Current state of whole blood transfusion for civilian trauma resuscitation

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BACKGROUND: Whole blood (WB) is rapidly emerging as the treatment modality of choice for the initial resuscitation of civilian trauma patients across the United States. The reemergence of WB has been rapid and driven in part by recognition of the importance of early plasma transfusion in the resuscitation process.
STUDY DESIGN AND METHODS: The study was designed as a critical analysis of the available literature on WB transfusion in civilian trauma patients. Studies were included if they reported on transfusion of cold-stored WB used in a civilian setting and measured safety, feasibility, or a direct clinical outcome.
RESULTS: Examination of the available literature supports the feasibility and safety of WB used in treatment of civilian trauma patients. The evidence regarding clinical outcomes, particularly with direct comparison to equivalent doses of component therapy, is more limited. The literature is predominantly descriptive and retrospective in nature and limited by the heterogeneity of clinical WB protocols being used. Based on this limited data set, there are limited conclusions that can be used to definitely support or refute the clinical superiority of WB to component therapy.
CONCLUSION: Current literature supports the safety and feasibility of WB, but prospective randomized trials comparing WB to component therapy are needed to provide the definitive evidence on this topic.

Traumatic hemorrhage causes of tens of thousands of preventable deaths each year in the United States.[1] Current strategies to reduce this preventable mortality include damage control resuscitation and the early use of plasma, both of which have greatly altered transfusion practice in this setting.[1,2] The study of fixed ratio resuscitation strategies for trauma (often one red blood cell [RBC]: one plasma: one platelet) has contributed to widespread recognition that early plasma administration improves mortality.[2] Whole blood (WB) delivers all components in a single product, providing early inclusion of plasma in a manner that allows the patient to be expeditiously transfused what they are bleeding.[2]

Until recently, WB was not widely available or used in the civilian setting. The development of component therapy (CT) and the ability to both efficiently deliver only the blood component needed, a form of personalized medicine, and generate multiple components from each donation revolutionized the practice of transfusion medicine. This transformation was so widely adopted that it resulted in decreased production and availability of WB. This decreased availability resulted in transfusion for trauma resuscitation being largely implemented by CT for several decades in the civilian setting.[3–5]

While WB has been absent from the civilian trauma setting, it has been in continuous use in military settings. Military experiences with WB have suggested that there is a mortality benefit to the use of warm fresh WB.[6,7] Warm fresh WB is not a US Food and Drug Administration–approved product and would have challenges in civilian

ABBREVIATIONS: ARC = American Red Cross; CT = component therapy; LTOWB = low-titer group O whole blood; MA = maximum amplitude; TEG = thromboelastography; WB = whole blood.

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application, particularly the inability to obtain the results of infectious disease testing before product use. Despite these issues, the observed mortality benefits of warm fresh WB may be achieved with cold-stored WB. Cold storage has emerged as a strategy that addresses many of the logistical limitations of warm fresh WB use in civilian populations. The current iteration of civilian WB is group O with low isohemagglutinin titers, referred to as low-titer group O whole blood (LTOWB). The latest AABB standards allow the use of LTOWB for non–group O patients or patients with unknown ABO group. The standards require each facility to determine the situations in which LTOWB can be used and the maximum volume allowed per transfusion event. Additionally, each facility must have a defined plan for monitoring adverse events in LTWOB recipients. The standards allow LTOWB to be used emergently across patient ABO blood types making it practical as the initial resuscitation product in appropriate patients.[8]

In addition to the proposed safety and logistical benefits, there may be other advantages to cold storage of WB compared to CT. Cold-stored WB is a more concentrated product, as it contains less anticoagulant and fewer additive solutions when compared with equivalent doses of CT with RBCs stored in additive solutions.[9] There is also evidence that the cold-stored platelets have improved in vitro hemostatic function.[10–13] It should be noted that there are not currently any data that this improved in vitro activity translates to a better clinical product than platelets stored at room temperature. Because the current iteration of cold-stored WB is required to feature low anti-A and anti-B isohemagglutinin titers, there is a reduced risk of hemolysis when compared to the risk from untitered plasma-containing blood products when transfused in a minor ABO-incompatible fashion.[13,14] Cold storage should reduce the incidence of bacterial contamination when compared to that of room temperature platelets.[15]

Cold-stored WB could also simplify transfusion logistics by providing all components in one product, and this benefit could also be extended to the prehospital setting.[16,17] In a post hoc combined analysis of the Control of Major Bleeding After Trauma (COMBAT)[18] and Prehospital Air Medical Plasma (PAMPer)[19] studies, Pusateri et al.[20] examined the effects of prehospital plasma transfusion in the context of hospital transport time. The results suggested that prehospital plasma was associated with a survival benefit when transport times were longer than 20 minutes and that the risk-benefit ratio for prehospital plasma was favorable. In addition, in a subanalysis of the PAMPer study,[19] Guyette et al.[20] analyzed 30-day mortality in patients at risk for hemorrhagic shock based on prehospital resuscitation with crystalloid only, RBCs, plasma, or RBCs and plasma. This analysis showed the greatest mortality benefit in patients receiving both prehospital RBCs and plasma.[21] These analyses support a possible role for the use of LTOWB in prehospital resuscitation in patients with traumatic hemorrhage.

Cold-stored LTOWB programs have been or are soon to be implemented at more than 40 organizations,[22] as reported by a recent survey conducted by the AABB–Trauma Hemostasis and Oxygenation Research Network collaboration. There has been a substantial increase in peer-reviewed literature on the topic of cold-stored WB in the past 5 years. In fact, an entire conference, the First National Whole Blood Symposium, was convened in May 2019 in San Antonio, Texas, to discuss its use.

As WB use increases, there are many issues that need to be addressed, including safety, feasibility, logistics, variability in practice, and clinical effectiveness compared to standard of care. Some of these issues have been better studied to date than others. This paper aims to show the current state of WB use in clinical practice and provides an analysis of current literature relating to safety, feasibility, and outcomes.

This paper does not address fresh warm WB and military applications of WB, but instead focuses on cold-stored WB for civilian use primarily in trauma patients. This distinction is fundamental to account for any hemostatic differences resulting from storage temperature and product storage duration, most notably on platelet function. Also, this paper does not present an exhaustive review of in vitro studies of WB function and will instead address only the critical issues raised by these studies as clinically relevant or likely to influence product manufacturing and storage issues of LTOWB.

METHODS

Articles included in this analysis were identified through a PubMed search with medical subject headings: whole blood, cold stored, and transfusion. Studies were included if they reported on transfusion of cold-stored WB used in a civilian setting and measured safety, feasibility, or a direct clinical outcome. Studies without direct a comparison of cold-stored WB to CT, review articles, or articles not available in English were excluded from analysis. Adherence to the inclusion criteria was determined by review of abstracts and/or full text of the articles identified. The literature search was performed by the primary author and verified by the other authors. Additional articles were identified through review of the references of previously included articles assuming they met all inclusion criteria.

RESULTS

The initial search yielded 65 results. Fifty-three articles were excluded based on review of the abstract for failure to include patient or outcome data. Excluded articles contained theoretical arguments for the benefits of WB, contained exclusively in vitro analyses, or suggested methods of implementing a clinical WB program. Thirteen articles underwent full text review. Six articles were excluded based on full text review for including only in vitro studies and no clinical outcomes, and one was

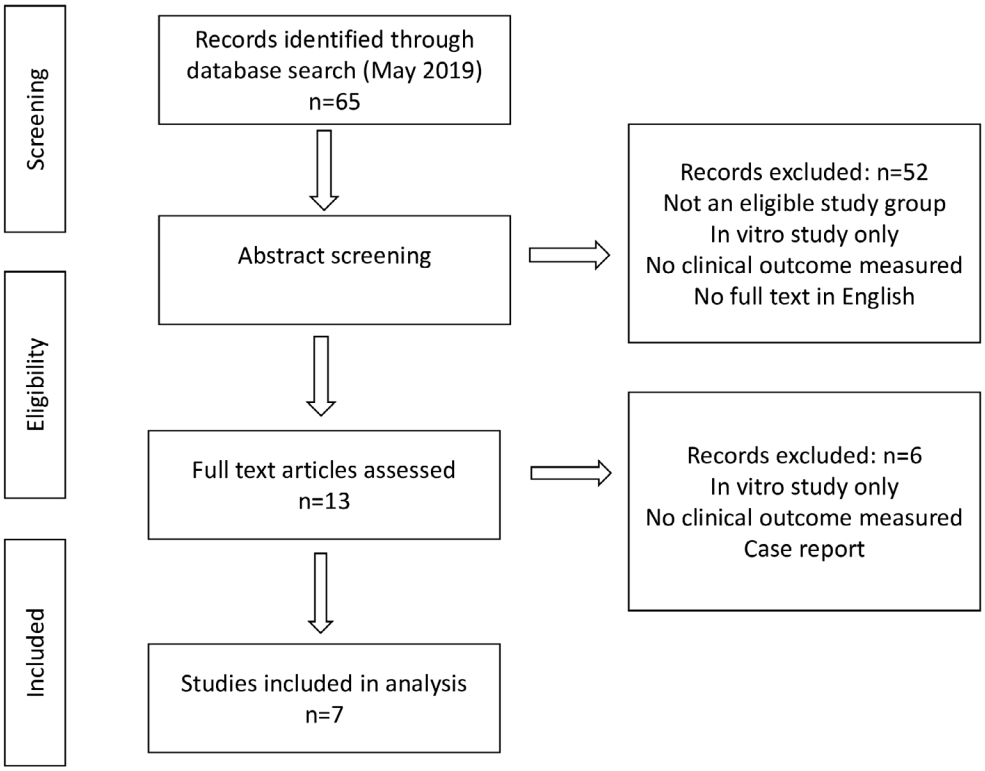

Fig. 1. Literature review analysis.

excluded for being a case report. The remaining six articles were included in the review.[23–28] Review of the references list of the included articles yielded one additional article that met inclusion criteria[29] and was therefore included in our analysis, for a total of seven articles (Fig. 1).

The WB used for the included studies was uniformly stored at 1 to 6°C per Food and Drug Administration requirements without agitation. The WB products were collected in citrate phosphate dextrose in six of the studies and citrate phosphate dextrose adenine in the seventh.[28] Yazer et al.[23] used the WB units until Day 10, and Zhu et al.[28] used the WB units until the Day 35 outdate. All other studies reviewed used the WB units until Day 14. The WB units were leukoreduced in all studies except for Zhu et al.[28] All studies used LTOWB, but the definition of low titer used in the studies ranged from less than 50 to less than 256 (Table 1). The titers were measured using room temperature immediate spin testing when reported.

Trauma-associated hemorrhage was the clinical indication for the use of WB in all the studies analyzed. The maximum number of LTOWB units that could be transfused to a patient ranged from 2 to 30 for adult patients. Pediatric patients were included in three studies,[27–29] for a total of 31 pediatric patients. Leeper et al.[27,29] used weight-based dosing in both studies that included only pediatric populations. LTOWB was restricted to male patients in all

TABLE 1. Included studies and outcomes

Study	Storage solution	Shelf life (days)	Titer	Leukoreduced	Max units	Subjects	Hemolysis observed*	Mortality
Yazer (2016)	CPD	10	<50	Yes	2	47	No	NR
Seheult (2017)	CPD	14	<50	Yes	2	44	No	NR
Leeper (2018)	CPD	14	<50	Yes	20 mL/kg	18	No	NR
Seheult (2018)	CPD	14	<50	Yes	4	172	No	NR
Seheult (2018)	CPD	14	<50	Yes	4	270	No	Yes (in hospital 24.4% vs. 18.5%; p = 0.24, 24 hours 12.6% vs. 8.9% p 0.33)
Leeper (2019)	CPD	14	<50	Yes	30 mL/kg	8	No	Yes* (secondary) (13% vs. 43% p = 0.20)
Zhu (2019)	CPDA-1	35	<256	No	2 (prehospital)	30	NR	36% (adults) 20% (peds)

* Determined by clinical observation, reported transfusion reactions, and laboratory monitoring of the biochemical markers of hemolysis.
CPD = citrate phosphate dextrose; CPDA-1 = citrate phosphate dextrose adenine; NR = not reported.

TABLE 2. Other clinical outcomes measured

Study	Outcomes measured	Category (n)		p value
		CT (145)	**WB (47)**	
Yazer 2016	Hospital LOS	10 (0-208)	10 (0-118)	0.71
	ICU LOS	4 (10-98)	3 (0-32)	0.09
	ICU free days	4 (0-110)	3 (0-107)	0.89
	Days on ventilator	2 (0-47)	2 (0-24)	0.78
	Ventilator-free days	7 (0-192)	8 (0-114)	0.72
		Non–group O WB (27)	**Group O WB (17)**	
Seheult 2017	Hospital LOS	14.0 (6.0-25.0)	16.5 (10.5-20.0)	0.82
	ICU LOS	4.0 (2.0-10.0)	1.5 (1.0-8.0)	0.49
	ICU free days	6.0 (1.0-15.0)	7.5 (1.5-15.5)	0.96
	Days on ventilator	2.0 (0-5.0)	3.0 (0-7.0)	0.82
	Ventilator free days	9.0 (5.0-15.0)	8.0 (1.0-14.0)	0.62
			WB (18)	
Leeper 2018	Hospital LOS		7.5 (3-13)	
	ICU LOS		3.5 (2-6)	
	Time receiving mechanical ventilation		2 (1-5)	
		Non–group O WB, all recipients (102)	**Group O WB, all recipients (70)**	
Seheult 2018	Hospital LOS	14.0 (7.0-26.0)	14.0 (5.0-21.0)	0.28
	ICU LOS	5.0 (3.0-13.0)	5.0 (2.0-11.0)	0.36
	ICU free days	6.5 (2.0-14.0)	5.0 (2.0-12.0)	0.61
	Days on ventilator	3.0 (0-8.0)	2.0 (0-7.0)	0.35
	Ventilator free days	9.0 (3.0-16.0)	8.0 (3.0-18.0)	0.57
	In-hospital mortality ratio	13/102 (12.8%)	9/69 (13.0%)	0.95
		Component therapy (14)	**Whole blood (8)**	
Leeper 2019	TEG maximum amplitude	60.2 mm	59.5 mm	0.92
	Hospital LOS	12 (3-19)	12 (9-14)	0.76
	ICU LOS	4 (1-9)	3.5 (2-6)	0.71
	Ventilator days	2 (0-7)	2 (1-5)	0.75

CT = component therapy; ICU = intensive care unit; LOS = length of stay; TEG = thromboelastography; WB = whole blood.

but one of the adult studies.[28] All included studies reported the use of WB in hospital, and Zhu et al.[28] also reported the use of WB in the prehospital setting.

The number of patients transfused with WB ranged from 8 to 270 with a combined total of 589. Hemolysis markers including haptoglobin, lactate dehydrogenase, total bilirubin, creatinine, and serum potassium were evaluated in six of the seven studies. There was no evidence of increased hemolysis for patients receiving WB in any of the included studies. Hemolysis comparisons were made either comparing patients who received LTOWB versus CT[23,26] or group O patients versus non–group O patients receiving LTOWB.[24,25,27,29] Other clinical outcomes measured are listed in Table 2. Leeper et al.[27] also included functional and lab measures of hemostasis, including platelet count and thromboelastography (TEG) maximum amplitude (MA). They reported no significant difference in posttransfusion platelet count or in the median pre- or posttransfusion TEG MA measured in patients receiving WB compared to CT. Two studies[24,25] compared clinical outcomes in blood group O versus non–group O transfusion recipients of LTOWB, showing no statistically significant difference in mortality between the two groups.[24,25] Additionally, these studies[24,25] collectively showed no significant differences in the other clinical outcomes measured (Table 2).

Only Seheult et al.[26] and Leeper et al.[27] evaluated mortality as a clinical outcome in patients treated with WB compared with component therapy and there was no significant difference (Table 1). Zhu et al.[28] reported mortality rates comparing patients who received WB in a prehospital setting compared to patients who did not receive prehospital transfusion. Zhu et al.[28] reported lower mortality in adult patients (63% CT in hospital vs. 36% WB prehospital and hospital) but did not include a measure of statistical significance. They also reported a decrease in pediatric mortality (42% CT in hospital to 20% WB prehospital and hospital), again with no measure of statistical significance and a WB experimental group of only five patients. Other studies reported mortality of patients receiving WB but did not compare that rate to any established baseline or component therapy group.[23–25,27]

DISCUSSION

In the limited studies examining the use of LTOWB in a civilian setting, the data suggest its use is both safe and feasible. The available data show no increased risk of hemolysis with limited volumes of cold-stored LTOWB when compared to CT or when given to non–group O recipients. The data on the efficacy of LTOWB compared to CT is more limited. The available data suggest no statistical difference in mortality for patients whose resuscitation included LTOWB compared with those treated with CT only. This efficacy data must be evaluated in the context of very limited sample sizes,

variations in dose, and inherent limitations of retrospective and nonrandomized studies.

Safety and hemolysis

Several of the included studies provide evidence that the use of LTOWB at these restricted doses dose not increase hemolysis and is feasible in the treatment of trauma patients regardless of patient ABO blood type. Yazer et al.[23] and Seheult et al.[24,25] compared biochemical markers of hemolysis between group O and non–group O patients who received LTOWB to demonstrate the safety profile of using type O WB in all patients. These studies did not identify significant differences in the measured hemolysis markers (haptoglobin, lactate dehydrogenase, total bilirubin, creatinine, and serum potassium) as measured on Day 0 through Day 2. They also did not show significant differences in the other clinical outcomes measured (Table 2). These studies, though limited by number of subjects, suggest that the use of type O WB in non–group O patients does not lead to worse outcomes among the non–group O recipients. These studies, however, do not show any evidence of the safety profile of LTOWB in a direct clinical comparison compared to that of traditional component therapy.

Mortality

The reported mortality outcomes in the studies that provided a direct comparison between patients receiving WB and those receiving only CT showed lower absolute mortality rates in the WB groups, but none were statistically significant. Seheult et al.[26] observed an almost 6% (24.4% vs. 18.5%; p = 0.24) absolute reduction in in-hospital mortality with a median dose of 2 units of LTOWB compared with the component therapy in the largest cohort included. Leeper et al.[29] reported mortality as a secondary outcome and showed 13% mortality in the WB group compared to 43% in the CT group. Zhu et al.[28] reported mortality rates of 36% for adults and 20% for pediatric patients receiving WB but did not control for confounding factors such as age and mode of hospital transport. While the raw overall comparisons are favorable to WB transfusion, they are still based on limited sample sizes, retrospective data, and failure to control for confounding variables.

Dose

The number of WB units used was limited in the included studies, and therefore the safety profile may not be extended broadly to transfusion of larger volumes of WB. The AABB standard requires as a safety measure that each institution define its own policy for the maximum volume of incompatible plasma from WB a patient can receive, but does not limit what volume can be selected.[8] Given the demonstrated safety profile at low doses, the next logical step is to conduct additional studies with increasing doses and concurrent active hemolysis surveillance. As a result of the limited volume of WB transfused, many of the included patients received other blood products, further complicating the analysis of the impact of WB.

Product attributes

Variations in product attributes and transfusion practices in the current studies restrict attempts at meta-analysis of the existing data. One large factor that limits comparability of published results stems from the variation in maximum storage age of products included in the protocols (Table 1). This variability in maximum allowable shelf life is relevant to the efficacy of the platelets in the WB. There are in vitro data that show cold storage improves the immediate hemostatic activity of platelets.[10,11] These studies show retention of in vitro platelet function out to Day 14 of cold storage.[10,11] There are much less compelling in vitro data regarding the efficacy of cold-stored platelets beyond Day 14. It should also be noted these studies examined cold-stored platelet components and not platelet function from platelets isolated from cold-stored WB products.[10,11] This existing research provides a rationale for the proposed in vivo hemostatic efficacy of cold-stored WB. However, these studies are limited by nature of being in vitro and not providing clinical measurements or outcomes.

AABB standards require the transfusion of LTOWB for non–group O patients, but do not specify what a "low titer" should be.[8] Most hospital centers surveyed by the American Red Cross (ARC) in 2017 cited less than 200 as a preferred low-titer cutoff, which is the current titer threshold for LTOWB units offered by the ARC.[30] The included studies mostly used a lower titer of less than 50 (Table 1). The use of this more restrictive titer may limit the applicability of the included results if higher titers are used in other settings. High titers are not always associated with hemolysis, which may instead depend on the antibody isotype and the presence of secreted A and B antigens in the plasma.[31,32]

Leukoreduction was almost uniformly performed in the included protocols (Table 2). Notably, the WB was not leukoreduced in the study by Zhu et al.[28] There have been recent studies that examine the impact of using platelet-sparing leukoreduction filters on the hemostatic function of WB. Remy et al.[33] as well as Thomas et al.[34] demonstrated a moderate but statistically significant reduction in some measures of WB hemostatic function using in vitro studies with a limited sample size. They reported in these leukoreduced units a significant reduction in platelet concentration and in impedance aggregation, but a lesser effect on other viscoelastic parameters and on thrombin generation. The translation of these in vitro parameters to in vivo hemostatic function is not well documented. To promote product standardization, risk-benefit analyses using in vivo studies of the effect of leukoreduction on the resultant WB product is needed.

Prehospital use

WB use in the prehospital setting, included in Zhu et al.[28] is one highly touted application for LTOWB as a way to ensure early administration of plasma. Existing studies on prehospital transfusion of plasma for traumatic hemorrhage suggest that plasma may be beneficial in patients with

longer transport times.[20] Prospective studies are needed to determine if the prehospital transfusion of WB has any impact on mortality compared to transfusion of RBCs and plasma or RBCs alone.

Logistics

In 2017, the ARC performed a survey of 350 Level I and II trauma center physicians, trauma surgeons, and transfusion service medical directors[30] to better assess the need for LTOWB. Although 80% of the respondents were using CT for trauma resuscitation, 60% confirmed they would prefer to use WB instead.

Production challenges for cold-stored WB limit the current supply. Blood centers have needed to readjust their collection practices to begin supplying WB on a larger scale. This increase in production has been limited by different collection and manufacturing requirements for WB and the need to identify type O donors with low-titer isohemagglutinins, not taking aspirin, and with low potential risk for causing transfusion-related acute lung injury. These limitations may be further exacerbated by the expansion of WB protocols to include pediatric patients and women of childbearing age, possibly necessitating the use of RhD-negative WB. As demand increases, these logistical issues will need to be addressed to ensure that adequate supply is available broadly.

While not reported in the included studies, high wastage rates due to outdate have been anecdotally observed by some early adopters of civilian WB programs. This has primarily been a result of the self-imposed limitations on shelf life secondary to concerns of platelet function. Some centers have limited wastage by manufacturing an RBC unit from the WB after 14 days. This may not be a widely practical solution, as it requires manufacturing capabilities not possessed by all transfusion services and potentially requiring special licensing to ship the product to where it will be transfused. There are other potential methods to limit wastage, including supplementing WB older than 14 days with platelets and using older WB units for nontrauma patients. A recent in vitro study by Meledeo et al.,[35] testing hemostatic function of WB stored in different solutions (citrate phosphate dextrose, citrate phosphate double dextrose, citrate phosphate dextrose adenine) over 35 days, did not show significant changes beyond 21 days for either thrombin generation, platelet aggregation and adhesion, as well as coagulation functions measured by thromboelastogram.[35] In light of these in vitro data, it is suggested that WB stored up to 21 days may be acceptable for trauma resuscitation and reduce wastage in that context. Other strategies to decrease wastage have yet to be developed, highlighting an area for future research. Rotations of WB inventories between prehospital depots and hospital-based transfusion services should be investigated to reduce wastage while maintaining safety and efficacy.

Other studies, beyond the scope of this review, have examined the role of WB in trauma patients, including the use of WB in military settings, in vitro examinations of the hemostatic capability of WB, logistical guidance for starting a WB program, and guidance on product selection.[3,6–9,30,31,36] Fresh warm WB studies provide a strong foundation to support the rationale for the civilian use of WB. These studies of fresh warm WB can inform civilian trauma center decisions when implementing an LTOWB program such as defining low titer and the decision to leukoreduce, but their results cannot be directly translated to civilian due to different civilian standards for testing and product selection.

CONCLUSION

There is a limited amount of data currently available on the use of LTOWB for the resuscitation of civilian trauma patients. Based on the current data set, there are a few conclusions that can be reached to guide clinical practice and decision making. There appears to be a reasonable case for a noninferior safety profile in the transfusion of limited volumes of cold-stored WB for the resuscitation of civilian trauma patients. This is significant in itself as it provides a solid clinical case for centers looking to launch a WB program. While feasibility and no evidence of increased hemolysis are a solid foundation, there are many more issues that would benefit greatly from continued research. There is a need to demonstrate improved clinical outcomes or at minimum noninferiority to CT in a number of clinical outcomes such as mortality, time to hemostasis, volume transfused, and hospital length of stay. Additionally, not all inventory and logistical issues around the widespread adoption of WB have been resolved. Given the uptick in use and interest in recent years, it is likely that this work is currently under way or will be shortly.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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