

Life-Threatening Bleeding in Children: A Prospective Observational Study

OBJECTIVES: The purpose of our study was to describe children with life-threatening bleeding.

DESIGN: We conducted a prospective observational study of children with life-threatening bleeding events.

SETTING: Twenty-four childrens hospitals in the United States, Canada, and Italy participated.

SUBJECTS: Children 0–17 years old who received greater than 40 mL/kg total blood products over 6 hours or were transfused under massive transfusion protocol were included.

INTERVENTIONS: Children were compared according bleeding etiology: trauma, operative, or medical.

MEASUREMENTS AND MAIN RESULTS: Patient characteristics, therapies administered, and clinical outcomes were analyzed. Among 449 enrolled children, 55.0% were male, and the median age was 7.3 years. Bleeding etiology was 46.1% trauma, 34.1% operative, and 19.8% medical. Prior to the life-threatening bleeding event, most had age-adjusted hypotension (61.2%), and 25% were hypothermic. Children with medical bleeding had higher median Pediatric Risk of Mortality scores (18) compared with children with trauma (11) and operative bleeding (12). Median Glasgow Coma Scale scores were lower for children with trauma (3) compared with operative (14) or medical bleeding (10.5). Median time from bleeding onset to first transfusion was 8 minutes for RBCs, 34 minutes for plasma, and 42 minutes for platelets. Postevent acute respiratory distress syndrome (20.3%) and acute kidney injury (18.5%) were common. Twenty-eight-day mortality was 37.5% and higher among children with medical bleeding (65.2%) compared with trauma (36.1%) and operative (23.8%). There were 82 hemorrhage deaths; 65.8% occurred by 6 hours and 86.5% by 24 hours.

CONCLUSIONS: Patient characteristics and outcomes among children with life-threatening bleeding varied by cause of bleeding. Mortality was high, and death from hemorrhage in this population occurred rapidly.

KEY WORDS: critical care; emergency medicine; pediatric; surgery; trauma; transfusion

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Over the past decade, management of life-threatening bleeding has incorporated damage control resuscitation (DCR) strategies (1). Principles of DCR include permissive hypotension; rapid surgical control; avoidance of hemodilution, acidosis, hypocalcemia, and hypothermia; and early empiric, balanced transfusion with RBCs, plasma, and platelets, or whole blood when available (2, 3). Medical centers use massive transfusion

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protocols (MTPs) to standardize the resuscitation of patients with life-threatening bleeding using DCR principles (4, 5).

Evidence for DCR is rooted in military and adult civilian trauma populations; however, through the implementation of MTPs, these strategies are being used to manage all causes of hemorrhage, including medical and surgical bleeding and for children (4). There are no prospective pediatric multicenter studies reporting the demographic characteristics of children with life-threatening bleeding, which therapies are most commonly used or the associated outcomes.

It is essential that DCR principles are studied in children (6). Children have different disease burden and pathophysiology than adults leading to different etiologies for bleeding and response to therapy. These differences may affect which resuscitative practices are efficacious and safe for children with life-threatening bleeding and warrant pediatric-specific clinical trials. The purpose of this study was to prospectively describe the patient characteristics, management, and outcomes of children with life-threatening bleeding as a requisite step to inform clinical trial design. We hypothesized that there would be differences in these data based on the etiology of bleeding which can inform future lines of inquiry.

MATERIALS AND METHODS

We conducted a prospective, observational study of children presenting with life-threatening bleeding at 24 medical centers in the United States, Canada, and Italy from January 2014 to October of 2018. The month that each participating center began enrolling varied from January 2014 to May 2017.

Children 0–17 years old were eligible for enrollment if they received greater than 40 mL per kg of total blood products over 6 hours or if they were transfused under MTP activation. The threshold of greater than 40 mL/kg of blood products is based on literature that it is predictive of increased risk of death in children with traumatic injury (7). Children were excluded if a MTP was activated, but no blood products were transfused. Hospital blood bank documentation was used to identify eligible subjects.

Data extracted from hospital medical records included demographics, cause of bleeding, Glasgow Coma Scale (GCS), vital signs, measures of end-organ function, fluids, blood products, hemostatic adjuncts,

morbidities, and mortality. The timing of mortality was based on when the first life-threatening event occurred. For patients with multiple events, only the first event was analyzed. The Injury Severity Score (ISS) was obtained from the hospital trauma registry. The Pediatric Risk of Mortality (PRISM) III score was calculated for the day of the bleeding event. Preevent data were collected for the 24-hour period prior to the event. Data categorized as “during” the event were collected from the initiation of the massive transfusion (MT) until the end of the MT. The initiation of the MT was defined as either the time the MTP was activated or the time of administration of the first blood product for children without MTP activation. The end of a MT was defined as the time MTP was terminated or the time that the last blood product was transfused with no other blood products being administered in the subsequent 60 minutes. Postevent data were collected at the time closest to the end of the event with a maximum of 12 hours. Patients were categorized into three groups according to the etiology of their bleeding: traumatic injury, operative, and medical. Traumatic injury was defined as bleeding due to blunt or penetrating trauma. Operative was defined as any bleeding related to an operative procedure in the procedural or immediate postprocedural period, including interventional radiology procedures. Medical bleeding was defined as being a result of the pathophysiology of medical illness (e.g., gastrointestinal bleeding).

Missing weight values were estimated based on age and sex from the Centers for Disease Control and Prevention Clinical Growth Charts in order to standardize volume of blood product administered (8). When calculating PRISM III scores, all missing values were assumed to be within the normal range according to the methods for calculating the score (9). During data quality monitoring, one site (10 patients) had missing data for many key variables and was eliminated from analysis.

This study was conducted under waiver of informed consent granted by each participating center’s institutional review board.

Statistical analyses were conducted using SAS/STAT software, v 9.4 (SAS Institute Inc., Cary, NC). When comparing between the three groups, tests of association included analysis of variance and chi-square unless distributional assumptions were not met in which case Kruskal-Wallis H and Fisher exact were employed. If

an overall test was significant ($p < 0.05$), pairwise tests were performed applying the Bonferroni correction ($p = 0.05/3 = 0.017$). The Kaplan-Meier method was used to calculate 28-day survival.

RESULTS

A total of 449 children with life-threatening bleeding met inclusion criteria. The median (interquartile

range [IQR]) age was 7.3 yr (1.7–14.7 yr) (Table 1). For those with documented race and ethnicity, 28.7% were Black, and 11.0% Hispanic. There were more males (55.0%); however, this related to a higher proportion of males with traumatic bleeding (62.3%). The causes of bleeding were traumatic injury in 207 children (46.1%), operative in 153 (34.1%), and medical in 89 (20.2%). Children with traumatic bleeding were older, 10.4 years (4.7–15.4 yr), and those with

TABLE 1.
Demographic and Blood Type Measures

Measures	Overall (n = 449)		Trauma (N = 207)		Operative (N = 153)		Medical (N = 89)		p
	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	
Age (yr) ^{a-c}	449	7.3 (1.7–14.7)	207	10.4 (4.7–15.4)	153	2.1 (0.3–11.8)	089	7.96 (1.2–14.7)	< 0.01
Age < 1 yr ^{a-c}	449	94 (20.9)	207	16 (7.7)	153	58 (37.9)	089	20 (22.5)	< 0.01
Sex ^{a, b}	449		207		153		089		0.02
Male		247 (55.0)		129 (62.3)		76 (49.7)		42 (47.2)	
Female		202 (45.0)		78 (37.7)		77 (50.3)		47 (52.8)	
Race ^{a, b}	380		173		131		076		< 0.01
White		242 (63.7)		98 (56.6)		91 (69.5)		53 (69.7)	
Black		109 (28.7)		72 (41.6)		20 (15.3)		17 (22.4)	
Other		29 (7.6)		3 (1.7)		20 (15.3)		6 (7.9)	
Hispanic/Latino	392	43 (11.0)	181	16 (8.8)	134	21 (15.7)	077	6 (7.8)	< 0.10
Blood group	436		197		152		087		0.98
A		157 (36.0)		67 (34.0)		58 (38.2)		32 (36.8)	
B		65 (14.9)		30 (15.2)		22 (14.5)		13 (14.9)	
AB		12 (2.8)		5 (2.5)		5 (3.3)		2 (2.3)	
O		202 (46.3)		95 (48.2)		67 (44.1)		40 (46.0)	
Rhesus factor	434		196		151		087		0.87
+		359 (82.7)		163 (83.2)		123 (81.5)		73 (83.9)	
–		75 (17.3)		33 (16.8)		28 (18.5)		14 (16.1)	

Obs = observations.

^a $p < 0.017$ trauma vs operative.

^b $p < 0.017$ trauma vs medical.

^c $p < 0.017$ operative vs medical.

operative bleeding were younger, 2.1 years (0.3–11.8 yr). Twenty-nine children had more than one life-threatening bleeding event; traumatic injury (3), operative (19), and medical (7).

Children with traumatic injuries had a median ISS (IQR) of 29 (20–38), indicating severe injury. Blunt trauma accounted for 66% of injuries and penetrating 34%. The surgical services for children with operative bleeding were cardiothoracic surgery (34%), neurosurgery (24%), general surgery (19%), liver transplant (8%), and other (23%). The conditions in children with medical bleeding were gastrointestinal bleeding (33%), sepsis (19%), oncologic (12%), and other (36%).

Most children (61.2%) had age-adjusted hypotension, and approximately a quarter were hypothermic (35°C) prior to the bleeding event (**Table 2**). Children with medical bleeding had higher PRISM III scores (median [IQR], 18 [12–24]) when compared with children with traumatic (11 [5–23]) and operative bleeding (12 [6–21]). However, GCS was lower for children with traumatic bleeding (3 [3–13]) compared with children with operative (14 [3–15]) and medical bleeding (10.5 [3–14]).

Children with traumatic and medical bleeding had lower serum pH values (median [IQR], 7.17 [7.00–7.24] and 7.20 [7.00–7.30], respectively), compared with children with operative bleeding (7.30 [7.20–7.30]). More children with medical bleeding (46.8%) had elevated creatinine levels compared with traumatic (27.3%) and operative bleeding (21.4%). Children with medical bleeding had lower hemoglobin levels (7.9 g/dL [6.0–9.7 g/dL]) and higher international normalized ratios (INRs) (1.78 [1.35–3.70]) compared with those with traumatic (9.8 g/dL [8.3–11.8 g/dL]; 1.50 g/dL [1.26–1.90 g/dL]) and operative bleeding (9.8 g/dL [7.7–11.6 g/dL]; 1.39 g/dL [1.15–1.70 g/dL]).

Regardless of the cause of bleeding, children frequently received RBC transfusion prior to MT (41.4%) (**Table 3**). Those with operative bleeding received higher volumes of RBCs pre-event (35.1 mL/kg [15.3–60.0 mL/kg]) compared with those with traumatic (17.9 mL/kg [10.6–28.8 mL/kg]) or medical bleeding (18.9 mL/kg [11.9–31.9 mL/kg]). Plasma, platelet, and cryoprecipitate administration prior to MT was more common for children with operative (24.8%, 24.8%, 14.4% respectively) and medical bleeding (32.6%, 28.1%, 7.9%) compared with those with traumatic bleeding (6.8%, 2.9%, 1.0.9%). Most children (62.8%) received crystalloid prior to MT with a median volume

administered of 25 mL/kg (12.4–41.4 mL/kg). Preevent use of tranexamic acid, aminocaproic acid, and recombinant factor VIIa was uncommon.

Most children were transfused under MTP activations: trauma (96.1%), operative (69.9%), and medical (82%) (**Table 4**). The median duration of MT events was 3.5 hours (1.5–6.1 hr). Thirty-six children (8%) were on extracorporeal membrane oxygenation; all had either operative or medical bleeding.

During MT, 92.0% received RBCs, 80.0% plasma, and 66.1% platelets. No patients received whole blood. Time to administration of the first product varied by blood product type. Overall median time to first RBCs was 8 minutes (0–42 min). Median time to plasma administration was 34 minutes (15–77 min) and to platelet administration 42 minutes (15–102 min). Total blood volume administered was greater for operative events (98.4 mL/kg [50.6–172 mL/kg]) compared with trauma (45.0 mL/kg [21.0–85.3 mL/kg]) and medical (55.8 mL/kg [29.0–109 mL/kg]). Volumes of crystalloid administered were higher for trauma (23.1 mL/kg [2.0–59.2 mL/kg]) than operative (10.0 mL/kg [0.63–43.0 mL/kg]) or medical events (14.6 mL/kg [0.19–45.6 mL/kg]). Hemostatic adjuncts were infrequently used: tranexamic acid (8.0%), aminocaproic acid (4.2%), and recombinant factor VIIa (12.5%).

Postevent, there was stabilization of blood pressure and normalization of hemoglobin, base deficit, platelet count, INR, and fibrinogen (**Table 5**). Although lactate concentrations were not routinely measured pre-event, they were mildly elevated postevent. Development of acute respiratory distress syndrome and acute kidney injury was common (20.3% and 18.5%, respectively); however, acute kidney injury disproportionately occurred in children with operative (28.8%) and medical bleeding (30.3%) as opposed to those with trauma (5.8%). Abdominal compartment syndrome was uncommon, occurring in only 1.8% of children.

Overall, 35.7% of deaths occurred during MT (trauma 40.5%, operative 22.2%, medical 37.9%) (**Table 5**). Operative and medical 6-hour mortality was almost exclusively from hemorrhage (100% and 92.0%, respectively), whereas 62.9% of trauma deaths were due to hemorrhage and 37.1% due to CNS injury. Twenty-four-hour mortality continued to be attributable to hemorrhage for children with

TABLE 2.
Clinical Measures Pre-Life-Threatening Bleeding

Measures	Overall (N = 449)		Trauma (N = 207)		Operative (N = 153)		Medical (N = 89)		p
	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	
Pediatric Risk of Mortality III ^{b, c}	428	12 (6–22)	193	11 (5–23)	150	12 (6–21)	85	18 (12–24)	< 0.01
Lowest Glasgow Coma Scale ^a	255	7 (3–14)	165	3 (3–13)	50	14.0 (3–15)	40	10.5 (3–14)	< 0.01
Fixed, dilated pupils ^{a, b}	362	64 (17.7)	180	54 (30.0)	116	3 (2.6)	66	7 (10.6)	< 0.01
Mechanical ventilation ^{b, d}	432	255 (59.0)	196	106 (54.1)	152	88 (57.9)	84	61 (72.6)	0.02
Age-adjusted hypotension	410	251 (61.2)	180	107 (59.4)	145	85 (58.6)	85	59 (69.4)	0.22
Lowest body temperature (°C)	339	36.2 (35.2–36.6)	123	36.0 (35.0–36.5)	136	36.2 (35.4–36.6)	80	36.2 (35.6–36.7)	0.13
Highest body temperature (°C) ^{a, b}	352	36.9 (36.3–37.5)	129	36.5 (35.7–37.0)	143	37.2 (36.8–37.7)	80	37.1 (36.7–38.0)	< 0.01
Lowest power of hydrogen (pH) ^{a, c}	308	7.20 (7.10–7.30)	102	7.17 (7.00–7.24)	135	7.30 (7.20–7.30)	71	7.20 (7.00–7.30)	< 0.01
Base deficit/excess (mmol/L)	272	–0.45 (–5.0 to 7.00)	89	–1.0 (–7.0 to 8.00)	123	0.00 (–4.0 to 5.00)	60	1.10 (–7.0 to 6.50)	0.89
Age-adjusted abnormally high serum creatinine ^{b, c}	299	90 (30.1)	110	30 (27.3)	112	24 (21.4)	77	36 (46.8)	< 0.01
Lowest hemoglobin (g/dL) ^{b, c}	339	9.5 (7.4–11.3)	130	9.8 (8.3–11.8)	130	9.8 (7.7–11.6)	79	7.90 (6.00–9.70)	< 0.01
Lowest WBC count (K/mm ³) ^{a, b}	323	10.4 (5.8–17.0)	130	12.5 (8.2–17.7)	117	8.6 (5.9–14.6)	76	6.6 (2.3–19.4)	< 0.01
Lowest platelet count (× 10 ⁹ /L) ^{a, c}	324	152 (76–242)	132	203 (149–282)	116	137 (78.5–230)	76	49 (20–126)	< 0.01
Highest international normalized ratio ^{b, c}	250	1.50 (1.20–2.03)	98	1.50 (1.26–1.90)	95	1.39 (1.15–1.70)	57	1.78 (1.35–3.70)	< 0.01
Highest prothrombin time (s) ^c	246	17.6 (15.0–21.9)	100	17.6 (15.0–21.7)	89	17.1 (14.0–20.3)	57	19.8 (15.7–31.4)	0.01
Highest partial thromboplastin time (s) ^b	259	42.9 (31.2–91.0)	103	38.0 (28.0–70.0)	98	43.3 (32.9–62.0)	58	61.9 (31.7–150)	0.02
Fibrinogen (mg/dL) ^{a, b}	131	158 (95.0–261)	27	121 (60.0–176)	63	181 (127–275)	41	178 (126–261)	0.01

Obs = observations.

^ap < 0.017 trauma vs operative.

^bp < 0.017 trauma vs medical.

^cp < 0.017 operative vs medical.

^dFor children with operative bleeding, mechanical ventilation status was assessed immediately prior to the bleeding event but did not include intubation and ventilation for the procedure.

TABLE 3.
Measures of Blood Product Use and Hemostatic Agent Administration Pre-Life-Threatening Bleeding

Measure	Overall (N = 449)		Trauma (N = 207)		Operative (N = 153)		Medical (N = 89)		p
	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	
Any RBCs	449	186 (41.4)	207	86 (41.5)	153	60 (39.2)	89	40 (44.9)	0.68
RBCs (mL/kg) ^{a,c}	186	20.2 (11.2–41.5)	86	17.9 (10.6–28.8)	60	35.1 (15.3–60.0)	40	18.9 (11.9–31.9)	< 0.01
Any plasma ^{a,b}	449	81 (18.0)	207	14 (6.8)	153	38 (24.8)	89	29 (32.6)	< 0.01
Plasma (mL/kg) ^{a,b}	81	13.1 (6.0–29.7)	14	5.2 (3.9–10.4)	38	18.8 (9.4–41.0)	29	18.0 (7.6–36.9)	< 0.01
Any platelets ^{a,b}	449	69 (15.4)	207	6 (2.9)	153	38 (24.8)	89	25 (28.1)	< 0.01
Platelets (mL/kg) ^c	69	12.3 (6.7–22.5)	6	17.0 (6.8–22.5)	38	16.8 (8.3–33.3)	25	8.3 (5.4–12.3)	0.01
Any cryoprecipitate ^{a,b}	449	31 (6.9)	207	2 (1.0)	153	22 (14.4)	89	7 (7.9)	< 0.01
Cryoprecipitate (mL/kg)	31	5.17 (2.9–15.2)	2	16.0 (2.9–29.1)	22	5.9 (3.3–15.2)	7	4.7 (2.2–8.8)	0.54
Any blood product	449	212 (47.2)	207	87 (42.0)	153	77 (50.3)	89	48 (53.9)	0.11
Total blood product (mL/kg) ^a	212	23.6 (12.0–55.1)	87	18.1 (10.7–31.4)	77	37.2 (16.1–80.3)	48	25.1 (13.2–54.7)	< 0.01
Any crystalloid ^{a,b}	449	282 (62.8)	207	110 (53.1)	153	107 (69.9)	89	65 (73.0)	< 0.01
Crystalloid (mL/kg)	282	25.0 (12.4–41.4)	110	27.1 (14.3–41.5)	107	24.5 (12.0–33.8)	65	25.2 (12.4–55.6)	0.24
Any colloid ^{a,b}	449	64 (14.3)	207	8 (3.9)	153	42 (27.5)	89	14 (15.7)	< 0.01
Any tranexamic acid ^{a,c}	449	20 (4.5)	207	4 (1.9)	153	15 (9.8)	89	1 (1.1)	< 0.01
Any aminocaproic acid ^a	449	14 (3.1)	207	0 (0.0)	153	12 (7.8)	89	2 (2.2)	< 0.01
Any recombinant factor VIIa ^a	449	10 (2.2)	207	1 (0.5)	153	7 (4.6)	89	2 (2.2)	0.03

Obs = observations.

^ap < 0.017 trauma vs operative.

^bp < 0.017 trauma vs medical.

^cp < 0.017 operative vs medical.

operative (94.1%) and medical bleeding (84.4%) compared with children with trauma (hemorrhage 56%; CNS 42%). At 28 days, hemorrhage was the most common cause of death for those with operative (52.8%) and medical bleeding (56.9%). For children with trauma, CNS injury (58.1%) was the most common cause of death. Mortality was greatest among

children with medical bleeding (**Supplemental Fig. 1**, <http://links.lww.com/CCM/G474>; **legend**, <http://links.lww.com/CCM/G475>).

DISCUSSION

In this multicenter prospective observational study of children with life-threatening bleeding, there was

TABLE 4.
Measures of Clinical Management During the Life-Threatening Bleeding Event

Measures	Overall (N = 449)		Trauma (N = 207)		Operative (N = 153)		Medical (N = 89)		p
	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	
Massive transfusion protocol activated ^{a,b}	449	379 (84.4)	207	199 (96.1)	153	107 (69.9)	89	73 (82.0)	< 0.01
Location of massive transfusion ^{a–c}	449		207		153		89		< 0.01
Emergency department		160 (35.6)		139 (67.1)		3 (2.0)		18 (20.2)	
Operative room		125 (27.8)		35 (16.9)		84 (54.9)		6 (6.7)	
ICU		154 (34.3)		31 (15.0)		61 (39.9)		62 (69.7)	
Other		10 (2.2)		2 (1.0)		5 (3.3)		3 (3.4)	
Extracorporeal membrane oxygenation ^{a,b}	449	36 (8.0)	207	0 (0.0)	153	26 (17.0)	89	10 (11.2)	< 0.01
Massive transfusion duration (hr)	449	3.5 (1.5–6.1)	207	3.0 (1.3–5.7)	153	3.8 (1.9–6.7)	89	4.0 (1.1–6.6)	0.11
Any RBCs	449	413 (92.0)	207	191 (92.3)	153	145 (94.8)	89	77 (86.5)	0.07
RBCs (mL/kg) ^{a,c}	449	30.2 (15.5–62.3)	207	25.3 (12.5–48.9)	153	48.5 (23.4–87.4)	89	26.4 (10.8–51.8)	< 0.01
Time to RBCs (min)	405	8.0 (0.0–42.0)	187	8.0 (0.0–44.0)	142	7.0 (0.0–40.0)	76	11.5 (0.0–45.5)	0.75
Any plasma	449	359 (80.0)	207	161 (77.8)	153	125 (81.7)	89	73 (82.0)	0.57
Plasma (mL/kg) ^a	449	17.1 (4.84–35.6)	207	13.2 (3.57–27.0)	153	22.0 (8.57–48.1)	89	18.1 (5.94–39.5)	< 0.01
Time to plasma (min)	347	34.0 (15.0–77.0)	156	33.5 (17.5–74.0)	123	39.0 (12.0–83.0)	68	30.0 (15.5–65.0)	0.86
Any platelets ^{a,b}	449	297 (66.1)	207	120 (58.0)	153	111 (72.5)	89	66 (74.2)	< 0.01
Platelets (mL/kg) ^{a,b}	449	7.30 (0.00–19.8)	207	3.85 (0.00–13.5)	153	13.3 (0.00–33.3)	89	10.4 (0.00–19.8)	< 0.01
Time to platelets (min)	293	42.0 (15.0–102)	118	42.0 (20.0–73.0)	109	43.0 (13.0–118)	66	42.0 (14.0–111)	0.96
Any cryoprecipitate ^a	449	152 (33.9)	207	49 (23.7)	153	71 (46.4)	89	32 (36.0)	< 0.01
Total blood product (mL/kg) ^{a,c}	449	61.3 (29.0–123)	207	45.0 (21.0–85.3)	153	98.4 (50.6–172)	89	55.8 (29.0–109)	< 0.01
Any crystalloid	449	346 (77.1)	207	163 (78.7)	153	116 (75.8)	89	67 (75.3)	0.73
Crystalloid (mL/kg) ^{a,b}	449	18.2 (0.8–51.0)	207	23.1 (2.0–59.2)	153	10.0 (0.6–43.0)	89	14.6 (0.2–45.6)	0.06
Any tranexamic acid	449	36 (8.0)	207	19 (9.2)	153	9 (5.9)	89	8 (9.0)	0.49
Any aminocaproic acid ^a	449	19 (4.2)	207	4 (1.9)	153	11 (7.2)	89	4 (4.5)	< 0.05
Any recombinant factor VIIa ^{a,b}	447	56 (12.5)	206	15 (7.3)	153	26 (17.0)	88	15 (17.0)	< 0.01

Obs = observations.

^ap < 0.017 trauma vs operative.

^bp < 0.017 trauma vs medical.

^cp < 0.017 operative vs medical.

TABLE 5.
Post-Life-Threatening Bleeding Clinical Measures and Outcomes

Measures	Overall (N = 449)		Trauma (N = 207)		Operative (N = 153)		Medical (N = 89)		p
	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	Obs	Median (Quartile 1–Quartile 3) or n (% Obs)	
Hemoglobin (g/dL)	358	11.3 (9.6–13.2)	161	11.3 (9.9–12.8)	137	11.7 (9.8–13.7)	60	10.5 (8.9–12.8)	0.08
Lactate (mmol/L) ^c	253	3.5 (1.7–6.9)	90	3.5 (2.0–5.9)	110	3.0 (1.6–6.2)	53	5.8 (2.2–12.5)	0.02
Base deficit/excess (mmol/L)	329	1.0 (–3.5–5.0)	146	0.6 (–5.0–5.00)	122	2.0 (–1.0–4.7)	61	1.1 (–2.2–5.6)	0.27
Fibrinogen (mg/dL)	247	204 (160–272)	107	197 (157–251)	95	216 (161–293)	45	225 (175–327)	0.07
Platelet count (× 10 ⁹ /L)	330	142 (99.0–187)	151	147 (111–193)	124	137 (85.0–187)	55	124 (94.0–171)	0.09
International normalized ratio	315	1.30 (1.18–1.50)	145	1.30 (1.20–1.41)	113	1.30 (1.10–1.50)	57	1.40 (1.18–1.80)	0.08
Lowest systolic blood pressure (mm Hg) ^{a, c}	354	104 (83–123)	162	114 (98–133)	130	89.5 (73–107)	62	107 (88–126)	< 0.01
Age-adjusted hypotension ^a	354	61 (17.2)	162	18 (11.1)	130	31 (23.8)	62	12 (19.4)	0.02
Acute respiratory distress syndrome ^a	449	91 (20.3)	207	31 (15.0)	153	39 (25.5)	89	21 (23.6)	0.04
Sepsis ^b	449	44 (9.8)	207	15 (7.2)	153	14 (9.2)	89	15 (16.9)	0.04
Acute kidney injury ^{a, b}	449	83 (18.5)	207	12 (5.8)	153	44 (28.8)	89	27 (30.3)	< 0.01
Abdominal compartment syndrome	449	8 (1.8)	207	1 (0.5)	153	4 (2.6)	89	3 (3.4)	0.14
Died within 6 hr ^{a, c}	445	69 (15.5)	205	35 (17.1)	151	9 (6.0)	89	25 (28.1)	< 0.01
During massive transfusion	69	49 (71.0)	35	24 (68.6)	9	6 (66.7)	25	19 (76.0)	0.78
Of hemorrhage ^b	69	54 (78.3)	35	22 (62.9)	9	9 (100)	25	23 (92.0)	0.01
Of CNS injury ^{b, c}	69	13 (18.8)	35	13 (37.1)	9	0 (0.0)	25	0 (0.0)	< 0.01
Died within 24 hr ^{a, c}	445	99 (22.2)	205	50 (24.4)	151	17 (11.3)	89	32 (36.0)	< 0.01
During massive transfusion	99	56 (56.6)	50	28 (56.0)	17	8 (47.1)	32	20 (62.5)	0.58
Of hemorrhage ^{a, b}	99	71 (71.7)	50	28 (56.0)	17	16 (94.1)	32	27 (84.4)	< 0.01
Of CNS injury ^{a, b}	99	23 (23.2)	50	21 (42.0)	17	1 (5.9)	32	1 (3.1)	< 0.01
Died within 28 d ^{a, c}	445	168 (37.8)	205	74 (36.1)	151	36 (23.8)	89	58 (65.2)	< 0.01
During massive transfusion	168	60 (35.7)	74	30 (40.5)	36	8 (22.2)	58	22 (37.9)	0.16
Of hemorrhage	168	82 (48.8)	74	30 (40.5)	36	19 (52.8)	58	33 (56.9)	0.15
Of CNS injury ^{a, b}	168	58 (34.5)	74	43 (58.1)	36	8 (22.2)	58	7 (12.1)	< 0.01

Obs = observations.

^ap < 0.017 trauma vs operative.

^bp < 0.017 trauma vs medical.

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significant heterogeneity in demographics, preevent clinical status, resuscitation management, and outcomes related to the etiology of bleeding. Further, most children with life-threatening bleeding were managed under hospital MTPs, a practice that is grounded in adult trauma literature. Despite this, there were substantial time lags in the administration of blood components essential to hemostasis. Many children did not receive plasma and/or platelets as part of their resuscitation, and the median time to both plasma and platelet administration was greater than 30 minutes in those who did. Death from hemorrhage, regardless of etiology, predominantly occurred within 6–24 hours of onset of MT.

Our analysis is unique from other retrospective studies of massive bleeding in children and large multicenter studies in adults (10, 13–20). We report blood product and hemostatic agent use during the event as opposed to during a 6- or 24-hour period or according to location of administration such as the emergency department or operating room (3). We also report blood product volume as mL/kg instead of in units which has more applicability to children than adults. This methodology allows for more precise examination of transfusion practice during actual bleeding events. This study also evaluated surgical and medical etiologies of hemorrhage managed under MTP, whereas previous literature on MT in children has been limited to trauma (14, 20–25). Clinical status at the onset of life-threatening bleeding and ultimate outcomes varied by etiology.

Although trauma was the most common etiology for life-threatening bleeding in our cohort, a comparable proportion of children had surgical bleeding. Children with surgical bleeding were substantially younger than those with bleeding due to trauma and medical causes. This is likely due to the combined surgical risk of young age and the type of procedures performed in young children, in particular, surgery for congenital deformities (e.g., craniofacial, heart, and liver) and neoplasms (e.g., neuroblastoma, Wilms tumor) (26–28). The effect of age-related maturation of the hemostatic system when considering approaches to life-threatening bleeding has not been thoroughly studied. Children less than 1 year old are particularly vulnerable and have the most pronounced differences compared with older children and adults (22, 29). Thus, infants are an important subpopulation in studies of life-threatening bleeding, and including children with surgical bleeding in studies of DCR may be important to accomplishing this goal.

Children with medical bleeding had higher PRISM III scores. Preevent data for the medical bleeding group are congruent with what we would expect for children who are experiencing primary or secondary failure of their hemostatic system, that is, increased INR, and lower platelet counts. Many received plasma, platelets, and cryoprecipitate prior to the onset of MT. Children with medical bleeding had high rates of end-organ injury and the highest death rates at all time points, with hemorrhage being the leading cause of death. MTPs in these children were likely activated later in their clinical course when goal-directed therapy was not keeping pace with the rate of bleeding (30). However, use of MTP is understudied in this population, and ideal ratios of empiric transfusion unestablished (30, 31).

Consistent with the literature, the mortality among injured children with life-threatening bleeding was approximately two to three times that reported in adult populations (10–12). Prior to onset of MT, these children had lower median GCS, and nearly 20% had fixed and dilated pupils. Death due to CNS injury was common within the first 24 hours, and CNS injury was the leading cause of death at 28 days (32). Children with traumatic injuries were also less likely to receive platelets and plasma prior to MT and received greater volumes of crystalloid and lower volumes of plasma and platelets during the event. Prior research suggested children with life-threatening bleeding and without CNS injury have improved survival when component balanced transfusion is achieved (19). However, timely and balanced transfusion was not often achieved, and high volumes of crystalloid were often used. This is surprising since the concepts of reducing crystalloid administration and balanced transfusion during MT were generated from the trauma community. Future analysis of our data will explore the impact of the ratio of blood components transfused, amount of crystalloid received, and the presence of comorbid CNS injury on outcomes for children with traumatic injuries.

The main purposes of MTPs are to expedite the availability of blood products and promote balanced transfusion under emergency circumstances. Despite the use of MTPs, many children in our cohort did not receive plasma (20.0%) or platelets (33.9%), and when they did, there were notable delays (> 30 min) from the onset of MTP. Timely balanced transfusion is a guiding principle of DCR and when attained for severely injured adult patients, reduces 24 hour mortality due to hemorrhage (11). Evidence in injured

adults indicates that for every minute delay, there is a 5% increase in mortality (33). Reducing delays in product availability can be accomplished by several measures including bedside emergency blood refrigeration, thawed immediate release plasma, use of shelf stable freeze-dried plasma, and rapid plasma thawing devices and procedures (34–43).

Another option for assuring timely and balanced transfusion for life-threatening bleeding is the use of low titer group O whole blood (LTOWB). Transfusion of LTOWB compared with individual blood components has been independently associated with improved 24-hour and 28-day mortality while requiring lower total blood products in adult trauma populations (44, 45). In children, LTOWB compared with blood components has been associated with improved time to normalization of base deficit and reduction in INR (46). It is critical that the use of LTOWB during MT be adequately studied in children before its use is widely adopted.

There are several limitations to this study. All participating centers were tertiary children's hospitals; thus, the patient population and clinical practice may not be reflective of other care settings. MTPs vary by center, and it is unknown whether the observed practice was consistent with protocol. There may be patients included in the study who were unnecessarily transfused under MTP. As this was a prospective observational study, we had missing data for variables if a test was not performed as part of routine clinical care or documented in the medical records. Further, tests were not obtained at the same time points pre- and postevent. From the data and analyses presented, we cannot determine causality.

CONCLUSIONS

Prevent clinical status and ultimate outcomes were distinctly different between children with traumatic, operative, and medical bleeding. MTPs were used during life-threatening bleeding events, regardless of the cause of hemorrhage. Despite use of MTPs, there were substantial delays in the administration of plasma and platelets. Randomized trials in children are needed for each major etiology of life-threatening bleeding to determine which resuscitation practices reduce morbidity and mortality.

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