Pre-hospital hypothermia is associated with transfusion risk after traumatic injury

Naheed K. Jivraj [*]; Lilia Kaustov[*]; Kennedy Ning Hao[*]; Rachel Strauss[†]; Jeannie Callum[†‡]; Homer Tien[§¶]; Asim Q. Alam[*‖**]

CLINICIAN'S CAPSULE

What is known about the topic?
In traumatically injured patients, excessive blood loss necessitating the transfusion of red blood cell units is common.

What did this study ask?
What is the association between pre-hospital hypothermia (<36°C) and transfusion risk within 24 hours after hospital arrival for traumatic injury?

What did this study find?
This cohort study highlighted that hypothermia was associated with a 68% increased odds of a red blood cell transfusion.

Why does this study matter to clinicians?
Hypothermia may be an early indication of transfusion risk and may highlight the need for early interventions to mitigate a temperature decrease.

ABSTRACT

Objectives: In traumatically injured patients, excessive blood loss necessitating the transfusion of red blood cell (RBC) units is common. Indicators of early RBC transfusion in the pre-hospital setting are needed. This study aims to evaluate the association between hypothermia (<36°C) and transfusion risk within the first 24 hours after arrival to hospital for a traumatic injury.

Methods: We completed an audit of all traumatically injured patients who had emergent surgery at a single tertiary care center between 2010 and 2014. Using multivariable logistic regression analysis, we evaluated the association between pre-hospital hypothermia and transfusion of ≥1 unit of RBC within 24 hours of arrival to the trauma bay.

Results: Of the 703 patients included to evaluate the association between hypothermia and RBC transfusion, 203 patients (29%) required a transfusion within 24 hours. After controlling for important confounding variables, including age, sex, coagulopathy (platelets and INR), hemoglobin, and vital signs (blood pressure and heart rate), hypothermia was associated with a 68% increased odds of transfusion in multivariable analysis (OR: 1.68; 95% CI: 1.11-2.56).

Conclusions: Hypothermia is strongly associated with RBC transfusion in a cohort of trauma patients requiring emergent surgery. This finding highlights the importance of early measures of temperature after traumatic injury and the need for intervention trials to determine if strategies to mitigate the risk of hypothermia will decrease the risk of transfusion and other morbidities.

RÉSUMÉ

Objectif: Il n'est pas rare, chez les blessés, que les pertes abondantes de sang nécessitent des transfusions de culots de globules rouges (GR). Toutefois, il faudrait établir des indicateurs de transfusion précoce de globules rouges en phase préhospitalière. L'étude visait à évaluer l'association de l'hypothermie (<36°C) et du risque de réaction transfusionnelle dans les 24 heures suivant l'arrivée à l'hôpital pour un trauma.

Méthode: Il s'agit d'un examen des dossiers de tous les blessés qui ont dû être opérés d'extrême urgence, dans un seul centre de soins tertiaires, entre 2010 et 2014. L'association de l'hypothermie préhospitalière et de la transfusion de ≥ 1 culot de GR, dans les 24 heures suivant l'arrivée dans l'aire de traumatologie, a été évaluée à l'aide d'une analyse de régression logistique plurifactorielle.

Résultats: Sur 703 patients chez qui a été évaluée l'association de l'hypothermie et des transfusions de GR, 203 (29%) ont eu besoin d'une transfusion dans les 24 heures suivant leur

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arrivée. Après la neutralisation de facteurs parasites importants, dont l'âge, le sexe, les troubles de la coagulation (plaquettes et RIN), l'hémoglobine et les signes vitaux (pression artérielle et fréquence cardiaque), l'hypothermie a été associée à une augmentation de 68% du risque de réaction transfusionnelle, selon l'analyse plurifactorielle (risque relatif approché : 1,68; IC à 95% : 1,11-2,56).

Conclusion: L'hypothermie s'est révélée fortement associée au risque de réaction transfusionnelle de GR dans une cohorte de blessés qui ont dû être opérés d'extrême urgence. La constatation souligne l'importance des mesures précoces de la température après un trauma ainsi que la nécessité de mener des essais d'intervention pour déterminer si l'atténuation du risque d'hypothermie par différents moyens permettrait de diminuer le risque de réaction transfusionnelle et d'autres troubles.

Keywords: Trauma, prehospital/EMS, resuscitation

INTRODUCTION

In both Canada and the United States, trauma remains the leading cause of death in individuals aged 1 to 34 years and is among the top five leading causes of death nationwide for patients of all ages.[1] Uncontrolled hemorrhage represents the leading cause of preventable death among these patients.[1]

Traditionally, the management of bleeding patients in the pre-hospital setting has been aggressive resuscitation with isotonic fluid to maintain tissue perfusion. However, this therapy may contribute to worsening coagulopathy, cellular injury, and bleeding.[2] As a result, "damage control resuscitation" has become the standard of care in the management of trauma patients. Damage control resuscitation allows physicians to integrate hemostatic resuscitation, permissive hypotension, and damage control surgery to prevent coagulopathy until definitive treatment is made available.[3] Implementing components of damage control resuscitation in the pre-hospital setting has shown to have clinical benefit.[4] Nevertheless, pre-hospital providers are limited in the care they can provide. The definitive management of massive hemorrhage in trauma patients is surgical control of the bleeding site,[5] yet most deaths from bleeding occur on route to the hospital or soon after admission.[6,7] Therefore, finding solutions to modify the risk of hemorrhagic death, particularly among patients requiring surgical intervention, is critical.

One such solution is the prevention of accidental hypothermia, defined as an unintentional reduction in patient temperature to <36°C that is associated with a higher risk of morbidity and mortality among trauma patients.[8,9] Given that hypothermia impairs coagulation enzyme activity and decreases platelet aggregation and the availability of fibrinogen, it can further increase bleeding risk.[10,11]

While hypothermia is conceivable in all pre-hospital patients, it is highly prevalent among those with a traumatic injury.[12] The etiology of hypothermia is multifactorial, including heat loss because of environmental exposure, infusion of cold intravenous fluids, and hemorrhagic shock.[13] Patients requiring emergency surgery in trauma pose additional challenges for the maintenance of normothermia. For example, they may require referral to tertiary centres and, as a result, experience prolonged transportation and environmental heat loss. Similarly, patients having specific surgical procedures such as cavitary surgery may be at an increased risk for hypothermia because of heat loss from the open abdomen. Finally, the induction of anesthesia, in both trauma and surgical patients, directly affects thermoregulation and is an independent risk factor for hypothermia.[14–16]

In this study, we aimed to evaluate the independent association between pre-hospital hypothermia and transfusion as it has important clinical consequences for the pre-hospital setting. First, hypothermia can have deleterious effects on the cardiac, neurologic, renal, and respiratory systems.[13,17] Therefore, evaluating its clinical utility beyond coagulopathy can help alert first responders early to communicate that these are individuals at high risk for transfusion. Second, reducing the severity and duration of hypothermia has been associated with an increased probability of successful resuscitation and reduced mortality in one, albeit small, prospective cohort of injured patients.[18] Hence, it may inform the need for early rewarming strategies in the pre-hospital setting.

METHODS

Subjects and setting

Sunnybrook Health Sciences Centre (SHSC) is a Level 1 trauma centre that services a population of approximately 6 million. SHSC maintains a trauma registry that meets the standards of the National Trauma Data Standard. We performed an analysis using the trauma registry and identified all adults aged 18 years or older, presenting with admission for traumatic injury and emergent surgery between July 2010 and June 2014. Emergent surgery was defined as any procedure performed in an operating room and occurring within six hours of arrival in the trauma bay or emergency department (ED).[19]

The following patients were excluded: 1) patients with thermal injuries, as they are treated through a different care pathway; 2) patients pronounced dead on arrival to the trauma bay or with an injury severity score of 75, as these are nonsurvivable injuries[20]; and 3) hyperthermic (>38.3°C) patients, as they may be at an increased risk of morbidity and mortality.[21] The research ethics board of SHSC reviewed this quality improvement project and advised that it did not require ethics approval.[19]

Data collection and variable definitions

Clinical data were abstracted from patient charts by two research assistants independently and in duplicate using an *a priori* developed data extraction form. Demographic information and patient outcomes were obtained from the trauma registry.

Outcomes

The study outcome was the receipt of one or more units of RBC within 24 hours of admission in the trauma bay, operating room, or intensive care unit (ICU).

Exposure

The primary independent variable of interest was pre-hospital hypothermia, defined as core body temperature <36°C,[22] measured within 15 minutes of arrival to the trauma bay using a calibrated tympanic membrane temperature measurement.

Covariates

The *a priori* model developed to evaluate the association between hypothermia and RBC transfusion included covariates known to be associated with transfusion in trauma. First, the injury severity score, which quantifies trauma severity, was included as a continuous variable because of its strong correlation with morbidity in trauma patients. The injury severity score ranges from 1 to 75, for which a score >15 represents a major trauma.[20] Given that we are a Level 1 trauma centre, our patients are often transferred from district hospitals and may be at an increased risk for transfusion because of the complexity of their injuries. Hence, we included this variable in the multivariable analysis.[23] Vital signs measured within 15 minutes of arrival to the trauma bay, such as systolic blood pressure (mm Hg) and heart rate (beats per minute), used as early indicators of hemodynamic instability, were considered continuous variables.[24,25] Clinical markers of bleeding, such as baseline hemoglobin (Hb), coagulopathy (international normalized ratio [INR]), and acidosis (pH), measured within one hour of arrival to the trauma bay, were also considered continuous variables.[3,9]

Missing data

Predictors with >10% missing data were excluded from further analysis. Furthermore, to evaluate the potential systematic exclusion of patients, those with missing temperature measurements in the trauma bay were compared with the cohort with complete data. A standardized difference (SD) between the included and missing cohorts has been reported (see Supplemental Appendix; Table 1), in which imbalance was defined as an absolute value of greater than 0.10. For variables with <10% missing data, contributing observations were excluded.

Statistical analysis

A univariable analysis was performed, stratified by temperature category, comparing predictors of RBC transfusion. Continuous, normally distributed variables were compared with Student's *t*-test, and for non-normally distributed variables, the Wilcoxon rank-sum test was used. Finally, comparisons of categorical variables were evaluated with the chi-square test.

To assess the relationship between hypothermia and transfusion risks, a multivariable logistic regression model was constructed. Variables were selected *a priori* and considered for inclusion if they were known to be associated with hypothermia, morbidity, or transfusion in trauma. To further evaluate the association between pre-hospital temperature and transfusion, the pre-hospital temperature was included in the model as a continuous variable in a *post hoc* sensitivity analysis.

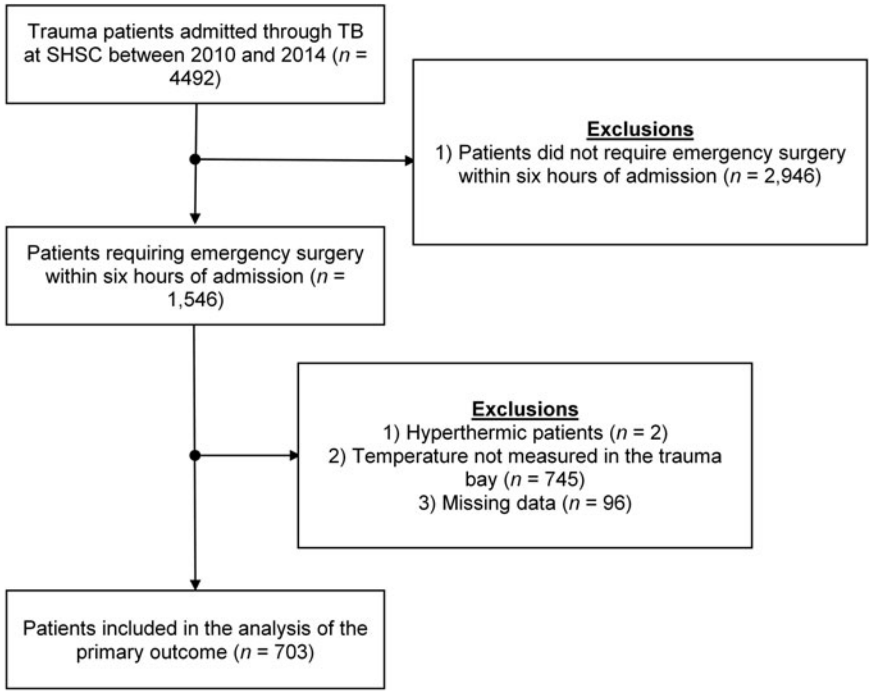

Figure 1. STROBE patient flow diagram (TB = trauma bay).

All analyses were conducted using SAS statistical software (University Edition, Version 9.4, SAS Institute Inc, Care, NC).

RESULTS

Data inspection and review

A total of 1,546 patients admitted between July 01, 2010, and June 30, 2014, met our inclusion criteria (Figure 1). A sample of 1,448 (94%) individuals remained after patients with data absent for these variables were excluded. Variables that had >10% missing values in this cohort (pH and lactate) were excluded from the analysis. The exposure of interest, baseline temperature, was not measured in 745 patients (51%). While these patients were excluded to facilitate analysis of the data, their characteristics were comparable with the included cohort (see Supplemental Table 1).

Description of cohort

A total of 703 patients (median age [interquartile range, IQR], 40 [27–55]; 77.5% male) who presented to the SHSC trauma bay were included to evaluate the association between hypothermia and transfusion (Table 1). The incidence of hypothermia was 51% ($n = 356$); 18% ($n = 128$) were <35°C, 5% ($n = 32$) were <34°C, and 0.3% ($n = 2$) were <33°C.

Rates of transfusion of blood products

The incidence of transfusion within 24 hours for the overall cohort was 29% ($n = 203$), with 37% ($n = 131$) in the hypothermia group and 21% ($n = 72$) in the normothermia group ($p < 0.001$). The proportion of hypothermic patients compared with that of normothermic patients requiring platelets (14.0% v. 4.0%, respectively; p value < 0.001), frozen plasma (18.5% v. 4.0%, respectively; p value < 0.001), and cryoprecipitate (9.5% v. 2.9%, respectively; p value < 0.001) were significantly higher. Moreover, 12% ($n = 42$) of hypothermic patients required >6 units of RBCs compared with 2% ($n = 8$) of patients in the normothermic group ($p < 0.001$).

The median length of stay in the hypothermic and normothermic cohorts was 12 days and 10 days, respectively ($p < 0.001$). The proportion of patients who died during the hospitalization was higher in the hypothermic than normothermic cohorts (7.5% v. 3.8%, respectively; $p = 0.03$).

Association between hypothermia and transfusion

Results of the unadjusted analysis are summarized in Table 2. Hypothermia was associated with a 2.22 fold

Table 1. Clinical characteristics of the hypothermic and normothermic trauma patients requiring emergency surgery			
Characteristic	Hypothermic (<36°C) $n = 356$	Normothermic (≥36 to <38.3°C) $n = 347$	*P* Value*
Age, median (IQR), y	42.0 (27.0, 56.0)	39.0 (26.0, 54.0)	0.18†
Male, *n* (%)	275 (77.2%)	270 (77.8%)	0.92†
Vital signs on arrival to trauma bay, mean (SD)			
Systolic blood pressure, mm Hg	135.7 (29.9)	143.9 (26.5)	0.001‡
Heart rate, beats/min	91.5 (21.3)	93.9 (20.7)	0.13‡
Baseline laboratory measures, median (IQR)			
Hemoglobin, g/dL	133.5 (120.0, 145.0)	136.0 (121.0, 147.0)	0.039†
Platelets, 10^9/L	223.0 (185.5, 270.5)	223.0 (185.0, 261.0)	0.85†
INR	1.09 (1.01, 1.18)	1.07 (1.00, 1.14)	0.012†
Referred from another centre, n (%)	113 (31.7%)	175 (50.4%)	<0.001+
Initial temperature, median (IQR)			
Trauma bay, °C	35.2 (34.6, 35.6)	36.5 (36.2, 36.9)	<0.001†
ISS, median IQR	22.0 (14.0, 30.0)	17.0 (10.0, 26.0)	<0.001†
Length of stay, median (IQR), days	12.0 (6.0, 28.0)	10.0 (5.0, 18.0)	<0.001†
Mortality, *n* (%)	27 (7.5%)	13 (3.7%)	0.033
Transfusion, *n* (%)			
RBCs, >1u	131 (36.8%)	72 (20.8%)	<0.001+
RBC, >6u	42 (11.8%)	8 (2.3%)	<0.001+
Platelets, >1 pool	50 (14.0%)	14 (4.0%)	<0.001+
Frozen plasma, >1u	66 (18.5%)	14 (4.0%)	<0.001+
Cryoprecipitate, >1u	34 (9.5%)	10 (2.9%)	<0.001+

ISS = injury severity score; INR = international normalized ratio; IQR = interquartile range; RBC = red blood cells; SD = standard deviation; u = units.
*Comparison between hypothermic and normothermic patients.
†Wilcoxon rank-sum test.
‡*t*-test.
+Chi-square test.

increased odds of transfusion of RBCs (95% confidence interval [CI] 1.58–3.11). After adjusting for available confounders including age, sex, coagulopathy (INR and platelets), referral status, vital signs (blood pressure and heart rate), and injury severity score, we found that hypothermia was associated with a 68% increase in the odds of transfusion within 24 hours (adjusted odds ratio [OR] 1.68; 95% CI 1.06–2.56; Table 3). Furthermore, in a subsequent sensitivity analysis, we found that each 1°C reduction in temperature was associated with a 30% increase in the odds of transfusion within 24 hours (adjusted OR 1.30; 95% CI 1.06–1.60; Appendix Table 2).

DISCUSSION

This study aimed to evaluate the independent association between pre-hospital hypothermia and transfusion of RBCs among trauma patients. As hypothermic patients had an associated 68% increased odds of an RBC transfusion, we showed that hypothermia is an important early physiologic measure for RBC transfusion in trauma. Hypothermic patients were also noted to have a greater length of stay and mortality.

The incidence of hypothermia in our cohort was 51% which, albeit high, is consistent with other studies where the incidence of hypothermia ranges from 17% to 54%.[26,27] While there is a widespread understanding that hypothermia may be associated with poor outcomes in trauma, it remains a commonly observed phenomenon suggesting potential room for improvement in care.

While hypothermia was associated with an increased transfusion of RBCs, these patients were also more likely to receive other blood products including platelets, frozen plasma, and cryoprecipitate. Approximately one-third of patients in our study required at least one unit of RBCs. Como et al. showed that the transfusion rate among direct from scene trauma patients presenting to the University of Maryland's trauma centre was approximately 10%.[28] Our

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Table 2. Univariable predictors of transfusion (≥1 RBC in the first 24 hours) in a cohort of trauma patients requiring emergency surgery

	Receipt of RBC transfusion	
Characteristic	OR (95% CI)	*p* value
Age, y (per one-year increase)	1.01 (1.00–1.02)	0.051
Male	0.79 (0.54–1.16)	0.24
Vital sign		
Systolic blood pressure, mm Hg (per five-unit decrease)	1.02 (1.01–1.03)	<0.001
Heart rate, beats/min (per five-unit increase)	1.13 (1.09–1.18)	<0.001
Baseline laboratory measures		
Hemoglobin, g/dL (per 10-unit increase)	0.63 (0.58–0.69)	<0.001
Platelets, 10^9/L (per 50-unit decrease)	1.00 (1.00–1.00)	0.57
INR (per 0.5 unit increase)	1.23 (1.13–1.34)	<0.001
Referred from another centre	0.45 (0.34–0.62)	<0.001
ISS, (per one point increase)	1.06 (1.04–1.08)	<0.001
Initial core temperature, (per one-degree decrease)		
Trauma bay, °C	1.63 (1.38–1.93)	<0.001
Hypothermic (<36 °C)		
Trauma bay	2.22 (1.58–3.11)	<0.001

Abbreviations: CI = confidence interval; INR = international normalized ratio; ISS = injury severity score; OR = odds ratio; RBC = red blood cell.

Table 3. A multivariable model of the association between hypothermia and transfusion among trauma patients requiring emergency surgery

	Receipt of blood product transfusion	
Characteristic	Adjusted OR (95% CI)	*p* value
Hypothermia		
Trauma bay	1.68 (1.11–2.56)	0.016
Age, y (per one-year increase)	1.01 (1.00–1.02)	0.13
Male	2.16 (1.28–3.64)	0.004
Vital sign		
Systolic blood pressure, mm Hg (per five-unit decrease)	1.09 (1.05–1.13)	<0.001
Heart rate, beats/min (per five-unit increase)	1.10 (1.05–1.16)	<0.001
Baseline laboratory measures		
Hemoglobin, g/dL (per 10-unit increase)	0.62 (0.55–0.71)	<0.001
Platelets, 10^9/L (per 50-unit decrease)	1.35 (1.14–1.58)	<0.001
INR (per 0.1 unit increase)	1.01 (0.94–1.08)	0.71
ISS (per one point increase)	1.05 (1.03–1.07)	<0.001
Referred from another centre	0.56 (0.37–0.87)	0.011

Abbreviations: CI = confidence interval; ISS = injury severity score; OR = odds ratio.
No variables were found to be collinear.
Omnibus likelihood ratio (chi-square [df], *p* value) 232.79 (10), *p* value <0.001; c-statistic: 0.84.

rate was higher as all patients in the cohort required emergency surgery, indicating an increased need for vigilance in this population. Hypothermia was the strongest predictor of transfusion in our study cohort that continues to be seen in a variety of clinical and research settings. In another study of over 15,000 trauma patients presenting to an ED, hypothermia was associated with a two-fold increased risk of transfusion of RBC.[27] They identified that an increasing injury severity score was also associated with a transfusion risk. However, injury severity score is often calculated much later as the trauma evolves, requiring diagnostic information from radiography. While it is an important confounder in the relationship between hypothermia and outcome, it may not be a useful clinical indicator of transfusion given the complexity of its calculation.

We also demonstrated that hypothermia was associated with transfusion independent of coagulopathy. Patients may be transfused RBCs in response to the unpredictable hemodynamic, rather than coagulopathic, effects of hypothermia in trauma. The effect of hypothermia on cardiac output and contractility is highly dependent on the severity of hypothermia, volume status, and level of sedation.[29] In normovolemic patients, severe hypothermia reduces cardiac contractility, increases the risk of arrhythmia, and induces hypovolemia because of cold diuresis.[30,31] Therefore, the body's physiologic response to reductions in core temperature contrasts the normal physiologic response to hypovolemia in the polytrauma patient, namely a rise in heart rate with a corresponding initial increase in cardiac output.[32] For example, in a rat model of trauma and hemorrhage, animals that were maintained hypothermic (32°) during resuscitation had reduced cardiac output relative to those who were restored to normothermia during resuscitation.[33] Similarly, in a porcine model, shock and hypothermia were shown to be additive. A decrease in cardiac output persisted in hypothermic animals, despite controlling bleeding and infusing volume expanders.[34] As advanced trauma life support (ATLS) guidelines suggest the treatment of hemorrhagic shock and reduced cardiac output with blood products, it is possible that we are also transfusing in response to the

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cardiac effects of hypothermia.[35] Our study is an important addition to the literature and further suggests the need for research into this area to evaluate the mechanism behind this association and the impact of warming interventions.

These findings are significant for the pre-hospital setting for two reasons. First, information regarding coagulopathy is often unavailable in the pre-hospital setting or is gathered late while managing severe hemorrhage. For example, in our institution, blood is drawn within 15 minutes, transported to the laboratory in 5 minutes, and analyzed within 20 minutes; hence, actionable lab results take at least 40 minutes to become available after patient arrival. Hypothermia represents a potentially useful early indicator of transfusion requirements. Second, and more importantly, clinicians tend to rely on platelets and INR as clinical endpoints for the management of coagulopathy. However, our work indicates that despite correction of coagulopathy, hypothermia is likely still a clinical indicator of transfusion requirements and may need to be "resuscitated."

Resuscitating hypothermia in the pre-hospital setting

Our study did not assess the impact of hypothermia management on RBC transfusion, and there are no other randomized patient studies that evaluate the effect the pre-hospital temperature management on transfusion. However, we propose that resuscitating hypothermia represents an opportunity to improve the quality of care in the pre-hospital setting. A recent review highlights the considerable laboratory evidence for the management of hypothermia,[36] and a second review has proposed an early goal-directed approach to hypothermia, stressing the importance of "prevention first and treatment second."[17] While pre-hospital providers should prioritize the management of life-threatening injuries, a variety of interventions can be performed to resuscitate a temperature less than 36°C aggressively. These patients should be passively warmed by removing any cold or wet clothing and placing them in a wrap that should include insulation, vapour protection, and, ideally, a heat source.[37] In patients with moderate to severe hypothermia, namely a temperature less than 32°C, active rewarming is necessary, particularly if patients cannot generate endogenous heat from shivering.[38] Effective rewarming modalities include chemical heat packs, hot water bags, electrical heating blankets, or forced warm air.[36] Furthermore, while only limited fluids are usually provided in the pre-hospital setting, providers should ensure that infused fluids are warmed, with the avoidance of overzealous use of crystalloid. Finally, emergency medical services (EMS) should notify the receiving hospital to plan for active warming and the increased likelihood of transfusion in these patients.

Limitations

As this was an analysis of a trauma registry, data were limited to only specific risk factors that were measured at the time of collection. Therefore, it was difficult to incorporate other potential confounders such as lactate or acidosis into our models. Similarly, this study was unable to measure diagnoses or interventions that may alter temperature regulation. Furthermore, as this data were representative of only one trauma centre, the results may not apply to another trauma centre. We also concede that over 50% of our patients had missing values for temperature. While we demonstrated that these groups were largely similar on measured characteristics, it is still possible that the excluded patients were systematically different than those who were included in our study. The lack of consistent temperature monitoring is an important finding and calls for innovation in temperature monitoring to overcome the measurement challenges. Nevertheless, we find that both the missing and included patients were similar on measured variables. Finally, it is unclear whether hypothermia may directly increase transfusion requirements or whether it is merely a sign of a more severely injured trauma patient who requires transfusion.

Conclusion

In summary, this single-centre cohort study suggests that pre-hospital hypothermia is independently associated with RBC transfusion in the first 24 hours of arrival in trauma. This work highlights an opportunity to manage and resuscitate hypothermia actively in the trauma setting. Future research should focus on effective monitoring technologies, warming prevention, and management both in the pre-hospital and hospital settings. Prospective randomized controlled trials evaluating whether these warming strategies improve patient morbidity, mortality, and transfusion risk are warranted and will be critical for any health care practitioner involved in trauma care.

Supplementary material: The supplementary material for this article can be found at https://doi.org/10.1017/cem.2019.412.

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