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Clinical paper

Coordination and management of multicenter clinical studies in trauma: Experience from the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) Study☆

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ABSTRACT

Aim: Early death due to hemorrhage is a major consequence of traumatic injury. Transfusion practices differ among hospitals and it is unknown which transfusion practices improve survival.

This report describes the experience of the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) Study Data Coordination Center in designing and coordinating a study to examine transfusion practices at ten Level 1 trauma centers in the US.

Methods: PROMMTT was a multisite prospective observational study of severely injured transfused trauma patients. The clinical sites collected real-time information on the timing and amounts of blood product infusions as well as colloids and crystalloids, vital signs, initial diagnostic and clinical laboratory tests, life saving interventions and other clinical care data.

Results: Between July 2009 and October 2010, PROMMTT screened 12,561 trauma admissions and enrolled 1245 patients who received one or more blood transfusions within 6 h of Emergency Department (ED) admission. A total of 297 massive transfusions were observed over the course of the study at a combined rate of 5.0 massive transfusion patients/week.

Conclusion: PROMMTT is the first multisite study to collect real-time prospective data on trauma patients requiring transfusion. Support from the Department of Defense and collaborative expertise from the ten participating centers helped to demonstrate the feasibility of prospective trauma transfusion studies. The observational data collected from this study will be an invaluable resource for research in trauma surgery and it will guide the design and conduct of future randomized trials.

1. Introduction

In civilian trauma systems nearly 50% of in-hospital deaths occur within 12 h of Emergency Department (ED) arrival and 70–80% within 48 h.[1–3] Hemorrhage is a contributing factor in 26–41% of early in-hospital deaths[1–5] and many of these patients receive a massive transfusion (MT ≥ 10 U of red blood cells (RBCs) within 24 h of admission). Coagulopathy plays a significant role in these deaths as truncal hemorrhage patients are the ones who most often present with coagulopathy in the ED.[6;7]

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While a recent paper documents that the majority of MT patients receive 10 or more units of blood in the first 3–6 h after injury and have the highest incidence of death during that period,[8] essentially none of the specifics are known about the type and timing of resuscitative intervention during the critical 3–6 h after admission, including the rates and sequence of infusions. Evidence suggests that increasing delay to the operating room (OR) worsens outcome in patients with truncal hemorrhage[9] and that delivering a 1:1:1 ratio of plasma:platelets:RBCs is associated with improved survival.[10] But it is clear from the existing MT literature that significant variation in practice and survival exists between trauma centers. Therefore, prospective minute-to-minute data collected during the first few hours after injury are critical for identifying practices that are associated with reduced mortality.

Responding to a request for proposals from the US Department of Defense, Army Medical Research and Materiel Command, we conducted the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study that aimed to identify practices leading to improved survival for trauma patients who require massive blood transfusions. Specific aims for PROMMTT were: (1) to compare survival of massively transfused trauma patients in 2009–2010 from PROMMTT to those who received the standard of care in 2006, as analyzed in a previously completed retrospective study[10]; (2) to prospectively validate an evidence-based algorithm to predict MT within 10 min of arrival in the ED; and (3) to document in real-time the timing of all lifesaving interventions and critical decisions in the ED, operating room (OR) or interventional radiology (IR) suite.

The Biostatistics/Epidemiology/Research Design component of the Center for Clinical and Translational Sciences at the University of Texas Health Science Center at Houston (UTHealth) serves as the Data Coordination Center (DCC) for PROMMTT. The DCC was responsible for providing the comprehensive supportive research infrastructure for (1) developing, maintaining, and administering contractual agreements with each clinical site[11,12]; (2) standardized data collection processes and management across the Consortium including the training of clinical site personnel in project management and data entry, quality and security[13,14]; and (3) site monitoring and statistical analysis.[11,15] The main objectives of this article are: (1) to describe in detail the design and development of PROMMTT and (2) to discuss key methodological challenges associated with conducting a multicenter study of massive transfusion and lessons learned related to the coordination, and management of PROMMTT.

Table 1
Eligibility criteria for PROMMTT.

Inclusion criteria	Exclusion criteria
(1) Major trauma patients who required trauma team activation (determined by EMS or upgraded by ED physicians)	(1) Received any care at an outside hospital or other healthcare facility
(2) Estimated age 16 or older	(2) Declared dead within 30 min of ED admission
(3) Received directly from the injury scene by a participating PROMMTT clinical site	(3) Received more than 5 min of CPR prior to ED admission
(4) Required at least 1 U of RBCs within 6 h of ED admission	(4) Received more than 5 min of CPR within 30 min of ED admission (5) Prisoners (6) Children less than age 16 (7) Greater than 20% burn injury (8) Inhalation injury diagnosed by bronchoscopy (9) Obvious pregnancy or positive pregnancy test at ED admission

Table 2
Criteria for site selection.

Criteria	Judgment standard
A. General criteria for all sites	
1. Number of MT patients reported in the retrospective study	Multiple of the median number of MT patients among 22 sites
2. Diverse range of platelet:RBC ratios among MT patients	Multiple of the median interquartile range among sites
3. Diverse range of mean plasma:RBC ratios among MT patients	
4. Site management/ compliance with retrospective protocol, deliverables and timeline based on the cumulative site monitoring documentation at the end of the retrospective study	One point if expectations were met
5. Is an NIH/NCRR-funded Clinical and Translational Science Award Consortium Member?	One point if yes
6. Experience in performing clinical studies of MT trauma patients that includes the use of blood samples collected at ED admission for research laboratory studies	
7. Experience in changing transfusion practice guidelines (since 2006) to increase plasma:platelet:RBC ratios	
8. Is a member of the NIH/NHLBI-DoD-funded Resuscitation Outcomes Consortium (ROC)?	
9. Is a priority site based on the experience of the PI of retrospective study?	One point if first priority, 0.5 if second priority
Total individual score = sum of points on previous 9 criteria	
B. Criteria for candidate group of 10 sites (of 646,646 possible combinations of 10 sites)	
1. Diverse range of 24 h mortality rates among sites	Interquartile range among the 10 sites within the group/interquartile range among all 22 sites
2. Diverse range of platelet:RBC ratios across sites	
3. Diverse range of plasma:RBC ratios across sites	
4. Diverse geographic representation	One point if all 4 US regions (N, S, E, W) are represented among the 10 sites within the group, 0.75 points if only 3 regions are represented
Total group score = sum of points on previous 4 criteria	

2. Materials and methods

2.1. Study design and participating sites

PROMMTT was a prospective, consecutive patient, multicenter observational cohort study conducted at 10 clinical sites in the US. At each site, data collectors screened and enrolled consecutive severely injured trauma patients according to the inclusion and exclusion criteria found in Table 1.

The PROMMTT-DCC was responsible for selection of the study sites. Because of the intensive nature of real time data collection, we considered the existing research infrastructure at each potential site, their ability to enroll an adequate number of eligible patients in the study,[16] and active participation of an experienced and knowledgeable principal investigator at each site[17] to be important

Table 3
Patient population and description of participating academic sites and associated hospitals.

Research collaborator	Hospital name	Location	Population served (in millions)	Trauma admissions 2010	% of 2010 trauma admissions with ISS ≥ 25
Brooke Army Medical Center	BAMC	San Antonio, TX[a]	1.7	1236	16.0
Medical College of Wisconsin	Froedtert Hospital	Milwaukee, WI	2.0	1976	4.7
Oregon Health and Science University	OHSU Hospital	Portland, OR[a]	1.5	2320	12.1
University of California, San Francisco	San Francisco General Hospital	San Francisco, CA	1.5	1594	18.0
University of Cincinnati	University Hospital	Cincinnati, OH[a]	2.1	2792	12.0
University of Pittsburgh Medical Center	UPMC Presbyterian	Pittsburgh, PA	4.7	5267	8.2
University of Texas Health Science Center at Houston	Memorial Hermann Hospital – Texas Medical Center	Houston, TX[a]	5.5	5805	17.1
University of Texas Health Science Center at San Antonio	University Hospital	San Antonio, TX[a]	2.4	3297	12.0
University of Texas Southwestern Medical Center	Parkland Hospital	Dallas, TX	2.5	2983	11.0
University of Washington	Harborview Hospital	Seattle, WA	3.0	5298	18.2

[a] Sites that participated in residual blood sample collection and analysis.

selection criteria. The DCC developed a formal two-stage selection procedure to rank order individual candidate sites and performed an analysis of data quality from a previously completed retrospective study.[10] Twenty-two potential clinical sites were subjected to rigorous metrics and a final group of 10 high-scoring sites that sufficiently represented the diverse patient populations and clinical practices across the country were chosen to become part of the Consortium. The criteria for selection of sites are shown in Table 2. Additionally, an External Advisory Committee was formed to provide guidance with respect to the suitability of the clinical sites and their ability to carry out study procedures.

The PROMMTT Consortium consists of 10 clinical sites and a DCC located in the US. The DCC is located at the University of Texas Health Science Center at Houston (UTHealth) and the clinical sites are all accredited Level 1 trauma centers. The Consortium is composed of academic and governmental research institutions and affiliated hospitals (Table 3). The 10 clinical sites served a combined population of 26.9 million people and admitted 32,568 total trauma patients in 2010.

2.2. Regulatory oversight

The DCC developed an Institutional Review Board (IRB) application in accordance with all national regulations in consultation with human subjects experts. We applied for a waiver of consent for the study on the basis that as an observational study, patients would be subject to no more than minimal risk and that the research could not be practicably carried out because we expected a 30–60% refusal rate based on previous studies.[18–22]

Once both DCC/UTHealth site IRB and US Army Medical Research and Materiel Command Office of Research Protections approvals were received, an IRB packet was sent to the nine external sites. The DCC provided assistance to each site during their local IRB application process, submitted all local approval documents to the Army for final approval, and continued to act as a facilitator between the Army and local IRBs throughout the study. One site (University of Washington) was required by its local IRB to obtain delayed consent for surviving patients. All sites were required to submit subsequent correspondence to or from their local IRB to the DCC, which submitted them to the Army as required in order to maintain compliance and to protect human subjects throughout PROMMTT. In total, the initial IRB approval process took 10 months to complete (range at clinical sites: 6 weeks to 4 months).

2.3. Data elements

Detailed patient data were collected on all routine clinical procedures and life-saving interventions administered to eligible trauma patients, as well as patient outcome data up to the time of death or discharge from the hospital. These data were captured in real-time at the patient bedside and included amount and timing of packed red blood cells, fresh frozen and thawed plasma, platelets, colloids and crystalloids infused and sequence and timing of interventions. The PROMMTT Consortium collected 874 data fields using ten data forms (Table 4).

The primary endpoint for this study was mortality. Secondary endpoints included event-free survival, cause of death, incidence of multiple organ failure (MOF), severe head injury, and incidence of specific surgical procedures.

2.4. Data collection system

The DCC implemented an informatics platform to support and automate data collection operations across the Consortium. To facilitate real-time data collection, the PROMMTT data collection system was developed for use on tablet computers. The resulting system, the Survey On Demand System (SODS) was developed in collaboration with the School of Biomedical Informatics at UTHealth to function both online or offline and to provide 24/7 data capture, review, and submission by the sites. Paper-based backup case report forms were also provided to the sites. The DCC provided training and user support for SODS by conference call, email, meetings, and in written training documents.

2.5. Data management and quality control

To monitor quality, data submitted in SODS were exported nightly into a Structured Query Language (SQL) Server relational

Table 4
PROMMTT data collection forms and included fields.

Form	Example data fields
1. Eligibility	ED admission date/time, sex, patient status on all inclusion and exclusion criteria
2. Trauma pager	Information transmitted on hospital trauma pager system (varied by site), mechanism of injury, field vital signs
3. Pre-hospital care	Pre-hospital fluids, life saving interventions, and medications
4. ED	Initial vital signs, life saving interventions, diagnostic tests, medications, and initial labs
5. Infusions	Infusion type, amount, start and stop time, and hospital location
6. OR	Initial OR vital signs, surgical procedures performed
7. IR	Initial IR vital signs, IR procedures performed
8. Initial ICU data	Initial ICU vital signs
9. Daily follow-up data	Death/discharge, fields for determining multi-organ failure, acute respiratory syndrome and other secondary endpoints, additional blood product infusions, life saving interventions, ventilator changes, complications
10. Record abstraction	Patient race/ethnicity, discharge circumstances, DNR information, history of anticoagulant use, Injury Severity Score, and diagnosis and mortality codes

database and weekly into the PROMMTT data warehouse. Once in the data warehouse, records were reviewed and edited, and when necessary, transformed to comply with the PROMMTT data dictionary.

Because the majority of data were collected in real-time, the data entered on the tablet computer (or paper forms used for back-up) were the source documents for the study. While the hospital medical record may help clarify recorded data in some instances, the study protocol considered the medical records to be less reliable than the real-time data specifically for timing and sequence of infusions.

The DCC identified unacceptable data entries using custom software applications programmed to detect missing, impossible and improbable values, and logical inconsistencies between data fields and across forms. From detailed error logs, the DCC generated site-specific queries listing potential errors. Once the sites resolved these queries, the DCC updated and verified the patient records in the data warehouse and documented the resolution in the error log.

2.6. Management of laboratory specimens

As part of standard clinical practice, blood samples are obtained, processed, and analyzed on all newly admitted trauma patients at the clinical labs at the Consortium sites. In PROMMTT, these lab results were collected and recorded in SODS. Additional laboratory research was implemented to further improve understanding of the role of hemostatic proteins and cellular factors in early pathologic changes in massively injured and transfused trauma patients. Discarded patient blood samples were collected from patients at five IRB approved centers (identified in Table 3) and shipped to the UTHealth Center for Translational Injury Research central laboratory. The samples were analyzed using specialized laboratory assays that are not routinely done for clinical care. One site (University of California, San Francisco) had existing IRB approval to collect serial blood samples from trauma patients under a different protocol and performed a coordinated analysis on their samples with guidance and approval from the PROMMTT Laboratory Committee.

At the time of the initial ED blood draw for standard clinical blood tests, participating PROMMTT sites obtained any residual blood on all eligible trauma patients. If a patient received an MT, a second residual blood sample was obtained from a routine draw at the time of the 10th unit of RBC administration, 6 h after ED admission or at arrival to the ICU, whichever occurred first. All blood samples were identified by identification number which also indicated the site, date and time of the specimen collection.

Available residual samples were transferred into either sodium citrate or special flow cytometry specimen tubes in a standardized order. The flow cytometry tubes contained a combination of ethylenediaminetetraacetic acid (EDTA) and a blood cell membrane stabilizer and were used for characterizing blood cell populations in whole blood.[23] The sodium citrate tubes were used for measuring clotting factors and inhibitors, soluble inflammatory markers, and cellular microparticles.

2.7. Data analysis plan

In order to achieve Aim 1 of the study, we will explore both parametric and semi-parametric (Cox proportional hazards modeling) survival analyses to examine the data at both the site and individual patient levels to account for the potentially important variation in patient follow-up times and time-dependent covariates (e.g., patient-level changes in plasma and platelet ratios). We will check the underlying model assumptions and perform model diagnostics. In the event assumptions are violated or models fit poorly, we will identify alternative and appropriate data analysis strategies. We will apply the same data analysis approach for each of the secondary outcomes as well. However, because of potential inflation of the alpha level (type I error probability) due to multiple comparisons, the results from these analyses will be interpreted with caution.

In order to achieve Aim 2, we will split the prospective data into two random halves for a two-stage approach incorporating a training set and validation set. We will then develop an algorithm to predict the need for massive transfusion based on covariates identified from the training set. This model will then be tested for its predictive value on the validation set. It is important to note that different estimated risk cut-points produce different sensitivity and specificity profiles for a predictive model. Thus, we will define a classification rule that improves the accuracy of the predictive model by maximizing the area under a receiver operator characteristic (ROC) curve for the optimal cut-point of massive transfusion.

To achieve Aim 3, we will calculate point and interval (95% confidence limits) estimates for the rates, volume and timing of all crystalloid, colloids and blood products.

2.8. Target sample size and study power

The necessary sample size estimated for the research question described in Specific Aim 1, with 30-day survival, two-sided testing, power of 80% and a significance level of 5%, was 208 in each group. To allow for incomplete data on some patients and multivariable analyses, we planned to enroll 300 MT patients. We enrolled 297 MT patients and 948 non-MT patients over 15 months. These enrollment numbers allow 99% power to detect a difference in 30-day survival between MT and non-MT patients similar to the one detected in the previous retrospective study.[10]

2.9. PROMMTT scientific contributions

The PROMMTT Publication Committee includes one voting member from each site and one from the DCC. In order to use multisite data, investigators at the clinical sites or the DCC must

Table 5
PROMMTT final enrollment information by site.

Site	Screened	Eligible	MTs	Data collection period	Weeks collecting data	MTs/week
1	1344	308	78	7/1/09–10/15/10	67.3	1.16
2	969	138	33	8/1/09–9/11/10	58.0	0.57
3	1263	61	11	8/10/09–10/11/10	61.0	0.18
4	1562	128	33	8/24/09–9/5/10	53.9	0.61
5	1616	143	31	9/3/09–10/15/10	58.1	0.53
6	1229	110	23	8/18/09–10/14/10	60.3	0.38
7	1836	107	37	8/18/09–10/9/10	59.6	0.62
8	296	121	28	10/12/09–10/13/10	52.3	0.54
9	909	101	19	9/28/09–10/13/10	54.3	0.35
10	1537	28	4	9/4/09–9/26/10	55.3	0.07
All sites combined	12,561	1245	297		580.0	5.01

submit proposal requests to the Publication Committee for review. The Committee approves all appropriate projects, makes suggestions to improve the project, and recommends other interested investigators who have volunteered to contribute. The Committee has approved 17 investigator-initiated projects thus far. Prior to submission, the Publication Committee also reviews and approves manuscripts developed from approved proposals.

3. Results

A total of 12,561 patients were screened and 1245 were enrolled from July 1, 2009 to October 15, 2010 (see Table 5). Sites had varying start and end dates within this interval. Of the eligible patients, 297 received a massive transfusion. PROMMTT enrolled an average 5.0 patients who received an MT per week over the course of the study, representing a range of 0.07–1.16 MT patients/week at the sites (mean = 0.50 MT patients/week/site).

We collected 305 residual blood sample sets from enrolled patients at the five participating sites combined. Of these, 63 sample sets belonged to MT patients and 29 of the MT patients had a second sample collected.

4. Discussion

A major challenge early in the study was the coordination of Institutional Review Board approvals. The overall and site-specific regulatory approval process proceeded relatively smoothly and rapidly due to open lines of communication between the team of investigators and both local and US Army IRBs. Although we received all eleven necessary IRB approvals in 10 months, we had originally anticipated that the IRB process would take six months and thus our timeline was delayed at the start of data collection. Approval from the Army IRB alone required five months and no site could begin data collection until this approval was received. In hindsight, the IRB timeline may have been shortened considerably by not requesting a waiver of consent. The investigators were initially convinced that PROMMTT would have difficulty obtaining consent from a satisfactory percentage of patients if consent were required, but the only site required to obtain delayed consent received less than 5% refusals in this low-risk observational study.

Additionally, obtaining consent may have allowed more sites to participate in the blood sample collection as several sites informed the DCC that their local IRB would not approve the residual blood collection without consent. The use of residual samples was also less than ideal because frequently there was no residual blood available. If we had obtained consent, we would not have been restricted to residual samples and could have assured that samples were drawn for all enrolled patients. Another challenge was the operational difficulty of processing the residual samples. Hospital clinical laboratories have high volumes of clinical assays to run and were generally reluctant to commit staff time for processing research samples even for payment.

Another challenge was the performance of the tablet computers for real-time data capture in the ED due to (1) the large volume of complex, precisely timed data that had to be entered in a compressed time frame and (2) system demands across diverse operating environments (e.g., hardware or operating system crashes and institutional firewall idiosyncrasies). Nine of ten sites ultimately reverted to paper-based data collection with delayed computer-based data entry. Also challenging was the transfer and conversion of study data from the SODS format[24] to a traditional relational database warehouse.

Lastly, we were surprised by the variation among the sites in their clinical practices. For example, hospitals varied widely on trauma triage practices. Originally, PROMMTT had requested that data collectors begin data collection on patients who received the highest level of trauma activation. However, at some sites the highest level of activation missed a significant percentage of MT patients who were originally classified at lower trauma activation levels. To increase the number of MT patients enrolled, we changed the protocol to allow sites to start data collection on any trauma activation level.

The rich and complex database that PROMMTT has established will continue to be developed and mined for valuable clinical data for years to come. To that end, the DCC has received supplemental funds from the US Army to support further data management and statistical support for currently approved and future proposals through March 2013.

5. Conclusions

PROMMTT is the largest study to collect real-time prospective data on trauma patients requiring transfusion. PROMMTT was able to enroll, on average, 5 MT patients per week from a combination of high and low volume centers. Collaborative expertise from the ten participating centers helped to demonstrate the feasibility of prospective trauma transfusion studies. The observational data collected for this study will be an invaluable resource for answering important scientific questions regarding trauma medicine as well as to inform the design and conduct of future randomized trials.

Conflict of interest statement

No conflicts of interest have been declared by any authors in regards to this manuscript.

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Appendix A.

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