Massive Transfusion in Severe Trauma & Use of Liquid Plasma

Review & Summary of TMC Experience

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Introduction

- Injury is the leading cause of death in the United States among individuals between the ages of 1-44 years.
- It is the leading cause of years of life lost for those younger than 75, and it is the 3rd leading cause of death overall.
- Deaths from injury have increased 23% during the last decade.

Holcomb, JB et al. 2, 2013, JAMA Surg, Vol. 148, pp. 127-36

Introduction

- Hemorrhagic shock is the leading potentially preventable cause of death after injury.
- 20-40% of trauma deaths occurring after hospital admission involve massive hemorrhage from truncal injury.
- Coagulopathy is present in up to 25% of severely injured patients at the time of hospital presentation.

Holcomb, JB et al. 2, 2013, JAMA Surg, Vol. 148, pp. 127-36

Introduction

- Almost 50% of trauma related fatalities occur within the first 24 hours and up to 80% of intraoperative trauma deaths are directly related to hemorrhage.

- Massive transfusion (within 24 hours of treatment) is required in approximately 3-5% of civilian trauma patients.

- Improved survival has been documented when trauma patients requiring early extensive RBC support are quickly identified and massive transfusion protocols (MTPs) that provide prompt concomitant hemostatic support are activated.

Holcomb, JB et al. 2, 2013, JAMA Surg, Vol. 148, pp. 127-36

Introduction

- Damage control resuscitation is defined as rapid hemorrhage control through early administration of blood products in a balanced ratio of (1:1:1 RBC to plasma to platelets).

- This ratio is closest to approximation to reconstituted whole blood.

- This has been codified as a US department of defense clinical practice guideline in 2004 and has become the standard of care for battlefield resuscitation that is now used in many civilian trauma centers.

Holcomb, JB et al. 2, 2013, JAMA Surg, Vol. 148, pp. 127-36

Introduction

- Damage control resuscitation was developed to:
- ✓ Treat intravascular volume deficit.
- ✓ Manage the acute coagulopathy of trauma.
- ✓ Preserve Oxygen carrying capacity.
- ✓ Repair the endothelium.
- ✓ Prevent dilutional coagulopathy.

Holcomb, JB et al. 2, 2013, JAMA Surg, Vol. 148, pp. 127-36

The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study

Comparative Effectiveness of a Time-Varying Treatment With Competing Risks

John B. Holcomb, MD; Deborah J. del Junco, PhD; Erin E. Fox, PhD; et al

Article Information

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PROMMTT Study

- The PROMMTT study demonstrated:

- ✓ Patients did not receive a constant ratio during the period of active resuscitation.

- ✓ Early infusion of higher plasma and platelet ratios was associated with improved 6 hour survival after admission.

PROMMTT Study

- The protective association between higher transfusion ratios and in-hospital mortality:

- ✓ Appears strongest within 6 hours.

- ✓ Diminishes over time as the primary causes of mortality shift from exsanguination to head injury, respiratory distress, organ failure, and infection in 24 hours.

PROMMTT Study

- Survivors avoiding early hemorrhage related mortality face the longer term competing risks of death from complications of multi organ failure or multiple injuries (head injury).
- The significant protective association between higher blood product ratios and mortality that was observed was concentrated in the first 24 hours for plasma and 6 hours for platelets.
- Thereafter during the later time periods when other factors played a role, platelets and plasma transfusions were not significantly associated with mortality.

PROMMTT Study

- Among survivors at 6 hours, the subsequent risk of death by hour 24 was higher for patients with low plasma ratios.

- Among survivors at 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios.

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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

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PROPPR Trial Key Points

- Among patients with severe trauma and major bleeding early administration of plasma, platelets and red blood cells in a 1:1:1 ratio, compared with a 1:1:2 ratio did not result in significant difference in mortality at 24 hours or at 30 days.
- More patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours.
- Even though there is an increased use of plasma and platelets transfused in the 1:1:1 group no other safety differences were identified between the 2 groups.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- Five plasma products are available in the United States, three frozen plasma products and two liquid state plasma products.

- The frozen plasma products are:
- ✓ Fresh frozen plasma (FFP).
- ✓ Plasma frozen within 24 hours of phlebotomy (FP24).
- ✓ Plasma cryoprecipitate reduced.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- FFP and FP24 differ with respect to time before freezing (6-8 hour depending on plasma source and manufacturer vs. 24 hour).
- Both have a shelf life of 24 hours when thawed.
- They can be converted thereafter to thawed plasma.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- The two liquid-state plasma products are:
  - ✓ Thawed plasma
  - ✓ Liquid plasma (LP)

- Thawed plasma is made from a frozen product (FFP or FP24).

- Thawed plasma has a shelf life, when stored at refrigerated temperatures (1 to 6°C), of 5 days.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- With thawed plasma, losses occur in labile clotting factors and Protein S.
- Factor VIII declines significantly, falling to approximately 53-75% of baseline levels 5 days post-thawing with most of the decline occurring within the first 24 hours after thawing.
- Factor V levels drop to 70-86% of baseline and variable decreases occur in Protein S activity.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- Other Factor levels remain relatively constant.
- Some studies show increased levels of Factors VII and XII, related to cold or contact activation at refrigerated temperatures.
- Factor XI increases correlate with venous thromboembolism.
- Indications for thawed plasma partially reflect these observations emphasizing its use for management of preoperative or bleeding patients, massive transfusions, and rapid reversal of warfarin therapy.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- Liquid plasma is never frozen plasma.
- It is produced from whole blood donations within 5 days of expiration date of whole blood.
- It has a refrigerated shelf life (26 or 40 days) that is determined by the manufacturing process.
- In Sweden keeping a small stock of liquid plasma for urgent use has been in practice since the 1980s.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- The shelf life of the component was recommended to be 14 days based on studies of coagulation factor content.
- Contact activation increases with the duration of liquid storage.
- It is more pronounced in women more than men.
- The authors suggested that liquid plasma be produced from males to reduce this effect.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

Plasma Products & Utilization

- Markers of compliment activation C3a and C5b-9 also increase during storage of liquid plasma.
- Once generated C3a, and C5a both anaphylatoxins are rapidly converted in plasma to forms that are less active, and are eliminated following transfusion.
- In a retrospective study of 84986 patients there was no evidence that storage time of liquid plasma was associated with an increased risk of mortality.

Holcomb, JB et al. 2015 , JAMA Vol. 313, pp. 471-82

TRANSFUSION aaBB

BLOOD COMPONENTS

Coagulation profile of liquid-state plasma

Robert C. Gosselin, Carol Marshall, Denis M. Dwyre, Chris Gresens, Diana Davis, Lynette Scherer, Douglas Taylor

First published: 31 July 2012 | https://doi.org/10.1111/j.1537-2995.2012.03772.x | Cited by:8

Plasma Products & Utilization

- At least 50 % activity persists for all measured variables on Day 15 of storage compared to Day 1.
- During LP storage, there is a significant decrease in activity of FV, FVII, FVIII, VWF, and PS : Act on Day 15 onward compared to either Day 1 or Day 5 samples.
- There is a significant reduction of thrombin-generating capacity of LP associated with prolonged storage.

Gosselin et al. Coagulation profile of liquid-state plasma. Transfusion. 2013;53(3):579-90.

Plasma Products & Utilization

- An increase in Factor VII activity after day 15 was also identified for all blood groups except type B.
- Considerable heterogeneity was noted between the different blood groups for FVII, FVIII, and VWF results.
- Group O donors had lower VWF, and FVIII levels.

Gosselin et al. Coagulation profile of liquid-state plasma. Transfusion. 2013;53(3):579-90.

Plasma Products & Utilization

- Study conclusions:

- ✓ Despite FDA approval use for up to 40 days it may be appropriate to limit the storage of liquid plasma to 15 days.
- ✓ Combine its use with FFP when applied to the management of massively bleeding patients.
- ✓ The study didn't address the clinical efficacy of liquid plasma transfusion after prolonged storage.

Gosselin et al. Coagulation profile of liquid-state plasma. Transfusion. 2013;53(3):579-90.

Plasma Products & Utilization

The impact of long term storage on coagulation proteins may not lead to reduced clinical efficacy when using this product since hemostasis could be achieved in the context of massive transfusion, esp. if used in combination with FFP and thawed plasma.

Gosselin et al. Coagulation profile of liquid-state plasma. Transfusion. 2013;53(3):579-90.

Plasma Products & Utilization

Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma

Matijevic, Nena PharmD, PhD; Wang, Yao-Wei MD; Cotton, Bryan A. MD, MPH; Hartwell, Elizabeth MD; Barbeau, James M. MD; Wade, Charles E. PhD; Holcomb, John B. MD

Journal of Trauma and Acute Care Surgery: January 2013 - Volume 74 - Issue 1 - p 84–91
doi: 10.1097/TA.0b013e3182788e32

Plasma Products & Utilization

- Ten FFP and 10 LQP single-donor units, matched by sex and blood group, were analyzed.
- FFP was thawed and kept refrigerated for 5 days and LQP for 26 days.
- Plasma samples were evaluated at Days 0 and 5 for thawed plasma (TP) and 0, 5, 10, 20, and 26 for LQP.
- Evaluation through thrombelastography, thrombogram, platelet counts, platelet microparticles, clotting factors, and natural coagulation inhibitors.

Matijevic et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg. 2013;74(1):84-90.

Plasma Products & Utilization

- Study Conclusion:

- ✓ The hemostatic profiles of LQP were better than TP.

- ✓ Never-frozen plasma can be considered for use in trauma patients requiring immediate plasma resuscitation.

Matijevic et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg. 2013;74(1):84-90.

Plasma Products & Utilization

In the US:

- FFP and FP24 have near-identical indications, and both are contraindicated if a coagulopathy can be corrected more effectively with a specific therapy, such as vitamin K or other specific coagulation factor concentrate.

- FP24 is not indicated for the replacement of labile coagulation factors, such as Factor FV and FVIII.

Matijevic et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg. 2013;74(1):84-90.

Plasma Products & Utilization

- The recommended indications for thawed plasma are restricted to management of preoperative or bleeding patients, massive transfusions, and rapid reversal of warfarin therapy.

- The AABB, the American Red Cross, America's Blood Centers, and the Armed Services Blood Program recommend LP solely for massive transfusions in patients with life-threatening hemorrhages.

Matijevic et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg. 2013;74(1):84-90.

Plasma Products & Utilization

- Group A plasma in lieu of AB plasma as “universal donor” plasma takes advantage of a calculation showing 87% compatibility when un-typed recipients receive group A plasma.
- Only group B and AB patients would receive incompatible plasma albeit with a high likelihood of low titer anti-A.
- In studies at the Mayo Clinic, the median anti-B titer was 1:16; 92% of donors had titers of 1:64 or less.
- The Mayo Clinic implemented group A thawed plasma for emergency transfusions in 2008.

Matijevic et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg. 2013;74(1):84-90.

TRANSFUSION

HOW DO I...?

How we provide thawed plasma for trauma patients

James R. Stubbs ✉, Martin D. Zielinski, Kathleen S. Berns, Karafa S. Badjie, Craig D. Tauscher, Scott A. Hammel, Scott P. Zietlow, Donald Jenkins

First published: 27 May 2015 | https://doi.org/10.1111/trf.13156 | Cited by:5

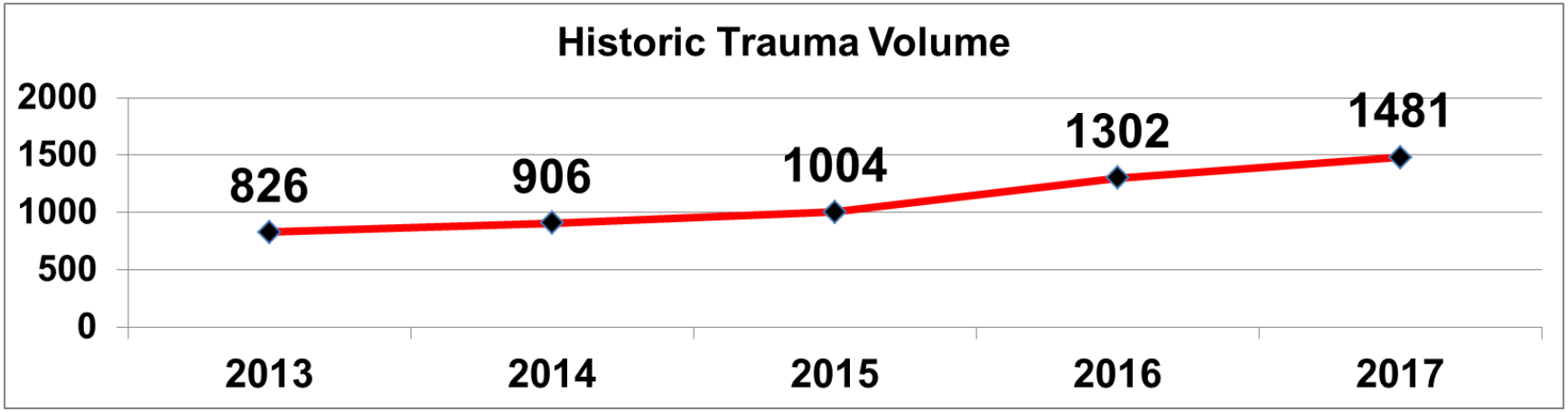
Plasma Products & Utilization

- They report a significant reduction in AB plasma use with no significant difference in adverse reactions in patients receiving incompatible group A plasma as a “universal donor” product as observed, similarly, in the PROPPR trial.

- Among the level I trauma centers surveyed in 2015, 88% keep thawed group A plasma available and 69% use group A plasma for trauma patients for whom blood type information is not available.

Stubbs et al. How we provide thawed plasma for trauma patients. Transfusion. 2015;55(8):1830-7.

Our Experience at TMC



Our trauma numbers have been steadily increasing in the past three years.

A 40% increase in our trauma numbers from 2013 to 2017 has been documented.

Trauma/ MTP Volume

Year	Number of MTPs >10 Units	Death within 12-24 hours	Rotem ordered	RBC:plasma ratio
2014/2015	18	8	N/A	3:1
2016	30	7	N/A	1.5:1
2017	27	7	7	1.39:1

Our Experience at TMC

- Numbers for 2014, and 2015 showed that 18 MTPs were documented requiring more than 10 units of products.
- 8/18 expired within 12/24 hours of protocol initiation.
- Liquid plasma was introduced in spring/summer of 2016.

Our Experience at TMC

- 61 massive transfusion protocols were initiated in 2017.
- 27 out of 61 cases required more than 10 units of products combined.
- Death within 12/24 hours of the protocol initiation was documented in 9/61 patients.

Our Experience at TMC

- With the help of liquid plasma, our Emergency room ED pyxis contains four units of O negative, 4 units of O positive, and 4 units of liquid plasma at all times.
- Units are readily available for trauma use only.
- This has helped ensure and facilitate rapid transfusion once deemed necessary.

Ratios or RBC and plasma transfusion utilized from ER pyxis/Blood Bank

3	Month	# MTP Called	RBC TX ED Fridge	RBC TX TOTAL	Plasma TX ED Fridge	Plasma TX TOTAL	Platelet TX	Cryo TX
4	Jun 2017	5	5	16	2	10	3	0
5	Jul 2017	6	10	41	1	23	3	2
6	Aug 2017	12	15	68	4	47	10	2
7	Sep 2017	8	13	30	8	27	6	1
8	Oct 2017	3	4	9	4	5	1	1
9	Nov 2017	7	10	35	2	26	7	2
10	Dec 2017	9	11	42	4	32	7	5
11	Jan 2018	11	15	43	1	32	10	4
12	Feb 2018	4	6	25	0	21	4	1
13	Mar 2018	12	18	106	8	89	18	1

Changes in MT Protocol Post Liquid Plasma Introduction

Pre liquid plasma	Post liquid plasma
2 thawed AB plasma units	4 units of liquid plasma immediately available with 4 O neg, and 4 O pos in the ED
PRBCs available in BB immediately	All male patients will receive O pos PRBC units
Additional plasma units available as soon as thawed (30 minutes)	Additional plasma and PRBC units immediately available (within 5 minutes packed for the runner)
Platelets ordered from community blood center as soon as MTP initiated	One platelet unit available in the Blood Bank at all times with the ordering of additional units upon receiving the notification of the MTP

Our Experience at TMC

- Observations:

- ✓ With liquid plasma availability our (1:1:1) ratio is always maintained from blood bank stand point.

- ✓ Overall survival within 12 hours has improved comparing the years 2014/2015 and 2016/2017.

THANK YOU