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Use of whole blood in pediatric trauma: a narrative review

Elissa Abou Khalil,[1] Katrina M Morgan,[1] Barbara A Gaines,[1,2] Philip C Spinella,[1,3] Christine M Leeper [1,3]

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[1]Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[2]Pediatric General and Thoracic Surgery, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, USA
[3]Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to
Dr Christine M Leeper; leepercm@upmc.edu

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SUMMARY

Balanced hemostatic resuscitation has been associated with improved outcomes in patients with both pediatric and adult trauma. Cold-stored, low-titer group O whole blood (LTOWB) has been increasingly used as a primary resuscitation product in trauma in recent years. Benefits of LTOWB include rapid, balanced resuscitation in one product, platelets stored at 4°C, fewer additives and fewer donor exposures. The major theoretical risk of LTOWB transfusion is hemolysis, however this has not been shown in the literature. LTOWB use in injured pediatric populations is increasing but is not yet widespread. Seven studies to date have described the use of LTOWB in pediatric trauma cohorts. Safety of LTOWB use in both group O and non-group O pediatric patients has been shown in several studies, as indicated by the absence of hemolysis and acute transfusion reactions, and comparable risk of organ failure. Reported benefits of LTOWB included faster resolution of shock and coagulopathy, lower volumes of transfused blood products, and an independent association with increased survival in massively transfused patients. Overall, pediatric data are limited by small sample sizes and mostly single center cohorts. Multicenter randomized controlled trials are needed.

INTRODUCTION

Injury is the leading cause of mortality and morbidity in children and adolescents in the USA.[1] Firearm-related injury has overtaken motor vehicle crashes as the most common mechanism of injury in children, and hemorrhage is the leading cause of early mortality in pediatric trauma.[2 3] Therefore, identifying optimal hemostatic resuscitation practice is of critical importance. Balanced resuscitation for bleeding is independently associated with improved outcomes in both injured children and adults.[4 5 1 6–10] Low-titer group O whole blood (LTOWB) has been increasingly used as a primary resuscitation product in adult trauma in recent years.[11] LTOWB use in pediatric trauma has been reported in several centers,[12] and small studies have suggested it is a safe and effective resuscitation product in injured children.[13–18] Here, we will present a narrative review of the data regarding the use, safety, and efficacy of LTOWB for acute resuscitation in injured children.

METHODS

An electronic search was conducted using PubMed and CINAHL databases from inception through December 1, 2022. Search terms included a combination of natural language phrases and Medical Subject Headings terms using "AND" and "OR" functions that captured topics: injured children and adults, hemorrhage, bleeding, blood transfusion, and whole blood. Studies were reviewed and chosen if they included injured children (aged <18 years old) who received LTOWB as part of their initial trauma resuscitation, with or without a comparison group to component therapy (CT). LTOWB was defined as cold-stored RhD-positive or RhD-negative group O whole blood with low titers of anti-A and anti-B antibodies (ranging from 50 to 256). Studies were excluded if modified LTOWB (leukoreduced without platelet-sparing filter plus room-temperature platelets transfused) or warm fresh whole blood were transfused. In cases where a comparison group was presented, CT was defined as transfusion of red blood cells, plasma, and/or platelets. Retrospective and prospective cohort studies were included. Only studies in English were included. Case reports, case series, reviews, opinions, historical accounts, editorial, or commentary articles were excluded if they did not report new data. Abstract-only texts without complete articles and data analysis and preclinical studies were excluded. Studies were reviewed and assessed for inclusion independently by two authors, and the final list of eligible studies was agreed on by all authors.

A total of seven studies are included in our review (table 1). No randomized controlled trials met the inclusion criteria. Extracted data from these studies included: details of LTOWB and CT transfusions, safety outcomes (hemolysis, transfusion-related adverse events, in-hospital complications), mortality outcomes, and blood product transfusion volumes. For the purpose of this review, based on the time points at which the studies reported mortality, early mortality was defined as <72-hour mortality and late mortality as 28-day, 30-day, or in-hospital mortality. Combining the early and late mortality data from all seven studies, a χ^2 unadjusted analysis was performed to evaluate for an association between children who received LTOWB or CT and mortality. Results were defined as statistically significant if $p<0.05$. Overall, the quality of evidence was moderate using the Risk Of Bias In Non-randomised Studies - of Interventions tool (online supplemental table 1).[19] Institutional review board approval was not required for this narrative review.

RESULTS

Use of LTOWB in children

At least 10 pediatric centers in the USA currently use LTOWB in the resuscitation of patients with

Table 1 Characteristics of studies included in the review

Author	Study design	Inclusion criteria	Exclusion criteria	LTOWB eligibility criteria	LTOWB	LTOWB patients	CT patients
Leeper,[13] 2018	Prospective observational Single center	▶ Injured children aged <18 years who received LTOWB on or during admission.		Age: ≥3 years old. Weight: ≥15 kg Indication: Traumatic hemorrhagic shock.	Titer: <50. LR: Platelet-sparing filter. RhD: neg. Max: 20 mL/kg.	18	–
Leeper,[14] 2020	Retrospective observational Single center	▶ Injured children aged <18 years who received LTOWB or CT during their initial resuscitation.	▶ Pre-existing coagulation disorders. ▶ Transfusion before arrival to ED. ▶ Death on arrival.	2016–2018 Age: ≥3 years old. Weight: ≥10 kg. 2018–2019: Age: ≥1 year old. Weight: no limit. Indication: Traumatic and hemorrhagic shock.	Titer: LR: Platelet-sparing filter. RhD: neg. Max: 2016–2019: 20 mL/kg. 2019: 40 mL/kg.	28	28
Anand,[15] 2021	Retrospective Multicenter	▶ Injured children 1–17 years old ▶ PRBC or LTOWB transfusion within initial 4 hours of presentation	▶ Burns ▶ Interfacility transfer. ▶ Pre-existing coagulation disorders. ▶ Potentially erroneous transfusion volumes (>100 units).	Not specified	Not specified	135	270
Leeper,[16] 2021	Retrospective observational Single center	▶ Injured children aged >18 years. ▶ Receipt of at least one unit of PRBC or LTOWB within 24 hours of admission.	▶ Pre-existing coagulation disorder. ▶ Death within 72 hours of injury.	2016–2018 Age: ≥3 years old. Weight: ≥10 kg. 2018–2019: Age: ≥1 year old. Weight: no limit. Indication: Traumatic hemorrhagic shock.	Titer: <50. LR: Platelet-sparing filter. Max: 2016–2019: 20 mL/kg. 2019: 40 mL/kg.	36	36
Morgan,[17] 2021	Retrospective observational Single Center	Injured and non-injured children aged <18 years with hemorrhagic shock who received LTOWB during admission.		2016–2018: Age: ≥1 year old. Weight: ≥10 kg. 2018–2020: Age: ≥1 year old. Weight: no limit. Indication: Traumatic or intraoperative hemorrhagic shock.	Titer: <50. LR: Platelet-sparing filter. Max: 2016–2019: 20 mL/kg. 2019: 40 mL/kg.	47	
Gaines,[18] 2021	Prospective observational Single center	▶ Injured children ▶ 0–17 years old. ▶ Massive transfusion (>40 mL/kg within 24 hours of admission).	▶ Death in ED.	2016–2018: Age: ≥1 year old. Weight: ≥10 kg. 2018–2020: Age: ≥1 year old. Weight: no limit. Indication: Traumatic hemorrhagic shock.	Titer: <50. LR: Platelet-sparing filter. RhD: neg. Max: 40 mL/kg.	27	53
Braverman *et al*,[26] 2022	Retrospective observational Single center	▶ Injured children age 5–18 years old. ▶ Receipt of LTOWB on arrival.	–	Age: >5 years old. Weight: no limit. Indication: Traumatic hemorrhagic shock.	Titer: <256. LR: non-leukoreduced. RhD: pos. Max: 20 mL/kg.	12	–

CT, component therapy; ED, emergency department; LR, leukoreduction; LTOWB, low titer group O negative whole blood; Max, maximum; Neg, negative; Pos, positive; PRBC, packed red blood cells.

pediatric trauma.[17] Although LTOWB appears to be a safe product in children, the characteristics of an optimal LTOWB product has not been defined. Thus, variations in the type of LTOWB product used (ie, anti-A and anti-B titer levels, leukoreduction, RhD-positive vs RhD-negative) as well as guidelines for LTOWB processing and administration exists between institutions. The studies included in this review largely reflect the experience of a single center. A study using the TQIP database did not specify the characteristics of LTOWB used across centers as this information was not available in the database and likely differed across institutions.[20] The characteristics of the LTOWB used in the studies reported here can be found in table 1.

More nuanced information regarding practice variation can be found in a survey of 10 pediatric LTOWB programs. In these

Table 2 Perceived barriers and potential solutions to initiating a low-titer group O whole blood transfusion program for injured children

Perceived barriers	Potential solutions
Complexity of starting LTOWB program	► Consult colleagues at other pediatric and adult hospitals who have effectively started LTOWB programs (11 pediatric centers as of August 2023). ► Conduct multidisciplinary discussions among trauma, blood bank, blood supplier, emergency medicine staff at your institution for buy in.
Waste	► Use LTOWB through its full shelf life (21–35 days). ► LTOWB approaching expiration can be sent back to blood bank, nearby adult hospitals, or processed into an RBC unit. ► Expand eligibility criteria to include non-injured massively bleeding children (ie, operating room, gastrointestinal bleed, cardiac surgery patients), prehospital administration, etc.
Safety concerns	► Multiple adult and pediatric studies showing no increased risk of hemolysis[13 16 17] or other adverse events (AKI, ARDS, VTE, multisystem organ failure)[13 15–18] in LTOWB compared with CT recipients, including non-group O patients[13 17] and RhD-positive women.[17]
RhD alloimmunization	► Studies show that women[32 33] and parents[34] will accept RhD-positive LTOWB transfusions with potential survival benefit knowing the risks of alloimmunization and HDFN. ► Educate providers on the potential risks of HDFN compared with potential benefits of RhD-positive LTOWB vs components when RhD-negative LTOWB is not available.[35 36] ► Targeted campaigns to increase blood donation from eligible RhD-negative donors. ► Prioritize use of RhD negative product when available. ► Research to assess D-alloimmunization rates in children after trauma. ► Develop post-exposure treatment and screening programs.
Cost	► Increasing use in adult and pediatric centers across the USA with increasing data showing its safety profile and benefits over component therapy alone. ► May be more cost efficient with data showing decreased individual component and total blood volume transfusions after receipt of LTOWB. ► Included total care costs (not only expenses related to blood products) in cost analyses.
Accessibility	► Request LTOWB from blood supplier. ► If the primary supplier cannot or will not provide, contract a secondary blood supplier for LTOWB. Learn the contracting details to understand your ability to purchase LTOWB from a contracted secondary blood supplier.
Efficacy	► Several multicenter randomized controlled trials in different countries are planned and will shed light on the efficacy of LTOWB compared with CT during resuscitation of injured patients. ► Current data is limited but several studies have shown some survival benefits,[18] quicker time to administration of balanced blood products,[13] faster resolution of shock and coagulopathy,[14] and decreased blood product transfusion volumes[14 15 18] in recipients of LTOWB compared with CT.

Table adapted and expanded from Meshkin.[12]
AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CT, component therapy; HDFN, hemolytic disease of the fetus and newborn; LTOWB, low titer group O whole blood RBC, red blood cells; VTE, venous thromboembolism.

centers, indications for LTOWB use were traumatic hemorrhage in 30% (3/10) of centers, all massively bleeding patients in 50% (5/10), and select non-trauma bleeding patients with medical and/or surgical bleeding in 2% (2/10) of centers.[12] The study reported 70% (7/10) centers used leukoreduced LTOWB as well as RhD-positive LTOWB. Regarding eligible recipients, 80% (8/10) include both male and female children, 70% (7/10) restricted the use of LTOWB by weight criteria, and 60% (6/10) restricted use by age criteria. Reported barriers to LTOWB use included logistical concerns (wastage and inventory managements, and small volume of bleeding patients to support LTOWB storage) and lack of supportive data comparing LTOWB to CT (ie, patient safety, cost, and efficacy).[12] Those barriers were similar to those identified in a survey of trauma medical directors at 30 pediatric trauma centers[20] and a survey of 103 level 1 adult trauma centers.[11] A table including perceived barriers and potential solutions can be found in table 2.

Safety of LTOWB in children

Hemolysis

Hemolysis is a potential risk factor associated with transfusion of LTOWB in non-group O patients due to the presence of anti-A and anti-B antibodies. Markers of hemolysis may include haptoglobin, lactate dehydrogenase (LDH), reticulocyte count, bilirubin, and assessment of renal function (creatinine and potassium).[21–23] Of the studies identified, three used markers of hemolysis to describe the safety profile of LTOWB after transfusion in injured children.[13 16 17]

The first civilian cohort of patients with pediatric trauma who received LTOWB was described in 2018 by Leeper. This retrospective cohort study included 18 children who received LTOWB, of which 8 were group O and 10 were non-group O. Criteria for receipt of LTOWB were age greater than 3 years and weight greater than 15 kg. The titer of LTOWB was <50 and maximum volume allowed was 20 mL/kg. The median (IQR) age of this cohort was 11 (5–14) years and the median (IQR) volume of LTOWB transfused was 15 (9–23) mL/kg. Hemolysis markers, including haptoglobin, total bilirubin, reticulocyte count, and LDH, in addition to creatinine and potassium, did not significantly differ between group O and non-group O recipients of LTOWB, at the time of transfusion and on days 1 and 2 post-transfusion. No signs of hemolysis were noted in any of the groups based on these laboratory markers.[13]

In a subsequent propensity-matched cohort study, 36 injured children who received LTOWB were compared with 36 patients who received CT exclusively. The titer of LTOWB was <50 and maximum volume allowed was 40 mL/kg. There were neither signs of hemolysis nor significant differences in hemolysis markers including total bilirubin, hemoglobin, and creatinine between LTOWB and CT cohorts.[16]

Lastly, Morgan reported a propensity-matched analysis of 47 children age >1 year with massive hemorrhage who received

LTOWB. Although this cohort included patients without trauma, the most common indication for LTOWB transfusion was hemorrhagic shock after trauma. Some of the injured subjects were included in the preceding studies, as this analysis expanded on the existing safety data after the maximum allowable volume of LTOWB transfused was increased at this institution to 40 mL/kg. Hemolysis markers including LDH, haptoglobin, total bilirubin, reticulocyte count, potassium, and creatinine were compared between group O and non-group O LTOWB subjects. The median (IQR) of LTOWB transfused was 16 (10–25) mL/kg to both group O and non-group O recipients. No clinical or statistical differences were found in baseline hemolysis markers at the time 0, day 1, or day 2 after transfusion between group O and non-group O recipients of LTOWB.[17] This is concordant with studies in adults that showed no evidence of hemolysis in adult patients in titers up to <256.[21 22 24 25]

Transfusion-related adverse events

Of the seven articles that include children age<18, no major transfusion reactions were reported in the LTOWB group.[13–18 26]

Adverse events

Several studies reported in-hospital complications, including organ failure (acute kidney injury (AKI), acute respiratory distress syndrome (ARDS)), venous thromboembolism (VTE), and sepsis or bacteremia.[15–18] Multiple system organ failure was assessed using the PEdiatric Logistic Organ Dysfunction-2 (PELOD-2) score.[16 17]

In the propensity-match analysis by Leeper, adverse outcomes after transfusion of LTOWB, including AKI, sepsis/bacteremia, VTE, and organ failure defined by the PELOD-2 score were evaluated. No significant differences in PELOD-2 score were found between groups either on day 3 (median (IQR) score of 7 (1–12) in LTOWB group vs 7 (1–10) in CT group, p=0.99) or on day 7 (median (IQR) score of 0 (0–7) in LTOWB group vs 0 (0–6) in CT group; p=0.87). Rates of AKI were low in both groups (6% in LTOWB group vs 11% in CT group, p=0.67). None of the subjects developed sepsis or bacteremia in either cohort.[16] In the study by Gaines, adverse events including AKI, VTE, and functional disability at discharge among survivors did not significantly differ between the recipients of LTOWB compared with component blood products.[18] Anand assessed the rate of major complications defined as AKI, ARDS, VTE, and sepsis. No differences were found between the whole blood and non-whole blood groups.[17] Morgan compared outcomes and found no differences in clinical outcomes between group O and non-group O LTOWB recipients, including hospital length of stay, intensive care unit (ICU) length of stay, ventilator days, and PELOD-2 scores on days 3 and 7 after LTOWB transfusion (day 3: 2 (1–13) in group O vs 7 (0–11) in non-group, p=0.82; day 7: 0 (0–9) in group O and 7 (0–10) in non-group O, p=0.48).[17] A summary of the safety outcomes provided in the text above can be found in table 3.

Outcomes and effectiveness of LTOWB in children

Mortality

Although mortality at various time points is reported in the pediatric literature, the majority of studies are not designed to detect a mortality difference between LTOWB and CT groups, either due to small sample sizes or confounding factors. Of the studies identified, two reported early mortality[15 18] and six reported late mortality.[13 14 16–18] All studies combined, in an unadjusted analysis, early mortality for LTOWB and CT recipients was 17.9% and 24.3%, respectively (p=0.13); late mortality for LTOWB and CT recipients was 34.7% and 37.5%, respectively (p=0.39).

In the propensity-match analysis by Leeper, where 28 injured children who received LTOWB were compared with 28 injured children from a historical CT cohort, no statistical differences were found in in-hospital mortality between the two groups (8/28 (29%) in the LTOWB group vs 12/28 (43%) in the CT group, p=0.40).[14]

Similar results were reported by Anand; 270 injured children received CT exclusively and 135 children received LTOWB and CT during trauma resuscitation. After 2:1 propensity score matching, mortality was not significantly different between the LTOWB and CT groups for 24-hour (26/135 (19.3%) LTOWB vs 59/270 (21.9%) CT groups, p=0.546) or in-hospital mortality (42/135 (31.1%) LTOWB vs 93/270 (34.4%) CT groups, p=0.502). Most late deaths (post 72-hour deaths) were due to TBI.[15]

In a single center study of children who received massive transfusion, Gaines reported a survival benefit at both early and late time points for recipients of LTOWB. After adjusting for age, injury severity score, total blood product volume transfused, admission base deficit, and admission international normalized ratio (INR) in a Cox proportional hazard regression model, children who received LTOWB as part of their resuscitation had significantly decreased mortality at both 72 hours and 28 days after injury (adjusted OR (AOR) 0.23, p=0.009 and AOR 0.41, p=0.02, respectively).[18] This in concordant with the mortality benefit shown in several adult studies,[27–29] specifically those at highest risk of mortality based on prehospital injury characteristics.[30]

Blood product volume

Reduction in blood transfusion volumes, including both total blood volumes and individual component volumes, is an outcome that has also been evaluated to assess the efficacy of LTOWB.[28] Out of the seven studies included in our review, four compared transfusion volumes between LTOWB and CT groups.[14–16 18] Leeper in 2020 found volumes of component blood products transfused was significantly lower in the LTOWB group.[14] In Leeper's (2021) propensity matched cohort of 36 recipients of LTWOB compared with 36 recipients of CT, there were no differences in the volume of any component product or total blood product transfused between groups, however fewer children in the LTOWB cohort received additional red blood cell (RBC), plasma, and platelet transfusions compared with children who received CT alone.[16] In the study by Gaines, which included 80 patients with massively transfused pediatric trauma, there were significant differences in 24-hour total RBC and plasma transfusion volumes between recipients of LTOWB compared with CT only (RBC 18 (12–25) mL/kg vs 30 (20–60) mL/kg, respectively, p=0.002; plasma: 15 (7–30) mL/kg vs 30 (14–37) mL/kg, respectively, p=0.02).[18] And lastly, in Anand, the volume of all component blood products as well as total volume of blood products transfused was lower in the LTOWB group both at 4 and 24 hours after admission[15] (table 4).

Other clinical outcomes

Additional clinical outcomes to assess the safety profile and potential benefit of transfusing LTOWB over CT have been described, including hospital length of stay, ICU length of stay, ventilator days, and disability on discharge defined by the Functional Independence Measure Score.[14 16 18] In the two propensity match studies by Leeper, clinical outcomes including functional

Table 3 Summary of the safety outcomes related to transfusion of low-titer group O whole blood (LTOWB)

Safety outcomes	Studies	Summary of findings
Hemolysis	► Leeper,[13] 2018. ► Morgan,[17] 2021. ► Leeper,[16] 2021.	► No difference in markers of hemolysis after transfusion of LTOWB in group O vs non-group O recipients.[13 17] ► No difference in markers of hemolysis after transfusion of LTOWB vs CT.[16]
Transfusion reaction	► Leeper,[13] 2018. ► Leeper,[16] 2021. ► Morgan,[17] 2021. ► Gaines,[18] 2021.	► No reported transfusion reactions after transfusion of LTOWB in group O or non-group O recipients.[13 17] ► No reported transfusion reactions in the LTOWB or CT cohorts.[16 18]
Organ failure	► Morgan,[17] 2021. ► Leeper,[16] 2021. ► Gaines,[18] 2021. ► Anand,[15] 2021.	► No difference in AKI after transfusion of LTOWB vs CT.[15 16 18] ► No difference in ARDS after transfusion of LTOWB vs CT.[15 18] ► No difference in PELOD-2 scores on days 3 and 7 after transfusion of LTOWB in group O vs non-group O recipients.[17] ► No difference in PELOD-2 scores on days 3 and 7 after transfusion of LTOWB vs CT.[16]
Venous thromboembolism	► Morgan,[17] 2021. ► Leeper,[16] 2021. ► Gaines,[18] 2021. ► Anand,[15] 2021.	► No difference in VTE after transfusion of LTOWB in group O vs non-group O recipients.[17] ► No difference in VTE after transfusion of LTOWB compared with CT.[15 16 18]
Sepsis/bacteremia	► Leeper,[16] 2021. ► Anand,[15] 2021.	► No reported events of sepsis/bacteremia in LTOWB or CT cohorts.[15 16]
Hospital length of stay	► Gaines,[18] 2021.	► Decreased hospital length of stay after transfusion of LTOWB vs CT.[18]
	► Leeper,[14] 2020. ► Leeper,[16] 2021. ► Morgan,[17] 2021. ► Anand,[15] 2021.	► No difference in hospital length of stay after transfusion of LTOWB in group O vs non-group O recipients.[17] ► No difference in hospital length of stay after transfusion of LTOWB vs CT.[14–16]
ICU length of stay	► Leeper,[16] 2021. ► Gaines,[18] 2021.	► Decreased ICU length of stay after transfusion of LTOWB vs CT.[16 18]
	► Leeper,[14] 2020. ► Morgan,[17] 2021.	► No difference in ICU length of stay after transfusion of LTOWB in group O vs non-group O recipients.[17] ► No difference in ICU length of stay after transfusion of LTOWB vs CT.[14]
Ventilator days	► Anand,[15] 2021. ► Gaines,[18] 2021.	► Fewer ventilator days after transfusion of LTOWB vs CT.[15 18]
	► Leeper,[14] 2020. ► Morgan,[17] 2021. ► Leeper,[16] 2021.	► No difference in ventilator days after transfusion of LTOWB in group O vs non-group O recipients.[17] ► No difference in ventilator days after transfusion of LTOWB vs CT.[14 16]
Functional Disability	► Leeper,[14] 2020. ► Morgan,[17] 2021. ► Leeper,[16] 2021. ► Gaines,[18] 2021.	► No difference in functional disability after transfusion of LTOWB in group O vs non-group O recipients.[17] ► No difference in functional disability after transfusion of LTOWB vs CT.[14 16 18]

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CT, component therapy; ICU, intensive care unit; PELOD-2, PEdiatric Logistic Organ Dysfunction-2; VTE, venous thromboembolism.

disability, hospital length of stay, ICU length of stay, and ventilator days were assessed. No significant differences were found in any of those outcomes between the two groups.[14 16] However, in the study of massively transfused injured children by Gaines, recipients of LTOWB had significantly shorter hospital length of stay (p=0.02), ICU length of stay (p=0.02), and fewer ventilator days (p=0.05) compared with the CT group.[18] Finally, Anand found ventilation days were shorter in patients who received

Table 4 Volumes of total blood products, low-titer group O whole blood (LTOWB) and blood component transfused for LTOWB and component therapy groups in studies of interest. All studies used mL/kg as a unit of measure. Values are all presented in median (IQR)

Volume based (mL/kg)										
	Total		LTOWB		PRBC		Plasma		Platelet	
Study	LTOWB group	CT group	LTOWB group	CT group	LTOWB group	CT group	LTOWB group	CT group	LTOWB group	CT group
Leeper,[13] 2018	–	–	15 (9–23)	–	–	–	–	–	–	–
Leeper,[14] 2020	29 (11–55)	48 (17–122)	15 (10–22)	–	15 (0–28)*	24 (10–62)	11 (5–35)*	5 (0–15)	3 (0–8)*	0 (0–2)
Anand,[15]2020	39 (24–97)*	53 (36–119)	14 (10–23)	–	22 (15–53)*	36 (2571)	11 (0–25)*	17 (11–46)	0 (0–9)*	6 (4–13)
Leeper,[16] 2021	23 (11–42)	21 (10–40)	15 (9–23)	–	10 (0–23)	13 (10–21)	10 (5–20)	11 (0–20)	0 (0–2)	0 (0–1)
Morgan,[34] 2021+	–	–	16 (10–25) 16 (10–25)	–	12 (0–38) 7 (0–10)	–	10 (0–20) 6 (0–12)	–	0 (0–5) 0 (0–4)	–
Gaines,[18] 2021	50 (41–74)	61 (45–84)	20 (15–33)	–	18 (12–25)*	30 (20–60)	15 (7–30)*	30 (14–37)	2 (0–5)	4 (0–10)
Braverman *et al*,[26] 2022	–	–	–	–	–	–	–	–	–	–

All studies reported 24-hour blood volumes in median (IQR).
*Volumes are significantly lower in the LTOWB compared to volumes in the CT group with p value<0.05.
CT, component therapy; PRBC, packed red blood cells.

LTOWB (median (IQR) 2 (2–6) days in LTOWB group vs 3 (2–8) days in CT group, p=0.02).[15]

Shock and coagulopathy

The association between transfusion of LTOWB and shock, using base deficit as a surrogate marker, and coagulopathy, using INR as a surrogate marker, have been assessed in limited studies. Leeper (2020) found the LTOWB group had a faster time to resolution of base deficit (median (IQR) 2 (1–2.5) hours vs 6 (2–24) hours, respectively; p<0.001)) suggesting a faster resolution of shock in the LTOWB cohort.[14] Additionally, post-transfusion INR was lower in children who received LTOWB compared with those who received CT (1.4 (1.3–2.5) vs 1.6 (1.4–2.2) respectively, p=0.01), suggesting that LTOWB may be beneficial in mitigation of trauma-induced coagulopathy (TIC).[14] These data are limited by small sample sizes and lack of global functional hemostasis assays. Given that TIC is a major contributor to morbidity and mortality in injured children, these limited findings should stimulate interest in further investigating the effect of resuscitation strategies on TIC.

Limitations

The described studies are mostly single center, include relatively small sample sizes, and have design limitations inherent to observational data. Although the number of pediatric trauma centers using LTOWB is increasing, quality multicenter and randomized controlled data are limited. Transfusion guidelines and the characteristics of the LTOWB in use may differ between centers, which is another source of potential confounding.

CONCLUSION

In this study, we reviewed data regarding the use, safety, and outcomes of LTOWB transfusion in patients with pediatric trauma. Transfusion of LTOWB in children was shown to be safe; no studies reported hemolysis, increased organ failure, or transfusion reactions. Some clinical outcomes differed between LTOWB and CT recipients, including decreased transfusion volumes and improvement in biochemical markers of shock and TIC after receipt of LTOWB. A survival advantage was shown in massively transfused injured children only, though the other studies included in this review were largely underpowered to detect a difference in mortality. Recent guidelines developed by a group of experts in pediatric trauma resuscitation recommended clinicians should consider transfusing low titer (≤200 anti-A and anti-B immunoglobulin G) group O whole blood to resuscitate traumatically injured children in hemorrhagic shock if available over individual component blood products.[31] Large, well-designed multicenter studies are needed.

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ORCID iD

Christine M Leeper http://orcid.org/0000-0001-9902-0340

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