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Association of Cryoprecipitate Use With Survival After Major Trauma in Children Receiving Massive Transfusion

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IMPORTANCE Although most massive transfusion protocols incorporate cryoprecipitate in the treatment of hemorrhaging injured patients, minimal data exist on its use in children, and whether its addition improves their survival is unclear.

OBJECTIVE To determine whether cryoprecipitate use for injured children who receive massive transfusion is associated with lower mortality.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included injured patients examined between January 1, 2014, and December 31, 2017, at one of multiple centers across the US and Canada participating in the Pediatric Trauma Quality Improvement Program. Patients were aged 18 years or younger and had received massive transfusion, which was defined as at least 40 mL/kg of total blood products in the first 4 hours after emergency department arrival. Exclusion criteria included hospital transfer, arrival without signs of life, time of death or hospital discharge not recorded, and isolated head injuries. To adjust for potential confounding, a propensity score for treatment was created and inverse probability weighting was applied. The propensity score accounted for age, sex, race/ethnicity, injury type, payment type, Glasgow Coma Scale score, hypoxia, hypotension, assisted respirations, chest tube status, Injury Severity Score, total volume of blood products received, hemorrhage control procedure, hospital size, academic status, and trauma center designation. Data were analyzed from December 11, 2019, to August 31, 2020.

EXPOSURES Cryoprecipitate use within the first 4 hours of emergency department arrival.

MAIN OUTCOMES AND MEASURES In-hospital 24-hour and 7-day mortality.

RESULTS Of the 2387 injured patients who received massive transfusion, 1948 patients were eligible for analysis. The median age was 16 years (interquartile range, 9-17 years), 1382 patients (70.9%) were male, and 807 (41.4%) were White. A total of 541 patients (27.8%) received cryoprecipitate. After propensity score weighting, patients who received cryoprecipitate had a significantly lower 24-hour mortality when compared with those who did not (adjusted difference, −6.9%; 95% CI, −10.6% to −3.2%). Moreover, cryoprecipitate use was associated with a significantly lower 7-day mortality but only in children with penetrating trauma (adjusted difference, −9.2%; 95% CI, −15.4% to −3.0%) and those transfused at least 100 mL/kg of total blood products (adjusted difference, −7.7%; 95% CI, −15.0% to −0.5%).

CONCLUSIONS AND RELEVANCE In this cohort study, early use of cryoprecipitate was associated with lower 24-hour mortality among injured children who required massive transfusion. The benefit of cryoprecipitate appeared to persist for 7 days only in those with penetrating trauma and in those who received extremely large-volume transfusion.

Invited Commentary

Supplemental content

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Trauma is the leading cause of death for children throughout the US.[1] For injured children, hemorrhage is one of the greatest contributors to mortality, second only to head injury.[2] Over the past decade, massive transfusion protocols (MTPs) have come to the forefront in the treatment of hemorrhage.[3] For severely injured patients with massive blood loss, MTP describes the recommended management of blood transfusion requirements and facilitates the communication of the treating physicians and the blood bank, thereby ensuring the judicious use of blood and blood components.[4] Moreover, MTP aims to provide patients with blood products at a ratio similar to that of whole blood.[5,6] The addition of cryoprecipitate, a blood product prepared from plasma that contains concentrates of essential clotting factors, to MTP in the management of these patients is believed to decrease hemorrhage.[7]

Plasma is the fluid portion of whole blood containing various clotting factors. Cryoprecipitate is a concentrated subset of plasma components including fibrinogen, factor VIII coagulant, von Willebrand factor, and factor XIII.[8] Fibrinogen is believed to be one of the earliest coagulation proteins to become depleted during major bleeding.

Trauma-induced coagulopathy is a systemic failure of the coagulation cascade to maintain homeostasis. It is thought to be caused by inflammation and shock due to trauma and aggravated by hypothermia, acidosis, and hemodilution.[9] Coagulopathy has been found to be highly prevalent in severely injured children who require transfusion, and it is strongly associated with mortality due to hemorrhage.[10] Thus, cryoprecipitate is thought to play a direct role in preventing and treating this coagulopathy.

Although most MTPs incorporate cryoprecipitate, evidence to support its use can only be found in the adult literature.[11] Children often do not have the same comorbidities that adults have, and extrapolating this evidence to children is difficult. Thus, the objective of this study was to determine whether using cryoprecipitate for injured children who receive a massive transfusion is associated with lower mortality.

Key Points

Question Are children with major trauma who receive massive transfusion including cryoprecipitate less likely to die in the first 24 hours compared with those who do not?

Findings In this propensity-weighted cohort study of 1948 patients from the Pediatric Trauma Quality Improvement Program, children receiving massive transfusion including cryoprecipitate had a significantly lower 24-hour mortality compared with those who did not.

Meaning The results of this study suggest that cryoprecipitate should be included in massive transfusion protocols for injured children with large-volume blood loss.

Methods

Data Source and Design

We performed a retrospective, multicenter cohort study using data from the Pediatric Trauma Quality Improvement Program (TQIP) from January 1, 2014, to December 31, 2017. This program is administered by the American College of Surgeons and collects data from over 850 participating trauma centers across the US and Canada. Data are deidentified before release to investigators. The TQIP database provides data on individual blood product components (packed red blood cells, plasma, platelets, and cryoprecipitate) and the volume of each transfused by 4 hours and by 24 hours after arrival at the emergency department (ED). The study protocol was approved by the institutional review board at the Albert Einstein College of Medicine and was granted an exemption from the need for informed consent because of the use of deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patients

We included patients aged 18 years or younger who had received massive transfusion, which was defined as at least 40 mL/kg of total blood products in the first 4 hours after ED arrival. Thus, all patients were likely severely injured and had received a substantial amount of blood products. We excluded patients who were transferred to or from an outside facility before 24 hours, those who arrived at the ED without signs of life, those for whom a time of death or hospital discharge was not recorded, and patients with isolated head injuries.

Exposure and Primary Outcome Measure

We compared patients who received cryoprecipitate within the first 4 hours with those patients who did not receive any cryoprecipitate within the first 4 hours. We chose to evaluate in-hospital 24-hour mortality as our primary outcome. Because the majority of injured patients who die from hemorrhage do so before 24 hours, we believed this outcome would be most affected by cryoprecipitate use.[12]

Covariates

We evaluated the following patient and hospital characteristics as potential confounders: age, sex, race/ethnicity, injury type, payment type, Glasgow Coma Scale score, hypoxia, hypotension, need for assisted respirations, chest tube status, Injury Severity Score, total volume of blood products received in the first 4 hours, hemorrhage control procedures received in the first 4 hours, hospital academic status, number of hospital beds available, and trauma center designation. Hemorrhage control procedures included angioembolization, laparotomy, neck exploration, sternotomy, and thoracotomy.

Statistical Analysis

Continuous variables were described using medians and interquartile ranges (IQRs), whereas categorical variables were described using frequencies and percentages. All tests were 2-tailed, and a P value of less than .05 was considered statistically significant. All analyses were performed from

December 11, 2019, to August 31, 2020, using Stata, version 15.1 (StataCorp).

Propensity Model

Children who receive blood products are often more severely injured than those who do not. To account for potential confounding in the association of cryoprecipitate use and mortality, we created a propensity score for each patient and applied inverse probability weighting. The propensity score represented the predicted probability of receiving cryoprecipitate and was determined using a logistic regression model with 4-hour cryoprecipitate use as the dependent variable and the aforementioned potential confounders as the independent variables. Each patient's propensity score was then used to create an inverse probability weight for that patient. After adjusting for these weights, a propensity-weighted sample was thus created that was more balanced with respect to potential confounders included in the regression model.

Before assessing the outcome, we confirmed that the weighted sample was balanced using the following parameters: standardized difference, −0.15 to 0.15; and variance ratio, 0.5 to 2.0.[13] We examined overlap plots of the propensity scores by treatment group to ensure that the area of common support was adequate. In addition, to meet the overlap assumption, patients with propensity scores smaller than the default tolerance of $1.00 \times e^{-5}$ were excluded from the model (eTable 1 in the Supplement).

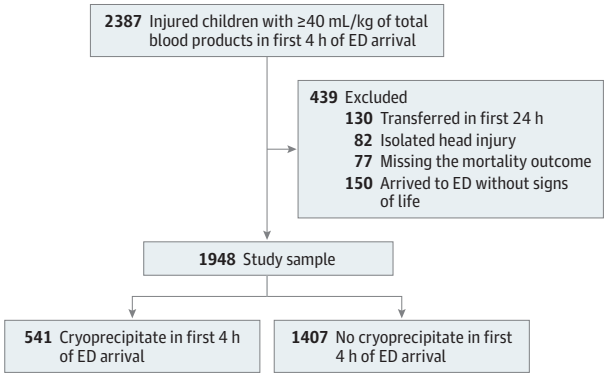
To avoid excluding patients with missing values for several of the potential confounders, we employed the missing indicator method. Missing values were coded as such, and a missing-value category was included as a separate category for the variable. In this way, the propensity score attempted to balance both the distribution of observed values and the distribution of missing data across treatment groups.[14]

Outcomes and Subgroup Analyses

For the primary outcome, we calculated the absolute risk difference and the relative risk of death within 24 hours after ED arrival between treatment groups. These values were determined for both the unadjusted and propensity-weighted samples. We also evaluated several subgroup analyses to determine whether any observed association was dependent on a particular group of patients. These subgroups included age, injury type, total blood product transfused, and pediatric trauma center status.

In addition, we explored several secondary outcomes: 7-day mortality, hemorrhage control after 4 hours, intensive care unit length of stay, time spent on a ventilator, and in-hospital complications. For these outcomes, we additionally excluded patients who were transferred before 7 days. Of note, we chose to evaluate hemorrhage control only after the 4-hour mark because TQIP does not provide the exact time of the transfusion but rather the amount of blood product transfused within 4 hours; therefore, we were unable to determine whether procedures performed before 4 hours occurred before or after cryoprecipitate transfusion. To evaluate the continuous secondary outcomes (ie, intensive care unit length of stay, time spent on ventilator) that were skewed in distribution, we performed multivariable quantile regression using the same aforementioned covariates as independent variables (eAppendix in the Supplement).

Figure. Diagram of Patient Eligibility and Flow



ED indicates emergency department.

Results

Patient Characteristics

From January 1, 2014, to December 31, 2017, there were 2387 injured patients who received at least 40 mL/kg of blood products in the first 4 hours of ED arrival. After exclusions, 1948 patients were eligible for analysis (**Figure**). The median age was 16 years (IQR, 9-17 years), 1382 patients (70.9%) were male, and 807 (41.4%) were White. A total of 541 patients (27.8%) received cryoprecipitate in the first 4 hours of ED arrival. Those who were transfused cryoprecipitate in this time frame received a median of 2.8 mL/kg (IQR, 1.5-4.9 mL/kg). Children who received cryoprecipitate were more likely to have hypotension (195 of 541 [36.0%] vs 441 of 1407 [31.3%]), require assisted respirations (297 of 541 [54.9%] vs 644 of 1407 [45.8%]), have a higher Injury Severity Score (median [IQR], 29 [24-43] vs 29 [21-41]), require a thoracostomy tube (251 of 541 [46.4%] vs 501 of 1407 [35.6%]), receive a larger volume of blood products within 4 hours of arrival (>125 mL/kg, 198 of 541 [36.6%] vs 200 of 1407 [14.2%]), require a hemorrhage control procedure in the first 4 hours (354 of 541 [65.4%] vs 693 of 1407 [49.3%]), and present to an adult trauma center (321 of 541 [59.3%] vs 758 of 1407 [53.9%]) than those who did not (**Table 1**). Standardized differences and variance ratios for the baseline covariates before propensity weighting ranged from −0.26 to 0.53 and 0.5 to 3.0, respectively. After propensity score weighting, differences observed for the baseline covariates that were apparent in the overall sample were no longer present. Accordingly, after propensity weighting, standardized differences and variance ratios for the baseline covariates were within the suggested parameters and ranged from −0.04 to 0.04 and 0.7 to 1.1, respectively.

To analyze the secondary outcomes, we excluded an additional 94 patients who were transferred to another hospital

Table 1. Patient and Hospital Characteristics by Cryoprecipitate Exposure Group for Overall and Weighted Samples[a,b,c]

Characteristic	Cryoprecipitate, No. (%)			Weighted cryoprecipitate, No. (%)		
	Yes (n = 541)	No (n = 1407)	Standardized difference	Yes (n = 963)	No (n = 985)	Standardized difference
Patient and hospital characteristics						
Age, median (IQR), y	16 (13-17)	16 (7-17)	0.30	16 (10-17)	16 (9-17)	0.03
Boys	395 (73.0)	987 (70.1)	0.06	702 (72.9)	700 (71.1)	0.04
Race/ethnicity						
White	218 (40.3)	589 (41.9)	1 [Reference]	388 (40.0)	404 (41.0)	1 [Reference]
Black	172 (31.8)	433 (30.8)	0.02	309 (32.1)	309 (31.4)	0.01
Asian or Pacific Islander	12 (2.2)	33 (2.3)	−0.01	22 (2.3)	23 (2.4)	−0.01
Hispanic or Latino	100 (18.5)	257 (18.3)	0.01	178 (18.5)	181 (18.4)	0.00
Other	39 (7.2)	95 (6.8)	0.02	66 (6.9)	67 (6.8)	0.00
Injury type						
Blunt	303 (56.0)	826 (58.7)	1 [Reference]	564 (58.6)	570 (57.9)	1 [Reference]
Penetrating	223 (41.2)	516 (36.7)	0.09	358 (37.2)	374 (38.0)	−0.02
Burn	1 (0.2)	4 (0.3)	−0.02	2 (0.3)	3 (0.3)	0.00
Other	14 (2.6)	61 (4.3)	−0.10	39 (4.0)	38 (3.9)	0.01
Payment						
Medicaid or Medicare	234 (43.3)	580 (41.2)	1 [Reference]	412 (42.8)	411 (41.8)	1 [Reference]
Private	194 (35.9)	499 (35.5)	0.01	349 (36.2)	349 (35.5)	0.02
Other	113 (20.9)	328 (23.3)	−0.06	203 (21.0)	224 (22.7)	−0.04
GCS score						
≥9	188 (34.8)	554 (39.4)	1 [Reference]	358 (37.2)	374 (38.0)	1 [Reference]
<9	346 (64.0)	847 (60.2)	0.08	560 (62.2)	604 (61.4)	0.02
Missing	7 (1.3)	6 (0.4)	0.09	6 (0.6)	6 (0.6)	0.00
Hypoxia						
≥94%	375 (69.3)	1024 (72.8)	1 [Reference]	675 (70.0)	704 (71.6)	1 [Reference]
<94%	121 (22.4)	286 (20.3)	0.05	208 (21.6)	206 (21.0)	0.01
Missing	45 (8.3)	97 (6.9)	0.05	81 (8.4)	74 (7.5)	0.03
Hypotension						
No	338 (62.5)	948 (67.4)	1 [Reference]	630 (65.4)	649 (65.9)	1 [Reference]
Yes	195 (36.0)	441 (31.3)	0.10	321 (33.3)	323 (32.8)	0.01
Missing	8 (1.5)	18 (1.3)	0.02	13 (1.3)	13 (1.3)	0.00
Assisted respirations						
No	223 (41.2)	708 (50.3)	1 [Reference]	463 (48.0)	470 (47.8)	1 [Reference]
Yes	297 (54.9)	644 (45.8)	0.18	468 (48.6)	476 (48.4)	0.00
Missing	21 (3.9)	55 (3.9)	0.00	33 (3.4)	38 (3.9)	−0.02
ISS, median (IQR)	29 (24-43)	29 (21-41)	0.14	29 (22-42)	29 (21-41)	0.04
Chest tube	251 (46.4)	501 (35.6)	0.22	358 (37.2)	377 (38.3)	−0.02
Total blood received in first 4 h, mL/kg						
≤50	55 (10.2)	389 (27.7)	1 [Reference]	207 (21.5)	224 (22.7)	1 [Reference]
51-60	45 (8.3)	236 (16.8)	−0.26	139 (14.4)	141 (14.4)	0.00
61-80	91 (16.8)	298 (21.2)	−0.11	189 (19.6)	195 (19.9)	−0.01
81-125	152 (28.1)	284 (20.2)	0.19	225 (23.3)	220 (22.4)	0.02
>125	198 (36.6)	200 (14.2)	0.53	204 (21.1)	203 (20.6)	0.01
Hemorrhage control procedure in first 4 h	354 (65.4)	693 (49.3)	0.33	538 (55.8)	532 (54.0)	0.04
Hospital type						
University	373 (68.9)	917 (65.2)	1 [Reference]	642 (66.7)	655 (66.5)	1 [Reference]
Community	141 (26.1)	397 (28.2)	−0.05	269 (27.9)	270 (27.5)	0.01
Nonteaching	26 (4.8)	90 (6.4)	−0.07	51 (5.3)	58 (5.9)	−0.02
Missing	1 (0.2)	3 (0.2)	−0.01	1 (0.1)	2 (0.2)	−0.01

(continued)

Table 1. Patient and Hospital Characteristics by Cryoprecipitate Exposure Group for Overall and Weighted Samples[a,b,c] (continued)

Characteristic	Cryoprecipitate, No. (%)			Weighted cryoprecipitate, No. (%)		
	Yes (n = 541)	No (n = 1407)	Standardized difference	Yes (n = 963)	No (n = 985)	Standardized difference
Hospital beds						
≤200	27 (5.0)	72 (5.1)	1 [Reference]	50 (5.2)	49 (5.0)	1 [Reference]
201-400	121 (22.4)	332 (23.6)	−0.03	218 (22.6)	229 (23.3)	−0.02
401-600	190 (35.1)	442 (31.4)	0.08	313 (32.5)	320 (32.5)	0.00
>600	203 (37.5)	561 (39.9)	−0.05	382 (39.7)	386 (39.2)	0.01
Trauma center						
Pediatric	291 (53.8)	750 (53.3)	0.01	520 (54.0)	526 (53.4)	0.01
Adult	321 (59.3)	758 (53.9)	0.11	549 (57.0)	548 (55.7)	0.03

Abbreviations: GCS, Glasgow Coma Scale; IQR, interquartile range; ISS, Injury Severity Score.

[a] Data presented as number and percentage unless otherwise indicated.

[b] Percentages may not total 100 because of rounding.

[c] Weighted frequencies are rounded to whole numbers and therefore group composite may not equal total.

Table 2. Propensity Score–Weighted 24-Hour Mortality Risk for Children Who Received Cryoprecipitate vs No Cryoprecipitate Within First 4 Hours of Arrival, Overall and by Subgroup

Variable	No.	Cryoprecipitate, No. (%)		Absolute risk difference, % (95% CI)	Relative risk (95% CI)
		Yes	No		
Unadjusted sample	1948	128 (23.7)	313 (22.3)	1.4 (−2.8 to 5.6)	1.1 (0.9 to 1.3)
Adjusted samples					
Overall	1948	173 (18.0)	245 (24.9)	−6.9 (−10.6 to −3.2)	0.7 (0.6 to 0.9)
Age, y					
≤10[a]	563	31 (11.4)	58 (20.0)	−8.5 (−14.9 to −2.2)	0.6 (0.3 to 0.9)
>10	1380	144 (21.1)	189 (27.2)	−6.1 (−10.7 to −1.5)	0.8 (0.6 to 0.9)
Injury type					
Penetrating	739	57 (15.6)	93 (24.6)	−9.0 (−14.8 to −3.3)	0.6 (0.5 to 0.9)
Blunt[a]	1127	119 (21.1)	147 (26.1)	−5.0 (−10.1 to 0.2)[b]	0.8 (0.6 to 1.0)
Total blood transfused, 4 h, mL/kg[c]					
≥100	600	94 (31.1)	120 (40.2)	−9.0 (−16.0 to −2.0)	0.8 (0.6 to 0.9)
<100[a]	1346	67 (10.0)	120 (17.7)	−7.7 (−11.7 to −3.7)	0.6 (0.4 to 0.8)
Pediatric trauma center					
Yes	1041	79 (15.2)	114 (21.9)	−6.6 (−11.6 to −1.7)	0.7 (0.5 to 0.9)
No[a]	904	99 (22.2)	130 (28.4)	−6.2 (−12.3 to 0.0)[b]	0.8 (0.6 to 1.0)

[a] To meet the overlap assumption, patients with propensity scores smaller than the default tolerance of $1.00 \times e^{-5}$ were excluded from the model.

[b] Blunt ($P = .059$); nonpediatric trauma center ($P = .049$).

[c] Total blood products transfused by 4 hours since triage.

before 7 days. Cryoprecipitate groups were similarly different before propensity score weighting (range for standardized differences and variance ratios, −0.25 to 0.54 and 0.6 to 3.0, respectively) and improved after weighting (range for standardized differences and variance ratios, −0.03 to 0.04 and 0.7 to 1.1, respectively).

Outcomes

Overall, 441 of 1948 (22.6%) patients died within 24 hours of ED arrival. In the unadjusted analysis, there was no significant difference in 24-hour mortality rate for children who received early cryoprecipitate compared with those who did not receive early cryoprecipitate (absolute risk difference, 1.4%; 95% CI, −2.8% to 5.6%). After propensity score weighting and accounting for potential confounding, however, patients who received early cryoprecipitate had a significantly lower 24-hour mortality rate when compared with those who did not (absolute risk difference, −6.9%; 95% CI, −10.6% to −3.2%) (**Table 2**). This association persisted in the subgroup analyses regardless of age (≤10 y, −8.5% [95% CI, −14.9% to −2.2%] vs >10 y, −6.1% [95% CI, −10.7% to −1.5%]), whether they received more or less than 100 mL/kg total blood products (≥100 mL/kg, −9.0% [95% CI, −16.0% to −2.0%] vs <100 mL/kg, −7.7% [95% CI, −11.7% to −3.7%]), whether they were seen at a pediatric trauma center (yes, −6.6% [95% CI, −11.6% to −1.7%] vs no, −6.2% [95% CI, −12.3% to 0.0%]), and in those with penetrating trauma (−9.0% [95% CI, −14.8% to −3.3%]). Of note, children with blunt trauma who were transfused cryoprecipitate demonstrated a lower 24-hour mortality rate compared with those who were not, but this association did not reach statistical significance (−5.0%; 95% CI, −10.1% to 0.2%; $P = .059$).

By 7 days, the benefit of giving cryoprecipitate within the first 4 hours was attenuated for the overall sample, and its association with a lower mortality was no longer significant (**Table 3**). When examining by subgroup, however, we found that cryoprecipitate use was associated with a significantly lower 7-day mortality, but only in children with penetrating trauma (adjusted difference, −9.2%; 95% CI, −15.4% to −3.0%)

Table 3. Propensity Score–Weighted 7-Day Mortality Risk for Children Who Received Cryoprecipitate vs No Cryoprecipitate Within First 4 Hours of Arrival, Overall and by Subgroup

Variable	No.	Cryoprecipitate, No. (%)		Absolute risk difference, % (95% CI)	Relative risk (95% CI)
		Yes	No		
Unadjusted sample	1854	195 (38.1)	429 (32.0)	6.1 (1.2 to 11.0)	1.2 (1.0 to 1.4)
Adjusted samples					
Overall	1854	308 (33.6)	328 (35.0)	−1.4 (−6.3 to 3.5)	1.0 (0.8 to 1.1)
Age, y					
≤10[a]	502	79 (32.5)	82 (31.8)	0.7 (−10.5 to 11.9)	1.0 (0.7 to 1.4)
>10	1342	220 (33.0)	246 (36.4)	−3.4 (−8.3 to 1.6)	0.9 (0.8 to 1.1)
Injury type					
Penetrating	717	75 (21.2)	111 (30.4)	−9.2 (−15.4 to −3.0)	0.7 (0.5 to 0.9)
Blunt[a]	1067	215 (40.4)	207 (38.7)	1.7 (−4.9 to 8.3)	1.0 (0.9 to 1.2)
Total blood transfused, 4 h, mL/kg[b]					
≥100	571	125 (43.6)	146 (51.3)	−7.7 (−15.0 to −0.5)	0.8 (0.7 to 0.99)
<100[a]	1266	173 (27.3)	172 (27.2)	0.1 (−6.1 to 6.3)	1.0 (0.8 to 1.3)
Pediatric trauma center					
Yes	977	156 (31.8)	163 (33.6)	−1.8 (−9.4 to 5.9)	0.9 (0.7 to 1.2)
No[a]	874	155 (35.9)	162 (36.6)	−0.7 (−7.5 to 6.1)	1.0 (0.8 to 1.2)

[a] To meet the overlap assumption, patients with propensity scores smaller than the default tolerance of $1.00 \times e^{-5}$ were excluded from the model.

[b] Total blood products transfused by 4 hours since triage.

Table 4. Secondary Outcomes for Children Who Received Cryoprecipitate vs No Cryoprecipitate Within First 4 Hours of Arrival[a]

Outcome	No.	Cryoprecipitate, median (IQR)		Absolute difference (95% CI)
		Yes	No	
Adjusted				
Hemorrhage control after 4 h, No. (%)	1854	88 (9.6)	70 (7.5)	2.1 (−1.4 to 5.6)
ICU LOS, d	1579	7.6 (3.7 to 10.0)	7.3 (3.7 to 9.4)	0.3 (−0.9 to 1.5)
Time on ventilator, d	1594	5.9 (2.8 to 8.6)	5.3 (2.6 to 8.1)	0.6 (−0.2 to 1.4)
Adjusted for 7-d mortality				
Hemorrhage control after 4 h, No. (%)	1854	87 (9.5)	70 (7.5)	1.9 (−1.5 to 5.3)
ICU LOS, d	1579	5.8 (3.5 to 13.3)	5.5 (3.1 to 12.2)	0.2 (−0.8 to 1.2)
Time on ventilator, d	1594	5.4 (2.6 to 10.0)	5.1 (2.3 to 9.5)	0.4 (−0.3 to 1.1)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

[a] Data are represented as median (IQR) unless otherwise specified.

and those transfused at least 100 mL/kg of total blood products in the first 4 hours (adjusted difference, −7.7%; 95% CI, −15.0% to −0.5%).

We also found that neither the need for a hemorrhage control procedure after 4 hours, the intensive care unit length of stay, nor the time on a ventilator was significantly different whether or not the patient received cryoprecipitate; these results were similar even after taking into account 7-day mortality (**Table 4**). Moreover, differences in complications between groups were all small, and none were statistically significant (eTable 2 in the Supplement).

Discussion

In this large, multicenter, propensity-weighted cohort study of pediatric trauma patients who received massive transfusion, we found that giving cryoprecipitate within the first 4 hours of arrival at the ED was associated with lower 24-hour mortality compared with when no cryoprecipitate was used. Multiple subgroup analyses also confirmed this association. By 7 days, however, the survival benefit of cryoprecipitate was lost overall and for every subgroup, except for those with penetrating injuries and those who received an extremely massive transfusion (≥100 mL/kg). We attempted to determine why cryoprecipitate was associated with an improved short-term survival but not with more long-term survival in all but the most severely injured. We failed to find a significant difference in any of our secondary outcomes that potentially could have affected more long-term survival.

The association of cryoprecipitate use with mortality is difficult to study for numerous reasons. Our study design attempted to carefully deal with each. First, although trauma is the most common cause of death for children in the US, death occurs infrequently. We used the TQIP database, which collects data from injured children across the country. The TQIP database provided us with a unique opportunity to study this outcome in a generalizable manner. Second, all retrospective studies that attempt to examine mortality need to consider immortal time bias. This bias arises because patients who die may not survive long enough to receive the intervention. Therefore, children who died early in their ED course would, by default, be assigned to the group who did not receive cryoprecipitate, thereby making the intervention appear to be falsely

beneficial. In order to ensure that all patients had an opportunity to receive cryoprecipitate, we included only patients who received a large volume of total blood products and thus had an opportunity to receive cryoprecipitate as well. Moreover, we excluded all patients who were dead on ED arrival and chose to evaluate only early cryoprecipitate usage (≤4 hours) in order to limit any potential effect of immortal time bias. Third, the association between cryoprecipitate use and mortality is probably subject to confounding by indication as well; in this case, those children who were more severely injured and thus more likely to die were the patients to whom the physician would most likely give cryoprecipitate. To account for the large number of potential confounding variables, our study used propensity weighting techniques to make the treatment and comparison groups more balanced with respect to these variables before analyzing the outcome.

The cause of death from trauma is often related to how soon after the injury that death occurs. In 1983, Trunkey[15] described the timing of trauma death as having a trimodal distribution: immediate (within minutes), early (within hours), and late (within days to weeks). Immediate deaths are usually due to nonsurvivable injuries and best addressed with prevention; we therefore excluded all patients who presented without signs of life.[16] As death due to hemorrhage is a major contributor to what Trunkey described as early death, we chose 24-hour mortality as our primary outcome. In our study, we found that this was the time frame most affected by early cryoprecipitate use. Conversely, late death often occurs long after hemorrhage is controlled and is most often due to complications such as multiorgan failure and sepsis. It is not surprising, then, that cryoprecipitate was not found to affect 7-day mortality in all but those children with the largest amount of hemorrhage. For example, the cause of death in children with severe blunt trauma is often multifactorial (eg, head injury), thus limiting the benefit of cryoprecipitate at 7 days in these patients compared with those children with penetrating trauma for whom the main cause of death is hemorrhage.

Owing to the lack of data concerning the use of cryoprecipitate in injured children, much of our knowledge on this issue is extrapolated from the adult literature.[17,18] The largest of these studies found that giving cryoprecipitate to injured adults receiving large-volume transfusion was associated with a significantly lower mortality.[19] Extrapolation from the adult literature in terms of mortality can be challenging, however, as comorbidities relatively nonexistent in childhood, such as hypertension or cerebrovascular and heart disease, are often quite prevalent and can factor strongly into this outcome.[20] Moreover, several medications used to treat these conditions, such as warfarin, can contribute to hemorrhage and associated mortality.[21,22]

Limitations

This study has some limitations. First, it is important to note that this study included only children who received a massive transfusion of blood products, and we recognize that deciding which children are going to require massive transfusion at triage can be challenging. Second, although our study aimed to make the 2 exposure groups as similar as possible, propensity score analyses can only balance these groups based on the variables included in the propensity score. Although we attempted to include as many potential confounders as possible using a large multicenter cohort, unmeasured confounding may have affected our results. Lastly, the TQIP database no longer provides a facility identifier; thus, we were unable to take into account clustering by facility. We did, however, include several hospital-level characteristics in our propensity score models in order to balance exposure groups by hospital factors that would make it more or less likely that a patient would receive cryoprecipitate.

Conclusions

In this cohort study, early use of cryoprecipitate within the first 4 hours of ED arrival was associated with a lower 24-hour mortality among injured children who required massive transfusion. However, the benefit of early cryoprecipitate appeared to persist for 7 days only in those with penetrating trauma and those who received an extremely large-volume transfusion (≥100 mL/kg). We did not identify an association between early cryoprecipitate use and any particular in-hospital complication.

Although these results appear promising, more studies are needed to validate these findings before they can be put into practice. Moreover, future study may seek to determine which group of children would be most likely to benefit from this intervention.

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