

The development and feasibility of a remote damage control resuscitation prehospital plasma transfusion protocol for warfarin reversal for patients with traumatic brain injury

Martin D. Zielinski, Dustin L. Smoot, James R. Stubbs, Donald H. Jenkins, Myung S. Park, and Scott P. Zietlow

BACKGROUND: The rapid reversal of warfarin in the setting of traumatic brain injury (TBI) has been associated with improved outcomes. Until now, remote reversal of hypocoagulable states has not been possible in the prehospital environment. This manuscript describes the development and analysis of a prehospital plasma transfusion protocol to reverse warfarin at the earliest possible moment after TBI.

STUDY DESIGN AND METHODS: A retrospective review of all TBI patients receiving plasma transfusion(s) in the prehospital environment for warfarin reversal between February 2009 and September 2010 was conducted. Thawed plasma was carried on every air ambulance flight centered at the main campus.

RESULTS: A total of 2836 flights carried over 2500 units of thawed plasma throughout the study period. During this time, 16 patients received prehospital plasma resuscitation, five of who were on warfarin with a concurrent TBI. The median Injury Severity Score was 17 (8.5-27.5) with a median Glasgow Coma Score of 13 (8-15) and a mortality rate of 40%. A median of 2 (1.5-2.0) units of thawed plasma and 0 (0-0) units of RBCs were transfused en route. The pretransfusion point-of-care international normalized ratio improved from 3.1 (2.3-4.0) to 1.9 (1.3-3.6) upon trauma center admission (serum sample). One hundred percent of the transported, but unused, thawed plasma underwent subsequent transfusion prior to expiration.

CONCLUSIONS: Remote prehospital plasma transfusions effectively reverse anticoagulation secondary to warfarin administration in TBI patients. It is feasible to transfuse thawed plasma in the prehospital setting via remote damage control techniques without increasing waste. Prospective studies are needed to determine if this practice can improve outcomes in this population.

INTRODUCTION

Traumatic brain injury (TBI) is the most common cause of death whether on the battlefield or within the civilian arena and is highly associated with concurrent injuries that can cause massive hemorrhage.¹ Prehospital treatment of hypocoagulable states, however, has not kept pace with advances instituted upon admission at military and civilian hospitals. These therapies include in-hospital rapid reversal of warfarin, in addition to massive transfusion (MT) protocols for hemorrhaging patients. Protocols such as these have been associated with significant mortality improvements by likely controlling hemorrhage and restoring blood flow.² The ideal fluid for resuscitation, therefore, maintains circulating volume, vital organ perfusion and augments hemostasis via coagulation protein replenishment.³ Plasma meets all of these criteria, but unfortunately has been unavailable in the prehospital setting. For massive life-threatening bleeding, the overwhelming consensus of trauma experts is that plasma should be administered rapidly before laboratory confirmation of coagulopathy, which, using classic measures, may take 45-60 minutes to perform.^{4,5} This has led to the utilization of thawed rather than frozen plasma thereby preventing delays by enabling empiric treatment of coagulopathy upon trauma center arrival.⁶ It would follow,

From the Departments of Surgery and Laboratory Medicine, Mayo Clinic, Rochester, Minnesota.

Address reprint requests to: Martin D. Zielinski, Division of Trauma, Critical Care and General Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: zielinski.martin@mayo.edu.

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therefore, that thawed plasma transfusion prior to arrival, via a remote damage control technique such as a mobile blood bank under the auspices of a prehospital plasma protocol, would ultimately lead to improved outcomes for injured, bleeding trauma patients.

The delay in plasma resuscitation is compounded by the inherent impediments present in rural systems, particularly for those patients requiring transfer to a higher-tier trauma center.⁷ Our American College of Surgeons (ACS) Level 1 Trauma Center serves a rural environment encompassing 29 counties in the states of Minnesota, Wisconsin, and Iowa. In order to overcome these negative geographical circumstances, we implemented several system-wide initiatives. Among these are an auto-launch air ambulance system and onboard availability of red blood cells (RBCs).⁸ Uniquely, in 2009 we implemented a remote damage control prehospital plasma protocol reliant on 1:1 blood product ratio resuscitation.⁹ This was the first civilian protocol of its kind since World War II. Outlined in its procedure statement, highly trained medical providers were empowered to transfuse thawed plasma and RBCs into patients that had evidence of severe hemorrhage or coagulopathy (Table 1). The goals of this protocol were to 1) ensure the earliest possible delivery of plasma to hemorrhaging trauma patients in an effort to quickly treat coagulopathy and therefore eliminate plasma deficits; and 2) correct medication-induced coagulopathy in TBI patients. We have previously published our experience with prehospital plasma resuscitation in trauma patients suffering from massive hemorrhage.⁹ The patients analyzed in this current study do not include patients previously reported. It provides a preliminary report on our initial experience of rapidly reversing anticoagulated states secondary to warfarin with concurrent TBI. We present this data, not as scientific justification, but to ensure that our protocol met its goals of providing early blood product resuscitation to those who met the criteria for inclusion and share the results with the trauma community. In addition, the current study focuses on the vital steps taken to incorporate the protocol and outlines the evolution of our prehospital

plasma transfusion practice. We hope that this effort will allow other trauma centers the necessary background to establish their own similar protocol.

METHODS

Institutional Review Board approval was obtained to review records of all trauma patients that received a prehospital plasma transfusion for the indication of warfarin reversal with concomitant TBI after the incorporation of the protocol in February 2009 through September 2010. Demographic and prehospital laboratory data were abstracted, including pre- and postadmission resuscitation fluid requirements. Patients without traumatic injury were excluded from the analysis.

Remote damage control prehospital plasma transfusion protocol

The Mayo Clinic Medical Transport (MCMT) Air Operations air ambulance system comprises three separate medical helicopter bases. This system-wide air ambulance network connects the main Rochester campus with our multiple outlying facilities. Air ambulances are positioned at three geographic locations: 1) Mayo Clinic, Rochester, MN (*Mayo 1*); 2) Chippewa Valley Regional Airport, Eau Claire, WI (*Mayo 2*); and 3) Mankato Regional Airport, Mankato, MN (*Mayo 3*).

These air ambulances fly within a 150-mile radius of each campus; the most critical patients are transported directly to the main Rochester, MN, facility. There are two medical providers present for direct patient care at all times in addition to the pilot crew. The medical providers are registered nurses or paramedics with an average of 10 years of critical care or prehospital professional experience that are handpicked by the MCMT medical director. In addition, the state of Minnesota requires critical care certification for any providers transfusing blood products. For paramedics, this is the Critical Care Paramedic Course (CCEMT-P; University of Maryland Baltimore County) as well as the Flight Paramedic Certification (FP-C; Board for Critical Care Transport Paramedic Certification) and for nurses this is the Certified Flight Registered Nurse certification (CFRN; Board of Certification for Emergency Nursing). There are also extensive mandatory training exercises throughout the year in the form of tests, live simulations, and mannequin instruction. This credentialing and training process was already in place as a result of our prehospital RBC transfusion practice. Once in flight, the providers have the ability to determine arterial blood gas measurements as well as lactate, hemoglobin, and international normalized ratio (INR) levels en route (I-STAT; Abbott Point of Care, Princeton, NJ). In addition, there is constant, intensive care unit-level monitoring

TABLE 1. Indications for prehospital plasma transfusion

Any adult injured trauma patient with ≥ 2 of the following plus evidence of active hemorrhage or traumatic brain injury:^{12,23}

- 1) Single reading of systolic blood pressure ≤ 90 mmHg
- 2) Single reading of heart rate ≥ 120
- 3) Penetrating mechanism (i.e., stabbing, gunshot)
- 4) Positive FAST
- 5) Point of care lactate ≥ 5.0 mg/dL
- 6) Point of care INR ≥ 1.5
- 7) Current warfarin use

FAST = Focused Assessment with Ultrasound in Trauma.

while in the air ambulances including telemetry, temperature, pulse oximetry, sphygmomanometry, capnography, and urine output. All of these data points are electronically charted. Further signs of deterioration, inclusive of transfusion reactions, can therefore be detected. There is a standardized review process by the MCMT medical director as well as blood bank personnel for every flight with a blood product transfusion with a specific emphasis on detecting potential transfusion reactions and other performance improvement issues.

The prehospital plasma protocol was developed with support and input from the Divisions of Laboratory Medicine/Pathology, MCMT, and Trauma. Initially, the air ambulances carried four units of RBCs (O⁻) along with two units of thawed plasma (group A exclusively) on every flight. For patients with signs of extracranial hemorrhage and confirmed need for plasma resuscitation (Table 1), two units of RBCs, followed by two units of thawed plasma, followed by an additional two units of RBCs were transfused. For TBI patients on warfarin, two units of plasma were transfused exclusively. This resuscitation strategy was amended mid-study. Currently, the air ambulances carry three units each of RBCs and plasma; two units of plasma is the initial product transfused, followed by two units of RBCs as needed. The final units are transfused as time permits. Transfusion is continued after disembarkation from the helicopter and completed in the trauma bay. Crystalloid resuscitation is minimized as blood products are the main source of volume expansion. All air ambulances had the ability to transfuse RBCs throughout the entire study period; however, only *Mayo 1* carried thawed plasma. As of September 2011, *Mayo 2* has thawed plasma available. *Mayo 3* began plasma transfusion in August 2012.

Data are expressed as median (interquartile range) and percentages as appropriate and were analyzed using JMP version 8 (SAS Institute, Cary, NC).

RESULTS

There were 2836 flights since the initiation of the prehospital plasma program; 1174 *Mayo 1*, 793 *Mayo 2*, 869 *Mayo 3*. In total, more than 2500 units of plasma were transported on these flights with 16 patients receiving 27 units

of thawed plasma. One hundred percent of the transported, but unused thawed plasma, underwent subsequent transfusion prior to expiration.

A total of five patients were administered prehospital thawed plasma for warfarin reversal with concomitant TBI. The mean age of these patients was 71 years (69-75) with four men. Four patients were transferred from other institutions. All had TBI as a result of blunt mechanisms. Median Injury Severity Scale (ISS) was 17 (8.5-27.5) with a Glasgow Coma Score of 13 (8-15). Median duration from injury to arrival at our trauma center was 370 minutes (161-563). The amount of time spent at the referring hospital was 80 minutes (60-110) with a transport duration from referring institutions or the scene to our trauma center of 15 minutes (13-21). Two units of thawed plasma (1.5-2.0) and 0 unit of RBCs (0-0) were transfused en route. Within the first 24 hours of injury, seven units of plasma (5-9) and 0 units of RBCs (0-2) were transfused. The hospital duration of stay was 7 days (3.5-16). Overall mortality was 40%. There were no deaths within 24 hours and no hemolytic reactions. One hundred percent of the transported but unused thawed plasma underwent subsequent transfusion prior to expiration.

Specific patient data are outlined in Table 2. The pretransfusion point of care (POC) INR improved from 3.1 (2.3-4.0) to 1.9 (1.3-3.6) upon trauma center admission (serum sample). INR levels were corrected to 1.3 or less within 3 hours of injury for all patients.

DISCUSSION

The ubiquitous but unpredictable nature of trauma events guarantees that severe trauma will occur; however, the timing, frequency, location, and severity of these events are impossible to foresee. This is the crux of rural trauma; low population densities ensure a lower incidence of traumatic injury, but most rural facilities are not equipped for definitive trauma care such as reversal of coagulopathy with plasma. For example, within our region, only three of the 22 trauma centers, including our own, have plasma available for transfusion. This is a prime example of where remote hemostatic resuscitation, as espoused by Remote Damage Control Conference, can and should influence trauma care. If an effective method of overcoming this

TABLE 2. Detailed per patient blood product consumption and laboratory data

Patient	Head injury type	GCS	Plasma en route (units)	RBC en route (units)	Pre-INR	Post-INR	24-hour plasma (units)	24-hour RBC (units)	Blood group	Outcome
1	IPH	7	3	0	1.8	1.5	10	0	O Pos	Death
2	SAH, IPH	15	1	0	2.7	2.6	4	0	O Pos	Survival
3	SAH	11	2	0	3.6	1.9	8	2	A Pos	Death
4	IPH	15	2	0	3.1	4.5	7	0	A Pos	Survival
5	SDH	3	2	0	4.4	1.0	6	2	A Pos	Survival

GCS = Glasgow coma scale; IPH = intraparenchymal hemorrhage; ISS = injury severity score; SAH = subarachnoid hemorrhage; SDH = subdural hematoma.

“geographic plasma deficit” can be developed by bringing the resources of the ACS Level 1 Trauma Center to the field and lower-tier trauma centers, then there is a strong chance of improving outcomes in hemorrhaging and coagulopathic trauma victims.⁹

The 18-month process to implement thawed plasma into our air ambulance system was a considerable undertaking. The MT protocol in place within the walls of our institution relied heavily on the immediate availability of thawed plasma (type AB). Only after proving the success of this program were we able to realize the natural progression to plasma intense resuscitation in the prehospital environment.¹⁴ To achieve this success, several obstacles were overcome.

Firstly, to ensure success of any prehospital plasma protocol, Laboratory Medicine (also known as “blood bank”) support is essential. There was considerable concern that a prehospital plasma protocol relying heavily on plasma resuscitation would result in reduced universal plasma donor stores.¹⁵ Due to recent data demonstrating the safety of incompatible plasma transfusions, the universal donor pool was expanded to include group A plasma.^{10,11,16} We believed that the benefits of transfusing potentially incompatible, yet safe, group A plasma outweighed the risks of delayed coagulopathy treatment. Upon arrival at the Trauma Center, our standard blood transfusion practice is implemented. An additional maneuver we utilized to ensure a robust plasma supply was the transfer of blood products to the operating room blood storage unit for use by Day 3 after thawing. Due to these changes, there has never been a discarded plasma unit or an incident of a patient not receiving a needed transfusion due to limited supply throughout the duration of our in-hospital MT protocol. Knowing this, as well as the quantity of units needed to implement the prehospital plasma protocol was small relative to the overall supply, we were able to obtain blood bank support.

Secondly, we needed to gain approval to extend the MT protocol to the prehospital environment from Mayo Clinic Rochester’s governing body that oversees all patient care activities. This required a unified team approach that included the support of the Divisions of Trauma, Laboratory Medicine, and MCMT. This body was responsible for approving and overseeing the in-hospital MT and warfarin reversal protocols. With the documented success of these protocols, there was little reluctance to apply these standards of care to a broader patient population.

The current study focuses on the rapid reversal of warfarin in the setting of TBI. Similar principles of prehospital plasma resuscitation, however, apply to those patients who have concomitant massive hemorrhage. Therefore, our third barrier was the lack of a validated method within our patient population of predicting which patients with traumatic hemorrhage might benefit from the aggressive plasma resuscitation contained within MT

protocols. The initial protocol called for plasma transfusion based on vital signs and the experience of the prehospital providers. This resulted in missed opportunities for plasma resuscitation. Consequently, we validated the Assessment of Blood Consumption score within our specific patient population.^{12,17} This scoring system, based on hypotension, tachycardia, penetrating mechanism, and a positive Focused Assessment with Sonography in Trauma (FAST) is now actively utilized to trigger both the in-hospital MT and prehospital plasma protocols. To date, however, we do not have FAST capabilities in the helicopter system. Unless a FAST exam was performed at a referring institution, the score was limited to the three available features of which two or more was considered positive.

To ensure appropriate inclusion of TBI patients on anticoagulation, we expanded the criteria to include patients with known warfarin use or $INR \geq 1.5$ with evidence for concurrent bleeding. We utilized the POC method for determining the INR level as this simple test, easily done in the prehospital setting, has been shown to be an accurate and reliable comparison to the corresponding plasma test (Table 1).¹³

Lastly, while TBI patients on warfarin were transfused plasma first, there was no universal agreement among the trauma surgeons at our institution as to which blood product to transfuse initially to hemorrhaging trauma patients given the equal availability of both plasma and RBCs. TBI and massive hemorrhage from other injuries resulting from blunt mechanisms are highly interrelated. Severe hemorrhage in the setting of coagulopathy, whether hemorrhage induced or iatrogenic from warfarin administration, must be treated early and aggressively. Due to the variable durations of transport, there was not necessarily time to transfuse plasma as the time was taken up by RBC transfusion. There have been multiple retrospective studies in both civilian and military populations that demonstrate high ratios of plasma to RBCs are associated with a significant improvement in mortality and that early plasma transfusion is likely best.^{5,18-21} In addition, negative plasma deficits, in other words plasma volume resuscitation lagging RBC resuscitation, have been associated with increased mortality during MT scenarios.¹⁶ As this evidence regarding the early transfusion of plasma was published, our group, in conjunction with the blood bank, elected to transfuse emergency release plasma as our initial fluid of choice in massive hemorrhage. RBC resuscitation then follows. In addition, the amount of plasma carried by the flight crews was amended to three units of plasma and three units of RBCs. Two units of plasma are now transfused initially, followed by two units of RBCs, then the remaining units as time permits. The goal of this resuscitation strategy is to as closely follow a 1:1 ratio as possible in real time. With the use of thawed plasma, survivor bias inherent in retrospec-

tive blood product ratio studies can be eliminated in future studies comparing high to low FFP : RBC ratios.²²

After obtaining permission and determining the mechanisms to proceed with plasma resuscitation, there were numerous practical issues that needed to be overcome such as dispersal and appropriate storage during transport for the blood products. Throughout the study period, the blood products were centrally located in the hospital central blood bank. Prior to every air ambulance flight, one of the flight crew medical providers would pick up a cooler (Credo coolers, Minnesota Thermal Science, Plymouth, MN) that contained the blood products. This occurred regardless whether blood products were thought to be needed or not. The coolers have been actively used to transport blood within the walls of our institution since 2008. To ensure conformation to Food and Drug Administration guidelines, the use of this cooler was independently validated at our institution to keep blood products between 1-10°C for 48 hours during both Minnesota winters and summers. Unused blood products were returned to the central blood bank immediately after each flight. Once thawed, if the unit was not used by Day 3, it was automatically removed from the central blood bank and sent to the operating theater blood bank. Rotating of units was done to ensure that products were not wasted as they are readily utilized due to our institution's high operative volume. This process is similar to the system of procedures developed for the thawed plasma stored in our trauma bays. Using these methods, no blood product was wasted; all plasma units were transfused prior to expiration.

Due to the lower volume of surgical practice in the Eau Claire and Mankato facilities, there was concern that the cost and potential waste of blood product would preclude successful implementation of a similar protocol. After demonstrating success of the protocol within *Mayo 1*, we have expanded the program to include *Mayo 2* and, recently, *Mayo 3*.

The goals of the prehospital plasma transfusion protocol were met. Within this substantially injured cohort, as demonstrated by the high mortality rate, elevated ISS and need for significant ongoing blood product resuscitation, we were able to keep the plasma deficits limited as well as show an improvement in trauma-induced coagulopathy. It should be stressed that the experience presented here is early. The data, however, can be used as an example on how to implement their own prehospital plasma resuscitation protocol and can serve as a basis for clinical trials in the prehospital setting. Further study in this manner is needed to determine if there is a mortality benefit to prehospital plasma transfusion, which cannot be shown in this feasibility study.

The need to provide optimal care to injured patients is the responsibility of the clinicians working within the trauma system in any given region. Remote damage control techniques such as the prehospital plasma trans-

fusion protocol presented are paramount to providing optimal care to the injured rural trauma patient. It must be noted that differences may exist between our trauma center/system and the majority of other academic trauma centers. Firstly, the medical providers responsible for transfusing the plasma are hand selected with multiple years of practice. Certainly, any program wishing to replicate a protocol of this nature would need to choose their most experienced providers. Secondly, our patient population tends to be older with a subsequent higher rate of anticoagulant use, which may be responsible for an increased plasma transfusion need within our area. Additionally, as a result of our rural location, there are inherently protracted referral and transport durations. Due to these impediments, we created an intervention to arrest the lethal triad and reverse medication-induced anticoagulation at the earliest possible moment, which was modeled after our successful in-hospital transfusion practice. We believe a prehospital protocol with the ability to transfuse plasma is the best potential method to avert preventable deaths due to hemorrhage and TBI exacerbated by warfarin. The protocol presented has been shown to be feasible and practical and can serve as a platform for other centers to incorporate prehospital plasma transfusion protocol into their respective trauma regions.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

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