The impact of hypothermia on outcomes in massively transfused patients

Erica Louise Walsh Lester, MD, MSc, Erin E. Fox, PhD, John B. Holcomb, MD, Karen J. Brasel, MD, MPH, Eileen M. Bulger, MD, Mitchell J. Cohen, MD, Bryan A. Cotton, MD, MPH, Timothy C. Fabian, MD, Jeffery D. Kerby, MD, PhD, Terrence O'Keefe, MB, ChB, MSPH, Sandro B. Rizoli, MD, PhD, Thomas M. Scalea, MD, Martin A. Schreiber, MD, Kenji Inaba, MD, *and* **On behalf of the PROPPR study group***, Los Angeles, California*

AAST Continuing Medical Education Article

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providership of the American College of Surgeons and the American Association for the Surgery of Trauma. The American College Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™

The American College of Surgeons designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Of the *AMA PRA Category 1 Credit*™ listed above, a maximum of 1 credit meets the requirements for self-assessment.

Credits can only be claimed online

AMERICAN COLLEGE OF SURGEONS

Inspiring Quality: Highest Standards, Better Outcomes

100+*years*

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery*, participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "e-Learning/MOC" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, the American College of Surgeons, as the accredited provider of this journal activity, must ensure that anyone in a position to control the content of *J Trauma Acute Care Surg* articles selected for CME credit has disclosed all relevant financial relationships with any commercial interest. Disclosure forms are completed by the editorial staff, associate editors, reviewers, and all authors. The ACCME defines a `commercial interest' as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients." "Relevant" financial relationships are those (in any amount) that may create a conflict of interest and occur within the 12'months preceding and during the time that the individual is engaged in writing the article. All reported conflicts are thoroughly managed in order to ensure any potential bias within the content is eliminated. However, if you'perceive a bias within the article, please report the circumstances on the evaluation form.

Please note we have advised the authors that it is their responsibility to disclose within the article if they are describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

Disclosures of Significant Relationships with Relevant Commercial Companies/Organizations by the Editorial Staff

Ernest E. Moore, Editor: PI, research support and shared U.S. patents Haemonetics; PI, research support, Instrumentation Laboratory, Inc.; Co-founder, Thrombo Therapeutics. Associate Editors David Hoyt, Ronald V. Maier and Steven Shackford have nothing to disclose. Editorial staff and Angela Sauaia have nothing to disclose.

Author Disclosures

John B. Holcomb, MD – Decisio Health/Prytime Medical/Terumo BCT, received money as consultant/employment; Martin A. Schreiber, MD – Arsenal Medical/Velico Medical/Haemonetics, received grants as principal investigator.

Reviewer Disclosures

The reviewers have nothing to disclose.

Cost

For AAST members and *Journal of Trauma and Acute Care Surgery* subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $25.

System Requirements

The system requirements are as follows: Adobe® Reader 7.0 or above installed; Internet Explorer® 7 and above; Firefox® 3.0 and above, Chrome® 8.0 and above, or Safari™ 4.0 and above.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

BACKGROUND: Hypothermia is associated with poor outcomes after injury. The relationship between hypothermia during contemporary large volume resuscitation and blood product consumption is unknown. We evaluated this association, and the predictive value of hypothermia on mortality.

METHODS: Patients predicted to receive massive transfusion at 12 level 1 trauma centers were randomized in the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial and were grouped into those who were hypothermic (<36°C) or normothermic (36–38.5°C) within the first 6 hours of emergency department arrival. The impact of hypothermia or normothermia on the volume of blood product required during the first 24 hours was determined via negative binomial regression, adjusting for treatment arm, injury severity score, mechanism, demographics, pre–emergency department fluid volume, blood administered before becoming hypothermic, pulse and systolic blood pressure on arrival, and the time exposed to hypothermic or normothermic temperatures.

RESULTS: Of 680 patients, 590 had a temperature measured during the first 6 hours in hospital, and 399 experienced hypothermia. The mean number of red blood cell (RBC) units given to all patients in the first 24 hours of admission was 8.8 (95% confidence interval [CI], 7.9–9.6). In multivariable analysis, every 1°C decrease in temperature below 36.0°C was associated with a 10% increase (incidence rate ratio, 0.90; 95% CI, 0.89–0.92; $p < 0.00$) in consumption of RBCs during the first 24 hours of admission. There was no association between RBC administration and a temperature above 36°C. Hypothermia on arrival was an independent predictor of mortality, with an adjusted odds ratio of 2.7 (95% CI, 1.7–4.5; $p < 0.00$) for 24-hour mortality and 1.8 (95% CI, 1.3–2.4; $p < 0.00$) for 30-day mortality.

CONCLUSION: Hypothermia is associated with increase in blood product consumption and mortality. These findings support the maintenance of normothermia in trauma patients and suggest that further investigation on the impact of cooling or rewarming during massive transfusion is warranted. (*J Trauma Acute Care Surg.* 2019;86: 458–463. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic, level III.

KEY WORDS: Hypothermia; normothermia; massive transfusion; resuscitation; hemorrhage.

The mechanism underlying the coagulopathy associated with trauma is an area of ongoing investigation. It is described by varying and combined degrees of dysfibrinogenemia, hyperfibrinolysis, endothelial dysfunction, and impaired platelet activity, dependent upon the magnitude of injury and severity of shock.[1–3] The impact of hypothermia on this process is a clinically relevant consideration, as the presence of decreased body temperature has been shown to impair clotting factor activity and platelet function.[1,4]

Trauma-induced hypothermia has an incidence of approximately 43% to 65% and is associated with progression of coagulopathy and poor outcomes in trauma patients.[5–16] Jurkovich et al.[9] demonstrated that mortality increases as temperature decreases across groups with similar injury severity scores (ISSs) and fluid requirements. In this seminal work, 32°C was identified as the critical temperature, below which mortality was 100%.[9] Subsequently Gentilello et al.[17] determined that rapid rewarming decreases mortality and reduces fluid requirements. Hypothermia after cavitary exploration for traumatic injury has also been found to be an independent predictor of mortality, with a stepwise decrease in morality with increasing postoperative temperature.[6]

While it has been suggested that hypothermia contributes to operative blood loss, its impact on blood product requirement in trauma patients undergoing contemporary large volume resuscitation has, to the best of our knowledge, not been determined.[14,18,19] The objective of this study was to ascertain the independent impact of hypothermia on blood product requirements during initial resuscitation. Furthermore, we sought to examine the association of hypothermia with mortality in critically injured trauma patients undergoing contemporary large volume balanced resuscitation.

METHODS

This secondary analysis was conducted using the data set that was collected during the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial.[20] This was an Exception From Informed Consent (EFIC) trial and was approved by all institutional review boards at each of the 12 study sites as well as the Human Research Protection Office of the US Army. The study design and results have been described in detail previously.[21] Briefly, severely injured patients, 15 years or older, expected to require a massive transfusion and admitted to a level I trauma center were randomized to a 1:1:1 or 1:1:2 ratio of plasma to platelets to red blood cells (RBCs). Clinical parameters including vital signs, diagnostic tests, and resuscitation measures, as well as the time of each intervention or measurement were captured in detail.

Submitted: August 2, 2018, Accepted: October 2, 2018, Published online: November 15, 2018.

From the Division of General Surgery (E.L.W.L.), Department of Surgery, University of Alberta, Edmonton, Alberta, Canada; Center for Translational Injury Research (E.E.F., J.H.), Division of Acute Care Surgery, Department of Surgery, Medical School, University of Texas Health Science Center, Houston, Texas; Division of Trauma (K.B.), Critical Care and Acute Care Surgery, School of Medicine, Oregon Health and Science University, Portland, Oregon; Division of Trauma and Critical Care (E.M.B.), Department of Surgery, School of Medicine, University of Washington, Seattle, Washington; Department of Surgery (M.C.), University of Colorado, Denver, Colorado; Center for Translational Injury Research (B.A.C.), Division of Acute Care Surgery, Department of Surgery, Medical School, University of Texas Health Science Center, Houston, Texas; Division of Trauma and Surgical Critical Care (T.C.T.C.F.), Department of Surgery, College of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; Division of Trauma (J.D.K.), Burns and Surgical Critical Care, Department of Surgery, School of Medicine, University of Alabama, Birmingham, Alabama; Division of Trauma (T.O.), Critical Care and Emergency Surgery, Department of Surgery, University of Arizona, Tucson, Arizona; Trauma and Acute Care Service (S.B.R.), St. Michael's Hospital, Toronto, Ontario, Canada; R Adams Crowley Shock Trauma Center (T.S.), University of Maryland, Baltimore, Maryland; Division of Trauma (M.A.S.), Critical Care and Acute Care Surgery, Department of Surgery, Oregon Health and Science University, Portland, Oregon; and Division of Trauma and Critical Care (K.I.), LAC+USC Medical Center, University of Southern California, Los Angeles, California.

Address for reprints: Kenji Inaba, MD, Division of Trauma and Critical Care, LAC+USC Medical Center, University of Southern California, 2051 Marengo St, IPT, C5L100, Los Angeles, CA 90033; email: kinaba@surgery.usc.edu.

DOI: 10.1097/TA.0000000000002144

Hypothermia was defined as a temperature less than 36.0°C, as per the Advanced Trauma Life Support guidelines and previous studies, and normothermia was considered to be greater than or equal to 36.0°C and less than or equal to 38.5°C.[22–24] Patients with a temperature greater than 38.5°C were excluded. Patients were grouped into those that experienced at least one measurement of hypothermia within the first 6 hours from arrival in the emergency department (ED) and those that maintained normothermia throughout the 6-hour period. The group characteristics were compared using the Wilcoxon rank sum or McNemars test where appropriate. A Kaplan-Meier curve for those remaining normothermic over the 6-hour period was constructed.

Data were organized chronologically, and blood products administered during a period of hypothermia or normothermia were iteratively tabulated for 24 hours from admission, defined as moment of arrival in the ED. Two models were created to explain administration of RBC units: hypothermic and normothermic. The independent variable of interest was temperature. The cumulative time a patient spent hypothermic or normothermic was used as the exposure variable in the respective models. The models were adjusted with the following covariates: treatment arm as defined by the study protocol; hospital site; initial systolic blood pressure; heart rate and serum lactate, defined as the first measurement recorded upon admission; fluids given prearrival in the ED, represented by a binary variable; and need for cavitary exploration (thoracotomy or laparotomy). The admission report of weight in kilograms, ISS, age in years, sex, and mechanism of injury (blunt vs. penetrating) were also used. For the hypothermic model, the number of RBCs administered before the first measurement of hypothermia was also included.

A backwards stepwise negative binomial regression (removal criteria, $p > 0.05$) approach was taken to model the RBCs administered while hypothermic or normothermic. Frequency weighting was applied. The fit was tested by plotting the dependant variables against both Poisson and negative binomial distributions, comparing the predicted values from each regression to the recorded values, and performing goodness of fit tests.

A backwards stepwise logistic regression (removal criteria, $p > 0.05$) was performed to determine the adjusted odds ratios (ORs) of 24-hour and 30-day mortality for patients presenting with hypothermia on initial measurement. The ORs were adjusted for the following covariates: number of RBC units used in 24 hours, need for emergent OR (within 90 minutes of arrival), ISS, mechanism of injury (blunt versus penetrating), weight, age, sex, and initial pulse and systolic blood pressure on arrival was assessed and modeled accordingly. The area under the receiver operating characteristic curve was calculated.

The analyses were conducted using STATA (version 13; College Station, TX).

RESULTS

Of the 680 enrolled patients, 590 (86.8%) had a temperature measured during the first 6 hours in hospital. Of these patients, 4 (6.8%) were hyperthermic and were excluded (Fig. 1). After exclusion, the mean initial temperature was 35.8°C (95% confidence interval [CI], 35.7–35.9). During the first 6 hours,

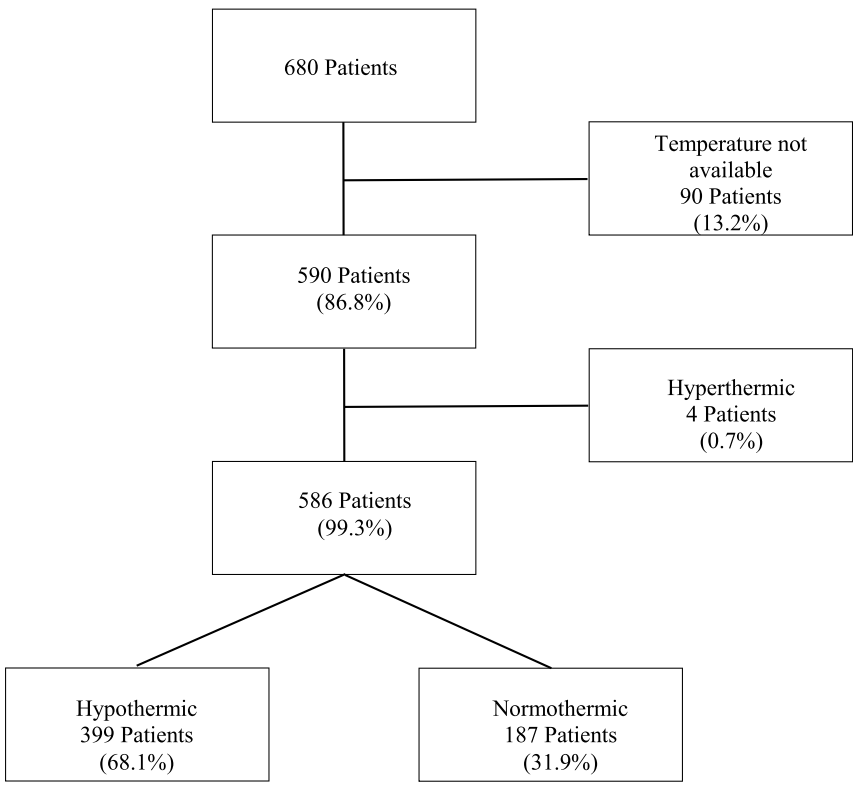

Figure 1. Cohort distribution by temperature in the first 6 hours in hospital.

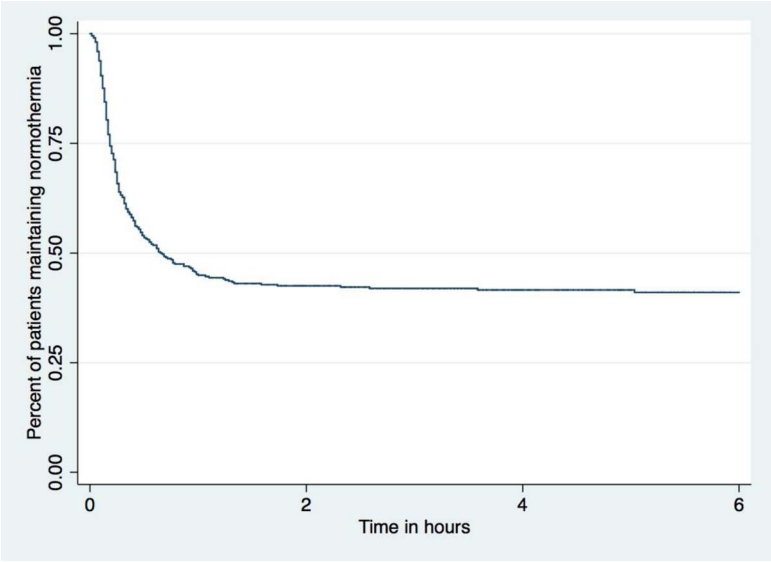

Figure 2. Kaplan-Meier analysis for those remaining normothermic (temperature >36 and <38.5) in initial 6 hours of admission.

399 patients (67.6%) experienced hypothermia. Of those patients, 195 (49%), 94 (24%), and 39(10%) experienced temperatures equal to or less than 35°C, 34°C, and 33°C, respectively. The percent of patients maintaining normothermia during the first 6 hours is demonstrated in Figure 2. The mean (SD) time to temperature measurement was 50.8 (88.2) minutes, and the median (IQR) time was 0 (0–55) minutes. The characteristics of patients that experienced hypothermia, compared with those that remained normothermic, are reported in Table 1. The mean (SD) number of RBC units transfused in 24 hours was 8.8 (10.5) overall, with 9.9 (11.4) and 6.3 (7.9) being transfused in the hypothermic and normothermic groups, respectively.

In multivariable analysis assessing blood transfused while hypothermic, temperature, lactate, cavitary exploration, treatment arm, hospital site, ISS, heart rate and systolic blood pressure on arrival to the ED, pre-ED fluid administration, mechanism, weight, sex, and age were found to be statistically significant predictors of RBCs required in the first 24 hours of admission. An increasing temperature was associated with a reduced number of RBC units required, with an incidence rate ratio of 0.90 (0.89–0.92). Blood products administered before becoming hypothermic was not a statistically significant covariate. In the normothermic model, temperature had no statistically significant effect on blood product administration. Treatment arm, ISS, heart rate and systolic blood pressure on arrival to the ED, pre-ED fluid administration, mechanism, and weight were significant variables in the model.

In the analysis of mortality, the presence of hypothermia upon arrival at a trauma center resulted in adjusted ORs of 2.7 (95% CI, 1.7–4.5; $p < 0.00$) and 1.8 (95% CI, 1.3–2.4; $p < 0.00$) for 24-hour and 30-day mortality, respectively. The number of units of RBCs received in the first day was also a predictor of 30-day mortality (OR, 1.0; 95% CI, 1.0–1.1; $p < 0.01$). The areas under the receiver operating characteristic curve for the 24-hour and 30-day mortality models were 0.785 and 0.830, respectively.

TABLE 1. Cohort Characteristics and Comparisons of Patients Who Had Measured Hypothermia Versus Those That Did Not Over First 6 Hours of Admission

	Experienced Hypothermia (n = 399)	Normothermic for Initial 6 h (n = 187)	*p*
Age, mean (SD), y	39.4 (18.0)	37.1 (15.6)	0.34
Sex, male, n (%)	314 (79)	158 (84)	0.00
Systolic blood pressure, mean (SD)	105.1 (32.2)	102.7 (28.5)	0.49
Heart rate, mean (SD)	112.6 (28.9)	112.6 (25.5)	0.81
ISS, mean (SD)	30.0 (14.9)	25.6 (14.4)	0.00
Weight, mean (SD), kg	83.1 (20.9)	86.9 (22.6)	0.01
Treatment arm 1:1:1	198 (49.9%)	91 (48.1%)	0.00
Fluids given pre-ED	321 (81.9%)	125 (66.7%)	0.00
Blunt, n (%)	220 (55.4)	84 (44.9)	0.00
First temperature measurement, mean (SD), °C	35.4 (1.2)	36.7 (0.5)	0.00
Time to first hypothermic measurement, mean (SD), min	63.6 (88.6)	—	—
Time to first temperature measurement, mean (SD), min	36.6 (70.8)	81.0 (112.2)	0.00
RBCs in 24 h, mean (SD), unit	9.9 (11.4)	6.3 (7.9)	0.00

DISCUSSION

In this large cohort of critically ill, massively transfused patients admitted to a level 1 trauma center, we described the independent association between hypothermic temperatures and both mortality and blood product requirement. Confirming previous work, despite the aggressive contemporary resuscitation efforts, hypothermia at ED presentation remained an independent predictor of mortality, with adjusted ORs of 2.7 (95% CI, 1.7–4.5; $p < 0.00$) and 1.8 (95% CI, 1.3–2.4; $p < 0.00$) for 24-hour and 30-day mortality, respectively. Furthermore, analysis of this comprehensive transfusion data set demonstrated that an increase in temperature by 1°C, when hypothermic, is associated with a 10% reduction in the RBC transfusion requirement. This relationship is independent of other factors thought to influence transfusion requirements. When normothermia is maintained during the first 6 hours in hospital, temperature increase is not a predictor of blood cell transfusion requirement. The implication is that, using the mean number of RBCs transfused in this study, a patient with a temperature of 34°C will require one more unit of RBCs when compared with a patient with a temperature of 36°C, after adjustment for injury severity and other factors influencing transfusion requirements. This represents a significant increase in resource use, cost, and patient risk, supporting the avoidance of hypothermia in trauma patients.

The size of our study cohort was suitable for determining the impact of hypothermia on both blood product use and mortality. The study exclusion criteria, which included the exclusion of patients requiring CPR for greater than 5 minutes and those undergoing an emergency thoracotomy, increase the homogeneity of the cohort. The rate of hypothermia and other patient demographics in our study was similar to that published in the literature.[1,15] The ISS was higher in the hypothermic group, which concurs with the findings of Beilman et al.[15] The hypothermic group weighed less than the normothermic group. This may suggest a protective effect of body mass, with regards to body temperature. Similarly, there were more females in the hypothermic group, which may be reflective of body composition and a subsequent protective effect. Importantly, the hypothermic patients were more likely to receive fluids before arrival in the ED. Whether this represents a more severe injury and tenuous hemodynamic state or a causal mechanism for hypothermia itself cannot be determined from this study. Adjusting for the use of prearrival fluids in the explanatory models parses its potential effect on transfusion requirements from that of temperature itself.

There was a statistically significant difference between the distribution of treatment arms between the two temperature groups. However, the difference may not be clinically relevant, as it was less than 2%. The presence of more 1:1:1 patients, who by definition received more blood product then the 1:1:2 patients, in the hypothermic arm may reflect the use of blood products or may simply be stochastic. The reported incidence rate ratios were adjusted for patient treatment arm.

While the granular and frequent data collection of the randomized controlled trial protocol creates an advantageous cohort in which to study the impact of hypothermia, several limitations of this work merit consideration. First, the anatomical location and method of temperature measurement were not standardized or documented. Given the variability in the devices used and the heterogeneity of temperatures taken at different locations, along with the pooling of data from 12 sites, the temperature measurements may have introduced endogeneity into the models. Moreover, warming protocols differ between sites and may have introduced bias as well.

The design of the trial was such that the massive transfusion protocol ceased once the most responsible physician deemed hemostasis had been achieved. However, further blood products could be administered based on institutional guidelines, local laboratory results, and clinical judgment.[25] Therefore, our use of RBC units as a surrogate for overall product use, based on the study ratios, may introduce error because of additional blood product use after protocol termination.

Of the 680 patients enrolled in the PROPPR study, 90 patients, or 13.2%, did not have temperature measured within 6 hours of ED arrival. The mean (SD) time to temperature measurement was 50.8 (88.2) minutes; however, the median (IQR) time was 0 (0–55) minutes. This demonstrates that, while most patients had a temperature measured, there was variability in the time to temperature measurement. As well, hypothermic patients had their temperature measured earlier: this may represent an increased propensity to check temperature in sicker, more severely injured patients. Given the evidence that hypothermia is associated with increased blood product use and mortality, this study illustrates possible areas for improvement in baseline vital sign assessment.

Caution should be applied to extracting causation from association within the context of this study. While initial temperature measurements occurred before few, or any, blood products were administered, many of the subsequent temperatures occurring during the initial 6 hours occurred after transfusions had occurred and thus may be influenced by the product temperature itself. Unfortunately, too few patients had temperatures recorded by EMS or before initiation of massive transfusion to power a model isolating the influence of body temperature during the time between injury and ED arrival or commencement of massive transfusion. Collecting this information is difficult, as the decision to commence a transfusion protocol is made based on parameters other than temperature, making temperature measurement lower priority than other metrics. Therefore, while temperature and transfusion requirements are associated in a well-adjusted model, supporting the paradigm that normothermia is superior, further work is needed to elicit the effect of actively warming hypothermic trauma patients. Furthermore, given the success of controlled hypothermia in organ preservation and cardiac arrest models, the interface between trauma-induced, uncontrolled hypothermia and induced hypothermia merits further investigation.[26] Studying the role of hypothermia in trauma on the full complex state of injury, rather than isolated components such as energy stores, acidosis, and coagulopathy, will aid in elucidating the optimal approach to resuscitation of the severely injured patient.[26,27]

CONCLUSION

Hypothermia is associated with an increase in blood product consumption and is an independent predictor of mortality.

Measuring the impact of restoring normothermia in severely injured patients warrants further investigation.

AUTHORSHIP

E.L.W.L. collaborated on the study design, performed the statistical and data analysis, and drafted and extensively revised the final article. E.E.F collaborated on the study design, reviewed the data analysis, aided with the navigation of the retrospective data, and contributed to the editing of the article. J.B.H., K.J.B., E.M.B., M.J.C., B.A.C., T.C.F., J.D.K., T.O., S.R., T.M.S., and M.A.S. extensively revised the final article. K.I. provided content expertise, oversaw and collaborated on the study design, and assisted extensively with the article revision. All authors have approved the final article.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Soreide K. Clinical and translational aspects of hypothermia in major trauma patients: from pathophysiology to prevention, prognosis and potential preservation. *Injury*. 2014;45(4):647–654.
2. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. *J Trauma*. 2008;65(4): 951–960.
3. Watts DD, Trask A, Soeken K, Perdue P, Dols S, Kaufmann C. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *J Trauma*. 1998;44(5): 846–854.
4. Ferrara A, MacArthur JD, Wright HK, Modlin IM, McMillen MA. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg*. 1990;160(5):515–518.
5. Trentzsch H, Huber-Wagner S, Hildebrand F, Kanz KG, Faist E, Piltz S, Lefering R, TraumaRegistry DGU. Hypothermia for prediction of death in severely injured blunt trauma patients. *Shock*. 2012;37(2):131–139.
6. Inaba K, Teixeira PG, Rhee P, Brown C, Salim A, DuBose J, Chan LS, Demetriades D. Mortality impact of hypothermia after cavitary explorations in trauma. *World J Surg*. 2009;33(4):864–869.
7. Engels PT, Rezende-Neto JB, Al Mahroos M, Scarpelini S, Rizoli SB, Tien HC. The natural history of trauma-related coagulopathy: implications for treatment. *J Trauma*. 2011;71(5 Suppl 1):S448–S455.
8. Kashuk JL, Moore EE, Millikan JS, Moore JB. Major abdominal vascular trauma—a unified approach. *J Trauma*. 1982;22(8):672–679.
9. Jurkovich GJ, Greiser WB, Luterman A, Curreri PW. Hypothermia in trauma victims: an ominous predictor of survival. *J Trauma*. 1987;27(9):1019–1024.
10. Beale E, Zhu J, Chan L, Shulman I, Harwood R, Demetriades D. Blood transfusion in critically injured patients: a prospective study. *Injury*. 2006;37(5): 455–465.
11. Martin RS, Kilgo PD, Miller PR, Hoth JJ, Meredith JW, Chang MC. Injury-associated hypothermia: an analysis of the 2004 National Trauma Data Bank. *Shock*. 2005;24(2):114–118.
12. Gregory JS, Flancbaum L, Townsend MC, Cloutier CT, Jonasson O. Incidence and timing of hypothermia in trauma patients undergoing operations. *J Trauma*. 1991;31(6):795–800.
13. Kongsayreepong S, Chaibundit C, Chadpaibool J, Komoltri C, Suraseranivongse S, Suwannanonda P, Raksamanee EO, Noocharoen P, Silapadech A, Parakkamodom S, et al. Predictor of core hypothermia and the surgical intensive care unit. *Anesth Analg*. 2003;96(3):826–833; table of contents.
14. Garrison JR, Richardson JD, Hilakos AS, Spain DA, Wilson MA, Miller FB, Fulton RL. Predicting the need to pack early for severe intra-abdominal hemorrhage. *J Trauma*. 1996;40(6):923–927; discussion 927-9.
15. Beilman GJ, Blondet JJ, Nelson TR, Nathens AB, Moore FA, Rhee P, Puyana JC, Moore EE, Cohn SM. Early hypothermia in severely injured trauma patients is a significant risk factor for multiple organ dysfunction syndrome but not mortality. *Ann Surg*. 2009;249(5):845–850.
16. Bennett BL, Holcomb JB. Battlefield trauma-induced hypothermia: transitioning the preferred method of casualty rewarming. *Wilderness Environ Med*. 2017;28(2S):S82–S89.
17. Gentilello LM, Jurkovich GJ, Stark MS, Hassantash SA, O'Keefe GE. Is hypothermia in the victim of major trauma protective or harmful? A randomized, prospective study. *Ann Surg*. 1997;226(4):439–449.
18. Bernabei AF, Levison MA, Bender JS. The effects of hypothermia and injury severity on blood loss during trauma laparotomy. *J Trauma*. 1992;33(6):835–839.
19. Arthurs Z, Cuadrado D, Beekley A, Grathwohl K, Perkins J, Rush R, Sebesta J. The impact of hypothermia on trauma care at the 31st combat support hospital. *Am J Surg*. 2006;191(5):610–614.
20. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471–482.
21. Baraniuk S, Tilley BC, del Junco DJ, Fox EE, van Belle G, Wade CE, Podbielski JM, Beeler AM, Hess JR, Bulger EM, et al. Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial: design, rationale and implementation. *Injury*. 2014;45(9):1287–1295.
22. Wade CE, Salinas J, Eastridge BJ, McManus JG, Holcomb JB. Admission hypo- or hyperthermia and survival after trauma in civilian and military environments. *Int J Emerg Med*. 2011;4(1):35.
23. Klauke N, Graff I, Fleischer A, Boehm O, Guttenthaler V, Baumgarten G, Meybohm P, Wittmann M. Effects of prehospital hypothermia on transfusion requirements and outcomes: a retrospective observatory trial. *BMJ Open*. 2016;6(3):e009913.
24. ATLS Subcommittee, American College of Surgeonsâ Committee on Trauma; International ATLS working group. Advanced trauma life support (ATLS(R)): the ninth edition. *J Trauma Acute Care Surg*. 2013;74(5):1363–1366.
25. UTHeatlh. Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Protocol. UTHeatlh; Houston, TX: 2012.
26. Alam HB, Pusateri AE, Kindzelski A, Egan D, Hoots K, Andrews MT, Rhee P, Tisherman S, Mann K, Vostal J, et al. Hypothermia and hemostasis in severe trauma: a new crossroads workshop report. *J Trauma Acute Care Surg*. 2012;73(4):809–817.
27. Tisherman SA, Alam HB, Rhee PM, Scalea TM, Drabek T, Forsythe RM, Kochanek McCm PM. Development of the Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma (EPR-CAT) Clinical Trial. *J Trauma Acute Care Surg*. 2017;83(5):803–809.

