.130]	<0.001
Tachycardia (age-adj)	1.766	[1.020, 3.056]	0.042
HCT	1.037	[0.999, 1.075]	0.054
Coagulopathy	4.858	[2.799, 8.431]	<0.001
Base deficit	1.063	[1.013, 1.115]	0.013
Total crystalloid	0.989	[0.982, 0.995]	<0.001
Total blood products	1.007	[1.002, 1.012]	0.008

The model includes n = 1,607 (36.9%) valid entries with 35 deaths for 24-hour mortality and 85 deaths for hospital mortality.

age-adj, age-adjusted.

nature of a resuscitation. As multiple investigators have noted, reporting an amalgamated resuscitation experience over even 24 hours loses much of the nuance with regard to timely administration of blood products and component selection that are now widely recognized as essential to resuscitation success.[13,29,30] Future studies on pediatric transfusion practice should capture these details. Second, although we report the overall resuscitation practice during the course of combat operations, our analysis says nothing about the appropriateness of patient selection or the precision of the resuscitation. Thus, we cannot be certain that specific patients were managed optimally with regard to recognition of hemorrhagic shock and avoiding both over- and under-resuscitation. Third, missing data throughout the registry further weaken the conclusions that can be drawn from these findings. For example, our finding of favorable O/E mortality using BIG scores could be flawed as more than 50% of patients were missing one or more constituent value. Finally, regarding outcomes, specific causes of death are not listed in the registry, so it is unclear whether those who died might have been saved with an improved resuscitation strategy or whether, in fact, their injuries were not survivable. Future detailed assessments on the preventability of death in host nation children managed in our combat facilities should be modeled after the landmark study by Eastridge et al.[31] on preventable in-hospital deaths in adult combat casualties.

In this study, we focus exclusively on the resuscitation of injured children in the austere environment of a combat zone. Thus, the nutritional status and general preinjury health of these patients is likely different from civilian pediatric trauma patients outside a combat zone. Furthermore, the injury mechanisms and demographics are markedly different with far more penetrating and explosive injuries than blunt mechanisms. Nonetheless, our findings can be directly used to inform medical planning for future combat operations and can be incorporated into predeployment education and training modules for those involved in direct patient care during combat.[14,32,33] Furthermore, this epidemiologic overview along with our other reports on pediatric resuscitation during combat[17,34] can be used to better inform the care of severely injured children in this country with unstable hemodynamics who require blood product resuscitation.

CONCLUSION

Transfusion practice in pediatric combat casualty resuscitation shifted toward a more hemostatic approach over the course of combat operations from 2001 to 2013 with a dramatic rise in the frequency of transfusions and massive transfusions in 2005-2006. Despite an increase in TBI, explosive mechanisms, and ISS over time, mortality remained stable in the entire cohort and even decreased in the massively transfused subgroup. Further improvements in outcomes may be possible by identifying appropriate epidemiologic, physiologic, and laboratory-based indications and end points for hemostatic resuscitation. Although this study provides a baseline for our experience, further study is required to determine the optimal resuscitation strategy for severely injured children.

AUTHORSHIP

J.W.C., L.P.N., H.F.P., A.P.C., and M.A.B. designed the study; M.A.B. performed the data acquisition; J.W.C., J.K.A., and M.A.B. performed data analysis; J.W.C., L.P.N., H.F.P., J.K.A., P.C.S., M.A.J., A.P.C., and M.A.B. interpreted the results; J.W.C. prepared the initial manuscript, which all authors critically revised.

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DISCLOSURE

The authors declare no conflicts of interest. No funding was received for this work.

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