Where does cryoprecipitate fit into balanced resuscitation? An evaluation of 2,117 hemorrhaging patients using viscoelastic-based resuscitation

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BACKGROUND: Empiric cryoprecipitate administration has recently failed to show survival benefit in hemorrhaging trauma patients. However, a recent Trauma Quality Improvement Program query suggested a survival benefit in massive transfusions when administering 1 U of cryoprecipitate to every 7 to 8 U of red blood cells (RBCs). We describe transfusion ratios when cryoprecipitate was indicated by viscoelastic testing (VET) and evaluated whole blood (WB)'s impact on this ratio.

METHODS: Adult trauma patients admitted from July 2017 to December 2021 who received emergency-release blood products prehospital or in the emergency department were included. Patients who died within 60 minutes were excluded. Massive transfusion patients received arrival VET, which was repeated serially while on massive transfusion protocol. Cryoprecipitate transfusion was based on VET results. Blood product ratios were calculated for RBC, plasma, platelets, and cryoprecipitate in the first four and 24 hours of resuscitation. Each WB unit was counted as 1 RBC, 1 plasma, and 0.17 U of platelets. Outcomes were evaluated based on blood component ratios. Patients receiving WB were compared with patients who only received blood components.

RESULTS: A total of 2,117 patients were included. Overall, the median age was 37 (25, 55) years, 74% were male, 37% were white, and 67% sustained blunt trauma. Overall survival was 77%. The median 4-hour RBC/plasma/platelet/cryoprecipitate ratio was 9:9.5:1.3:1. Patients who received WB did not require cryoprecipitate until later in their resuscitation when compared with blood components (10:9.5:1.7:1 vs. 7:6:1:1, $p = 0.008$).

CONCLUSION: When using routine VET to guide resuscitation for hemorrhage, cryoprecipitate transfusion occurred later in patients receiving WB incorporated resuscitations compared with the component only strategy. For centers that do not use VET and use algorithmic resuscitation protocols, cryoprecipitate transfusion should be considered after 7 U of RBCs/plasma and after 10 U of a WB incorporated resuscitation. (*J Trauma Acute Care Surg.* 2025;99: 73–78. Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.

KEY WORDS: Trauma; cryoprecipitate; massive transfusion.

Hemorrhage continues to be the leading cause of death in patients presenting to the hospital following trauma.[1–4] Trauma-induced coagulopathy (TIC) can occur after severe injury, which compounds morbidity and mortality.[5,6] Although the incidence of TIC is less prevalent following Trauma Quality Improvement Program Best Practices of balanced resuscitation with whole blood (WB) resuscitation or component therapy in a 1:1:1 ratio (packed red blood cells, plasma, and platelets), TIC may still occur in as many as 15% of severely injured patients with massive hemorrhage.[3,5,7]

Clot strength has been found to largely be due to fibrinogen.[8,9] Although poorly understood, the etiology behind hypofibrinogenemia is likely multifactorial, to include the following: dilution due to unbalanced blood products or crystalloid administration, consumption during clotting, and decreased synthesis from hypothermia.[10] Not unexpectantly, trauma patients who develop hypofibrinogenemia have an associated higher mortality.[7,11–14] Although different resuscitation strategies (balanced component therapy and WB incorporated resuscitations) provide different amounts of fibrinogen, the role that these strategies play into mitigating hypofibrinogenemia is unclear.[15] To this point, although both plasma and WB contain fibrinogen, replacement typically comes in the form of cryoprecipitate or fibrinogen concentrate (FC). To mitigate hypofibrinogenemia and its deleterious effects, investigators have attempted early empiric administration of cryoprecipitate. Previous studies have no demonstrable improvement in morbidity or mortality, which could be secondary to study design, timing of administration, inclusion criteria, and overall study heterogeneity. [6,16] This therefore calls in to question if, how, when, and where fibrinogen should be replaced during the resuscitation of traumatic hemorrhage.

A recent data query of Trauma Quality Improvement Program noted that transfusion of cryoprecipitate for every 7 to 8 red blood cells (RBCs) was associated with a reduction in mortality.[17] However, this study included hospitals across the nation with different massive transfusion protocols (MTPs), limiting granular patient level data on when and how fibrinogen is replaced. Because of the disparity within the

Submitted: December 1, 2024, Revised: February 7, 2025, Accepted: March 18, 2025, Published online: April 17, 2025.

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This work was presented at the 38th EAST Annual Scientific Assembly, January 14–18, 2025, Tucson, Arizona.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

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DOI: 10.1097/TA.0000000000004643

trauma community when it comes to the transfusion of cryoprecipitate, we sought to (1) describe transfusion ratios when cryoprecipitate transfusion was guided by viscoelastic testing (VET) and (2) evaluate how incorporating WB into resuscitations affects this ratio.

PATIENTS AND METHODS

Study Setting and Population

Following institutional review board approval, we evaluated all level 1 trauma patients (16 years and older) being cared for at our hospital between July 2017 and December 2021. Level 1 trauma patients include those with physiologic criteria indicating high-risk or life-threatening injuries (Glasgow Coma Scale score of <10, systolic blood pressure of <90 mm Hg, respiratory rate of <10 breaths per minute, heart rate of >120 beats per minute, or are intubated) or those who have anatomic criteria indicating severe injury (penetrating injury to the head/neck/torso or proximal extremity, mangled/crushed/amputated proximal extremity, open book pelvis/pelvic binder in place, prehospital tourniquet, para/quadriplegia, or prehospital blood transfusion). Only those patients who received emergency-release blood products in the prehospital and or emergency department (ED) settings were included in our analysis. To account for nonsurvivable injuries and the inability to feasibly administer cryoprecipitate (because of logistical constraints) and benefit from cryoprecipitate administration, patients who died within the first 60 minutes of arrival to our facility were excluded. Additionally, this study was conducted and reported in accordance with the STROBE guidelines for observational studies (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/E416).

Blood Transfusion Capability, Practice, and Management

Each of our helicopters carry 2 U of low-titer (<1:200) nonleukoreduced, group O whole blood (LTO-WB), as well as 2 U of RBCs and 2 U of plasma. In addition, our trauma bay refrigerator has 4 U of LTO-WB and 4 U of both RBCs and liquid plasma. Furthermore, if a MTP is activated, this consists of coolers that contain 6 U of RBCs, 6 U of thawed or liquid plasma, and 1 U of apheresis platelets.

The decision to initiate transfusions for both WB and/or component therapy is the same and includes the following: Assessment of Blood Consumption score of 2 or greater, or clinician gestalt for the need of massive transfusion in the presence of hemorrhagic shock. These criteria were adopted as clinical triggers for the use of uncross-matched blood products in both the prehospital (helicopter) and ED setting following their successful use in the research setting at our facility.[18] The decision to use LTO-WB or component therapies was left to the discretion of the prehospital flight team and the trauma attending on arrival to the trauma bay. Both blood product options were available on all helicopters and in the ED trauma bay refrigerator.

Our level 1 trauma center begins resuscitations with WB or balanced component products (that does not include cryoprecipitate/concentrated fibrinogen). Fibrinogen reflective thrombelastography (TEG) values are used to guide cryoprecipitate replacement. While other products such as platelets may also be added outside the standard 1:1:1 ratio, this is uncommon, with cryoprecipitate being the primary blood product that we add to our standard resuscitation protocol. At our center, cryoprecipitate is prepared by our blood bank in an "on-demand" fashion. All level 1 trauma activations have VET obtained on arrival by rapid thrombelastography (r-TEG). This provides an α angle (AA) and maximal amplitude. The AA represents the rate of clot formation, indicative of fibrinogen contribution to clot. The maximal amplitude reflects platelet contribution to cloth strength, but approximately 25% of overall clot strength is based upon fibrinogen in the first 24 hours.[19] α Angle values on r-TEG of 60 degrees or less receive transfusion of cryoprecipitate, in combination with ongoing MTP products.

If a hemorrhage control procedure is required, on arrival to the operating room or the interventional radiology suite, a standard TEG is obtained, and the results are relayed to the anesthesiology team to guide resuscitation. The standard TEG is used by our team, as it provides fibrinogen-specific values of functional fibrinogen. Patients are transfused cryoprecipitate based on TEG maximal amplitude of 55 mm or less and functional fibrinogen of level of 14 mm or less. The TEG is repeated every 30 minutes while on MTP. On arrival to the ICU, an r-TEG specimen is obtained with the same transfusion thresholds for cryoprecipitate as those on ED arrival (AA of 60 degrees or less).

Data Collection

Blood component ratios were calculated for RBC, plasma, platelets, and cryoprecipitate in the first 4 hours of resuscitation. Every unit of apheresis platelets was counted as a traditional "six-pack" of platelets. Therefore, 6 U RBC/6 U of plasma/one apheresis platelets were considered 1:1:1. Each WB unit was counted as 1 RBC, 1 plasma, and 0.17 U of platelets. Each release/dose of cryoprecipitate contains 10 U, arriving as either two bags of 5 U or one pooled bag of 10 U. For ratio purposes, each of these options would be one dose. As such, a ratio of 6 U of RBC/6 U of plasma/one apheresis platelets/one dose of cryoprecipitate would be expressed as 1:1:1:1.

Data including demographics, mechanism of injury, Abbreviated Injury Scale, Injury Severity Scores, prehospital and arrival variables, and outcomes were then reviewed. The median overall ratio in which cryoprecipitate was administered was then calculated for the entire cohort. Because of known differences between component products and WB, most notably coagulation profiles, patients receiving any WB as part of their resuscitation (whole blood with components [WB-COMP]) were compared with patients who only received blood components (COMP only). The median product ratio for when cryoprecipitate was used was then calculated for each cohort and outcomes were evaluated, to include 6-hour, 24-hour, and 30-day survival.

To better evaluate massively hemorrhaging patients, we then excluded all patients who did not receive an entire MTP cooler (6 U of RBCs and 6 U of plasma) in the first 4 hours. Finally, the median ratio for which cryoprecipitate was administered within each resuscitation strategy (WB-COMP vs. COMP only) was calculated.

Statistical Analysis

Continuous data are presented as medians with 25th and 75th interquartile range or as means with SDs; comparisons between groups were performed using the Wilcoxon rank sum (Mann-Whitney *U* test) or Student's *t* test, respectively. Categorical data are reported as proportions and, where appropriate,

tested for significance using χ^2 or Fisher exact tests. All statistical tests were two tailed with $p < 0.05$ set as significant. STATA Statistical software (version 17.0; StataCorp, College Station, TX) was used for univariate analyses.

RESULTS

All Patients

A total of 2,117 patients met the inclusion criteria. The median age was 37 (25, 55) years, and the majority were males (74%) who sustained blunt trauma (67%). The median Injury Severity Score was 25. The vast majority of patients were transported directly from the scene (85%), over half of which arrived by helicopter (57%). The median heart rate in the field was 110 (89, 130) beats per minute, with systolic blood pressure of 107 (86, 132) mm Hg. The median field shock index was 0.98 (0.76, 1.34), and the initial Glasgow Coma Score was 13 (3, 15). Prehospital resuscitation was minimal, with a median of 0 mL of crystalloid (0, 250), 0 U of RBC (0, 0), 0 U of plasma (0, 0), and 0 U of WB (0, 1).

These patients arrived to the trauma center with a median systolic pressure of 104 (85, 126) mm Hg and pulse of 106 (85, 126) beats per minute, resulting in arrival shock index of 0.98 (0.77, 1.29). Arrival Glasgow Coma Scale was 13 (3, 15), and 31% had a positive focused assessment with sonography in trauma (FAST) examination. The median ED RBCs were 1 (0, 2), plasma units were 1 (0, 2), 0 for platelets (0, 0), and 0 for WB (0, 1).

Overall survival was 77%, with median time to death of 27 (8, 88) hours. The median 4-hour RBCs were 3 (1, 7) U, plasma was 3 (1, 7) U, platelets were 0.17 (0, 1.17) U, and cryoprecipitate was 0 (0, 0) doses. For the entire population, the median 4-hour ratio (RBC/plasma/platelet/cryoprecipitate) in which cryoprecipitate was administered was 9:9.5:1.3:1. The median 24-hour RBCs were 2 (1, 6) U, plasma was 2 (1, 7) U, platelets were 0.17 (0, 1) U, and cryoprecipitate was 0 (0, 0) doses. The median 24-hour RBC/plasma/platelet/cryoprecipitate ratio in which cryoprecipitate was administered was 7:7.2:1.1:1.

WB Versus Component-Only Patients

Of the 2,117 patients included, 1,228 received WB as part of their resuscitation, while 889 received only components (Table 1). While there was no difference in age or race, WB-COMP patients were more likely to be male (because of early restrictions during enrollment on females receiving Rhesus positive WB) and to have sustained penetrating injury (34% vs. 27%). The WB-COMP patients were also more likely to have arrived directly from the scene and by helicopter. Furthermore, WB-COMP patients had higher chest, abdomen, and extremity Abbreviated Injury Scale scores, translating into higher overall Injury Severity Score.

The WB-COMP patients were more tachycardic and had lower systolic blood pressures at the scene, with resulting worse prehospital shock index. They were also more likely to have a positive FAST examination in the field. Furthermore, WB-COMP patients received more WB in the prehospital setting, and component patients received more RBCs and plasma.

Continuing their more severe physiological derangement in the field, WB-COMP patients arrived more tachycardic, with lower systolic blood pressures, and subsequent worse shock index (Table 2). Arrival FAST examination was also more likely to be positive in the WB-COMP arm. Arrival hemoglobin and platelet count were lower in the WB-COMP group, and r-TEG values were more likely to be hypocoagulable. Biochemical measures of shock, including lactate and base excess, were both worse in the WB-COMP patients.

TABLE 1. A Comparison of Baseline Data, Demographics, Injury Severity, and Field Physiology and Resuscitation Between Patients Receiving WB as Part of Their Resuscitation and Those Resuscitated With Component Only

	WB-COMP (n = 1,228)	COMP Only (n = 889)	*p*
Age	37 (25, 55)	38 (25, 54)	0.797
Male sex	84%	57%	<0.001
White race	39%	36%	0.130
Blunt mechanism	66%	73%	0.002
Direct from scene	88%	82%	<0.001
Helicopter transport	63%	50%	<0.001
Head AIS	3 (0, 4)	3 (0, 4)	0.396
Chest AIS	3 (2, 4)	3 (0, 3)	<0.001
Abdominal AIS	3 (0, 4)	2 (0, 4)	0.004
Extremity AIS	3 (2, 3)	2 (0, 3)	0.024
ISS	27 (17, 38)	22 (13, 33)	<0.001
Scene HR	112 (90, 132)	107 (85, 126)	<0.001
Scene SBP	101 (81, 128)	114 (91, 136)	<0.001
Scene GCS	12 (3, 15)	13 (3, 15)	0.001
Scene Shock Index	1.03 (0.80, 1.40)	0.92 (0.69, 1.23)	<0.001
Prehospital FAST (+)	53%	37%	<0.001
Field fluids, mL	0 (0, 250)	0 (0, 200)	0.091
Field RBCs, U	0 (0, 0)	0 (0, 1)	<0.001
Field plasma, U	0 (0, 0)	0 (0, 1)	<0.001
Field WB, U	1 (0, 1)	0 (0, 0)	<0.001

AIS, Abbreviate Injury Scale; GCS, Glasgow Coma Scale; HR, heart rate; ISS, Injury Severity Score; SBP, systolic blood pressure.

The WB-COMP patients received more blood products in the ED, as well as during the first 4 and 24 hours after arrival (Table 3). The median units of WB transfused to this group were 2 (1, 3) U. There were no differences in receipt of tranexamic acid among those whose resuscitation included WB (5%) and those whose was solely component therapy (4%) ($p = 0.710$). Transfusing based-off abnormal r-TEG and TEG values, patients who received WB did not receive cryoprecipitate until later into their resuscitation and, therefore, had ratios of 4-hour RBC/plasma/platelet/cryoprecipitate of 10:9.5:1.7:1 versus 7:6:1:1 in the COMP-only group ($p = 0.008$).

Subgroup Analysis of Massive Hemorrhage

After excluding all those who did not receive an entire MTP cooler (6 U of RBCs and 6 U of plasma) in the first 4 hours, this left us with 717 patients (WB-COMP, 510; COMP only, 207). Similarly, the WB-COMP group received cryoprecipitate later in their resuscitation (10:10:1.17:1) compared with the COMP-only group (8:7:1:1) ($p = 0.167$).

DISCUSSION

In this single-institution observational study, cryoprecipitate transfusion occurred after 7:6:1 of RBC/plasma/platelets in the

TABLE 2. A Comparison of Arrival Physiology and Laboratory Values, as well as ED Resuscitation Between Patients Receiving WB as Part of Their Resuscitation and Those Resuscitated With Component Only

	WB-COMP (n = 1,228)	COMP Only (n = 889)	*p*
Arrival HR	109 (86, 128)	102 (84, 124)	0.009
Arrival SBP	100 (82, 122)	110 (92, 132)	<0.001
Arrival GCS	11 (3, 15)	14 (3, 15)	<0.001
Arrival Shock Index	1.05 (0.82, 1.37)	0.90 (0.73, 1.15)	<0.001
Arrival FAST (+)	32%	27%	0.013
Arrival hemoglobin	12.7 (11.1, 14.0)	12.7 (10.4, 13.5)	<0.001
Arrival platelet count	205 (150, 259)	226 (170, 278)	<0.001
Arrival r-TEG ACT	113 (105, 121)	113 (105, 121)	0.201
Arrival r-TEG K-time	1.7 (1.2, 2.2)	1.4 (1.1, 1.9)	<0.001
Arrival r-TEG AA	71 (66, 75)	73 (69, 77)	<0.001
Arrival r-TEG MA	62 (56, 67)	64 (58, 69)	<0.001
Arrival r-TEG LY-30	0.4 (0.0, 1.9)	0.4 (0.0, 1.4)	0.404
Arrival lactate	4.4 (2.9, 7.0)	3.6 (2.2, 5.7)	<0.001
Arrival base excess	−5 (−9, −2)	−4 (−8, −1)	<0.001
ED RBCs, U	0 (0, 3)	1 (0, 2)	0.066
ED plasma, U	1 (0, 3)	1 (0, 2)	0.012
ED platelets, U	0 (0, 0)*	0 (0, 0)	<0.001
ED WB, U	1 (0, 1)	0 (0, 0)	<0.001

*Significant at 90th and 95th with WB (1, 1) versus component only (0, 1).

ACT, activated clotting time; GCS, Glasgow Coma Scale; HR, heart rate; K-time, clot kinetics; LY-30, percent amplitude reduction at 30 minutes after MA and reflects the degree of fibrinolysis; MA, maximal amplitude; SBP, systolic blood pressure.

COMP-only group and after 10:9.5:1.7 of a WB incorporated resuscitation. To our knowledge, this is the first study to describe blood product ratios when cryoprecipitate is clinically indicated using precision-guided VET fibrinogen replacement and additionally compared cryoprecipitate administration among different resuscitation strategies.

Hypofibrinogenemia has been shown to be associated with an increased mortality risk,[8,11,12,20] specifically when fibrinogen levels fall below 100 to 150 mg/dL.[12,14,20,21] The amount of fibrinogen (mg) varies among blood products given during balanced resuscitation strategies. Slightly higher fibrinogen levels are noted in WB (770 mg) compared with component WB-derived plasma (662 mg).[22] Depending on the resuscitation strategy used, WB incorporation versus component only, there can be differences in fibrinogen replacement within standard balanced resuscitations without a concentrated fibrinogen source (cryoprecipitate vs. FC). In our study, our WB-COMP group received approximately 200 mg more fibrinogen earlier than their component only counterparts (median of 2 U of WB administered).

Putting fibrinogen amount aside, despite using a balanced resuscitation with components or WB, the fibrinogen replacement product (cryoprecipitate vs. FC) and timing are ill-defined. Several studies have evaluated these topics and should be discussed. The fibrinogen early in severe trauma study trial showed faster administration using FC compared with cryoprecipitate, with similar fibrinogen levels and transfusion volumes, but a higher mortality noted in the FC group. [23] Conversely, a recent large retrospective study found that FC was associated with improved transfusion volumes and shorter length of stays but similar mortality rates compared with patients given cryoprecipitate.[21] Several notable studies have evaluated the timing of fibrinogen replacement, with the hypothesis that replacing fibrinogen closer to the time of injury is crucial to improved survival. The CRYOSTAT-2 investigators found that early empiric cryoprecipitate was not associated with an improvement in 28-day mortality.[6] Although the median time to administration of cryoprecipitate in the study was over an hour, and arguably not "early," the subanalysis of the US experience had faster administration times comparatively yet echoed the parent study's findings of no improvement in mortality.[16] Additionally, fibrinogen in the initial resuscitation of severe trauma, fibrinogen early in severe trauma study, and early-fibrinogen in trauma trials all found that fibrinogen supplementation increased fibrinogen levels, but none displayed an improvement in mortality.[24–26]

To further complicate the picture, it should be noted that blood component availability at regional blood centers and institutional differences within MTPs confound analysis, especially when pooling data from trauma center-level data sets. Pooling data from multiple centers with different transfusion triggers and makeups of MTPs makes it difficult to examine how and when concentrated fibrinogen should be administered. When taking this into account, it is unclear if the added benefit of clotting factors within cryoprecipitate (factor VIII, factor XIII, von Willebrand factor, fibronectin, and antithrombin) improves clinical outcomes compared with FC once the logistical hurdles (shelf-life, storage requirements, thawing, and administration speed) are factored into the resuscitation.[21,26]

Since our institution uses early WB resuscitation and guides cryoprecipitate administration based on VET, we sought to describe our experience for centers that do not have these luxuries, especially for US military providers downrange with limited blood supply and testing. We found that, in the current common MTP cooler construct (6:6:1), cryoprecipitate was needed, on average, at the start of the second cooler at our center. Cryoprecipitate administration occurred later into resuscitations when augmenting with early WB, ultimately giving centers time

TABLE 3. A Comparison of 4-Hour Transfusion Ratios and Outcomes Between Patients Receiving WB as Part of Their Resuscitation and Those Resuscitated With Component Only

	WB-COMP (n = 1,228)	COMP Only (n = 889)	*p*
4-h RBCs, U	3 (1, 8)	2 (1, 4)	<0.001
4-h Plasma, U	3 (1, 8)	2 (1, 4)	<0.001
4-h Platelets, U	0.34 (0, 1)	0 (0, 0.8)	<0.001
4-h Cryo, dose	0 (0, 0)*	0 (0, 0)	<0.001
4-h Ratio RBC/plasma/platelet/cryo	10:9.5:1.7:1	7:6:1:1	0.008
30-d Survival	76%	80%	0.029
24-h Survival	89%	93%	0.002
6-h Survival	95%	97%	0.014
Time to death, h	21 (7, 77)	34 (12, 117)	0.023

*Significant at 90th and 95th with WB (0, 2) versus component only (0, 0).
**Significant at 90th and 95th with WB (2, 2) versus component only (0, 2).
Cryo, cryoprecipitate.

to thaw cryoprecipitate or transport to centers with cryoprecipitate. Although the exact mechanism of why WB would confer such a benefit, it is consistent with other studies in that it has intangible advantages such as decreased transfusion requirements and an improved mortality benefit.[18,27–31] The majority of our patients in our study received early WB, which would confer an additional 200 mg of fibrinogen early into a resuscitation compared with the component only strategy. There is biologic plausibility for this to be advantageous, but this remains only speculation. Furthermore, it is theorized that WB and early plasma-based resuscitations improve the endothelium; therefore, it is possible that fibrinogen consumption is mitigated by replacing blood lost with a similar product.[32,33] More research is required to better define the physiological effect of different resuscitation strategies, as well as better define which populations may benefit from these strategies with the augmentation of fibrinogen supplementation. [16]

Limitations

The consistency of our region's blood components and, subsequently, what is used in our prehospital and hospital resuscitations, coupled with the use of VET to provide precision guided cryoprecipitate administration, are strengths in this study. However, this study has several limitations. First, this is a single institution's description of severely injured patients, with the majority of patients sustaining blunt injury, using VET-guided cryoprecipitate administration. Furthermore, our system has a robust prehospital transfusion capability, so our findings may not be generalizable. Additionally, we excluded patients who died within 60 minutes because of nonsurvivable injuries and the logistical constraint to quickly identify and administer cryoprecipitate to patients who may need it. Whether this population would benefit from cryoprecipitate remains unknown, and further research is required. Lastly, although cryoprecipitate administration is protocolized, because of the different VET systems used throughout the hospital, we are unable to capture granular data such as timing and which variable(s) triggered cryoprecipitate administration.

CONCLUSION

When using routine VET to guide resuscitation for hemorrhage, cryoprecipitate transfusion occurred later in patients receiving WB incorporated resuscitations compared with the component only strategy. For centers that do not use VET and use algorithmic resuscitation protocols, cryoprecipitate transfusion should be considered after 7 U of RBCs/plasma and after 10 U of a WB incorporated resuscitation.

AUTHORSHIP

J.-M.V.G., T.W.C., and B.A.C. were responsible for data collection. J.-M.V.G., T.W.C., J.M.G., and B.A.C. were responsible for study design. J.-M.V.G., T.W.C., J.M.G., and B.A.C. were responsible for data analysis. J.-M.V.G., T.W.C., J.M.G., and B.A.C. were responsible for literature search, data interpretation, manuscript writing, and revisions.

DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E417).

DISCLAIMER

The views expressed in this manuscript are those of the author and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of Defense, nor the U.S. Government.

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