Improved survival associated with pre-hospital blood product transfusion:

During medical evacuation of combat casualties in Afghanistan

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- There are no conflicts of interest to disclose.

Pre-hospital Transfusion (PHT)

Background

The existing literature offers…

1. Conflicting findings

2. Poor quality evidence

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OPEN

Review Article

PREHOSPITAL BLOOD PRODUCT RESUSCITATION FOR TRAUMA: A SYSTEMATIC REVIEW

Iain M. Smith,*†‡ Robert H. James,§‖¶ Janine Dretzke,** and Mark J. Midwinter*†

- 37 unique studies identified, 1 prospective, 0 RCTs, 10 excluded for ambiguities
- Significant heterogeneity precluded a valid summary relative risk (RR) from meta-analysis
- 25/27 studies rated very low quality
- **No survival benefit identified**

Three Major Methodologic Flaws

noted in systematic review by Smith et al

1. **Study groups not equivalent, bias/confounding**
   a. Indications for PHT (bleeding severity)
   b. Interventions other than PHT (pre-post designs)
   c. Time (from injury to start of PHT, post-PHT survival time)
   d. Misclassification of PHT (transported from scene vs. transferred)

2. **Sample sizes too small, too few patients at high risk of hemorrhage-related mortality**

3. **Key data often missing**

Our MEDEVAC PHT Study

Methods

Designed to overcome flaws in previous studies:

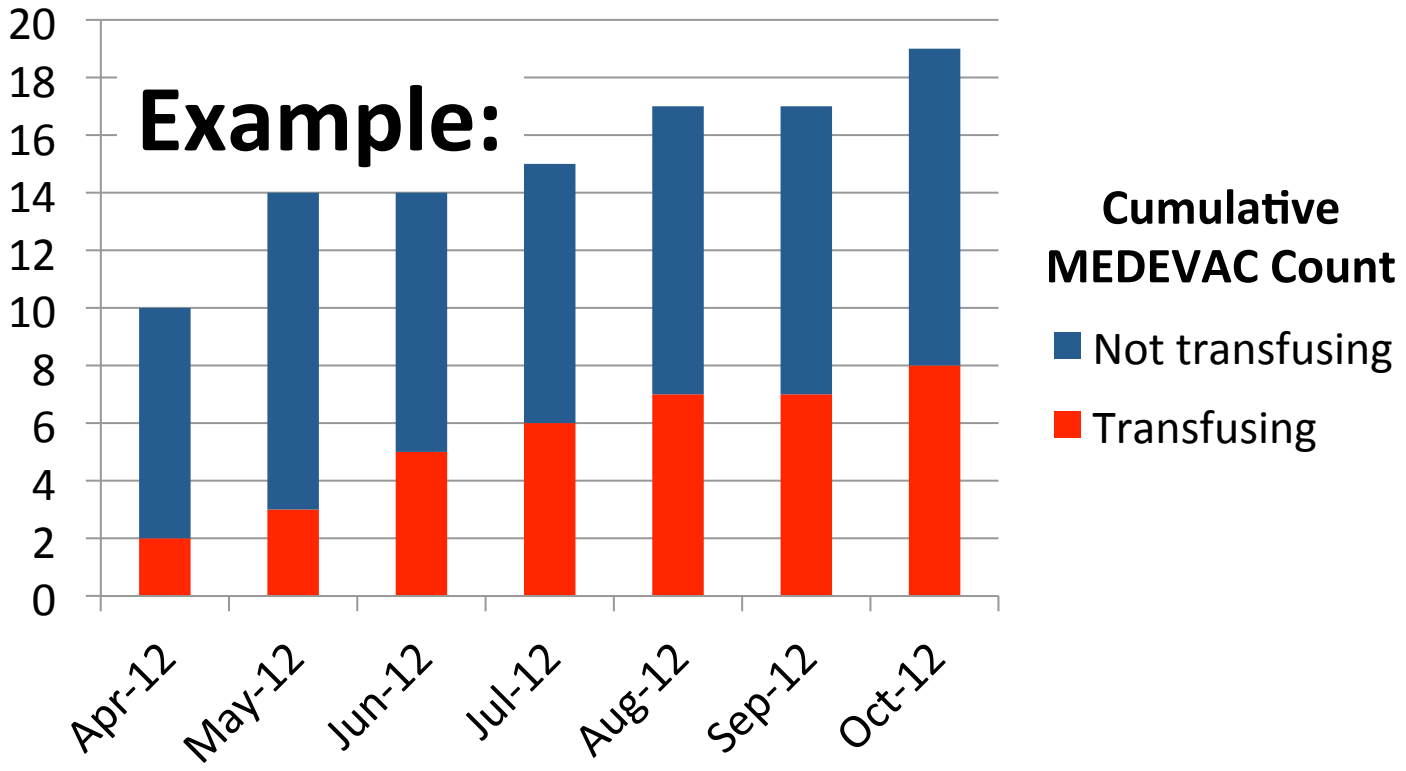
- ✓ Minimized bias & confounding
- ✓ Assembled a large sample of high-risk patients
- ✓ Tracked down missing data

Approved as an Exempt Performance Improvement Initiative by the DoD Joint Trauma System

Study Population: US military casualties in Afghanistan from April 1, 2012 to August 7, 2015

Study Design: Retrospective comparing concurrent cohorts

Gradual expansion of transfusion capability to different MEDEVACs



MEDEVAC PHT Study Data Resources

- DoD Trauma Registry
- Pre-hospital Database
- Hospital Records
- Armed Forces Medical Examiner
- Original paper-based records

MEDEVAC PHT Retrospective Study Flow Diagram

502 potential study candidates met 3 criteria:

1) U.S. military casualty in Afghanistan April 1, 2012 - August 7, 2015
2) Evacuated alive from the point of injury by MEDEVAC helicopter
3) Documented one of the established indications for PHT:
   a) Multiple traumatic amputations, at least one above knee or elbow
   b) Pre-hospital heart rate >120 beats/minute or systolic blood pressure <90 mmHg

55 PHT recipients were stratified based on 5 factors:

1) Mechanism of injury (gunshot vs. explosion)
2) Positive indicator of hemorrhagic shock (Yes/No)
3) Traumatic limb amputations
   a) 0=none
   b) 1=1 below knee/elbow
   c) 2=2 or more below knee/elbow or 1 above knee/elbow but below hip
   d) 3=2 or more above knee/elbow
4) Maximum severity of head injury by Abbreviated Injury Severity (AIS) score (0-1 vs. 2 vs. ≥3)
5) Significant torso hemorrhage by AIS score (Yes/No)

447 non-recipients were group-matched to recipients

=

345 matching non-recipients

102 unmatched non-recipients.

Because the PHT capability of non-recipients' transport teams was undocumented,

we chose matching factors and other covariates that transport teams likely observed

to better balance the two study groups

and statistically adjust our survival analyses.

MEDEVAC PHT Study

Results

Primary Hypothesis:

Pre-hospital transfusion is associated with improved survival from hemorrhagic shock.

MEDEVAC PHT Study
Unadjusted Mortality Differences

Mortality Follow-up Period	PHT-Recipients (n=55)	All non-recipients (n=447)	Unadjusted *P* values	Matched non-recipients (n=345)	Unadjusted *P* values
Death within 24 hours of MEDEVAC rescue (%)	3 (5%)	85 (19%)	0.013*	69 (20%)	0.007*
Death within 30 days of MEDEVAC rescue (%)	6 (11%)	102 (23%)	0.043*	78 (23%)	0.050

MEDEVAC PHT Study: Group-Matching Factors

Injury Characteristics	PHT-Recipients (n=55)	All non-recipients (n=447)	Unadjusted *P* values	Matched non-recipients (n=345)	Unadjusted *P* values
Mechanism of Injury			0.029*		0.051
Gunshot Wound (%)	9 (16%)	119 (26%)	-	101 (29%)	-
Explosives (%)	46 (84%)	303 (68%)	-	244 (71%)	-
Other (motor vehicle crash, falls, etc.) (%)	0 (0%)	25 (6%)	-	0 (0%)	-
Documented Pre-hospital Shock (SBP<90, HR>120, shock index >0.9) (%)	51 (93%)	405 (91%)	0.805	330 (96%)	0.313
Traumatic Limb Amputations			<0.0001*		<0.0001*
None (%)	15 (27%)	331 (74%)	-	251 (73%)	-
1 below knee/elbow (%)	12 (22%)	48 (11%)	-	38 (11%)	-
Bilateral, >1 below knee/elbow, or 1 above but below hip/shoulder (%)	12 (22%)	38 (8%)	-	31 (9%)	-
Bilateral or > 1 above knee/elbow (%)	16 (29%)	30 (7%)	-	25 (7%)	-
Significant Torso Hemorrhage by AIS Diagnostic Code (%)	31 (56%)	164 (37%)	0.005*	122 (35%)	0.004*
Maximum AIS Score for Head Injury Severity			0.602		0.620
0-1 (%)	26 (47%)	185 (41%)	-	163 (47%)	-
2 (%)	18 (33%)	176 (39%)	-	129 (37%)	-
≥3 (%)	11 (20%)	86 (19%)	-	53 (15%)	-

MEDEVAC PHT Study

Additional covariates adjusted along with matching factors in Cox proportional hazards survival analysis

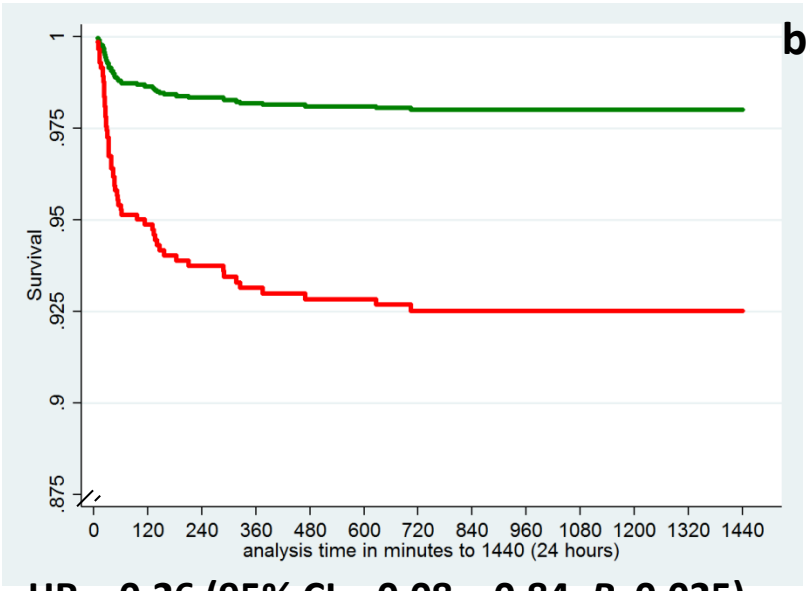
- Age
- Injury year
- Transport team's level of care
- Pre-hospital tourniquet used
- Minutes from injury occurrence to MEDEVAC rescue

We used the delayed entry approach to appropriately adjust for immortal time bias given recipients had to survive long enough for PHT to be initiated after MEDEVAC rescue.

Adjusted Cox Proportional Hazards Models

a.

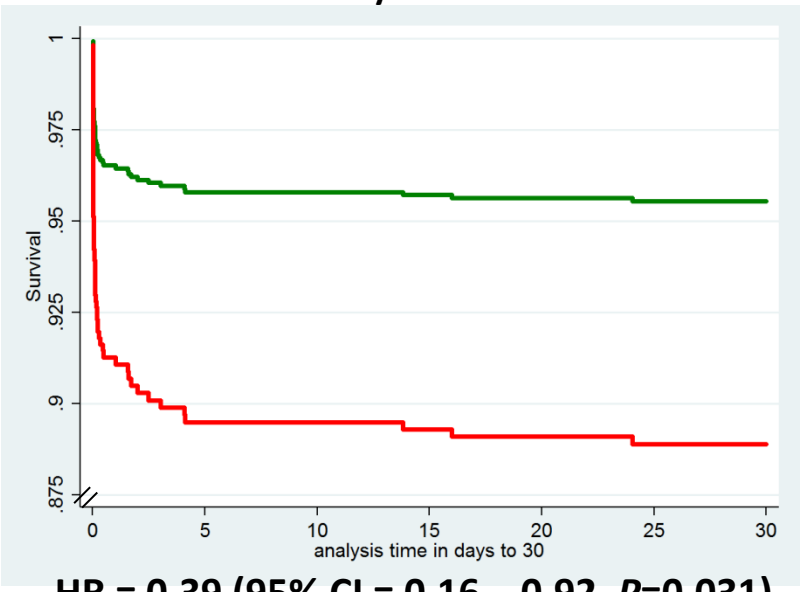
24 hour survival



HR = 0.26 (95% CI = 0.08 – 0.84, *P*=0.025)

b.

30 day survival



HR = 0.39 (95% CI = 0.16 – 0.92, *P*=0.031)

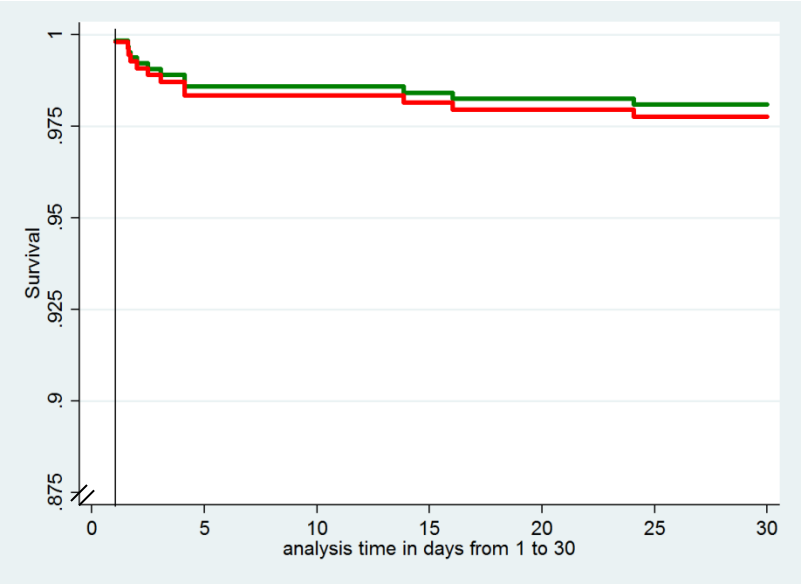
PHT recipients

Non-recipients

HR = 0.84 (95% CI = 0.18 – 4.00, *P*=0.831)

c.

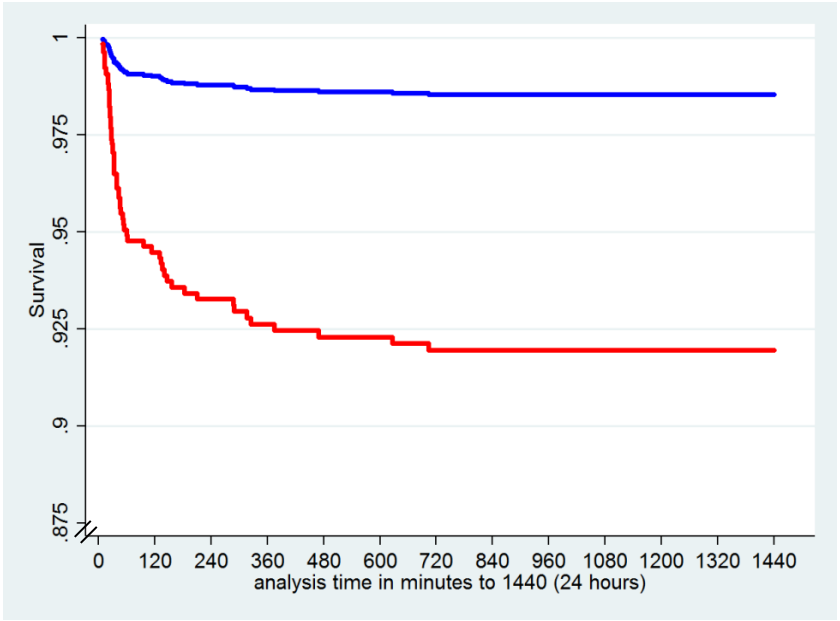
Conditional 30-day survival among 24-hour survivors



Early Transfusion, Pre- or In-Hospital

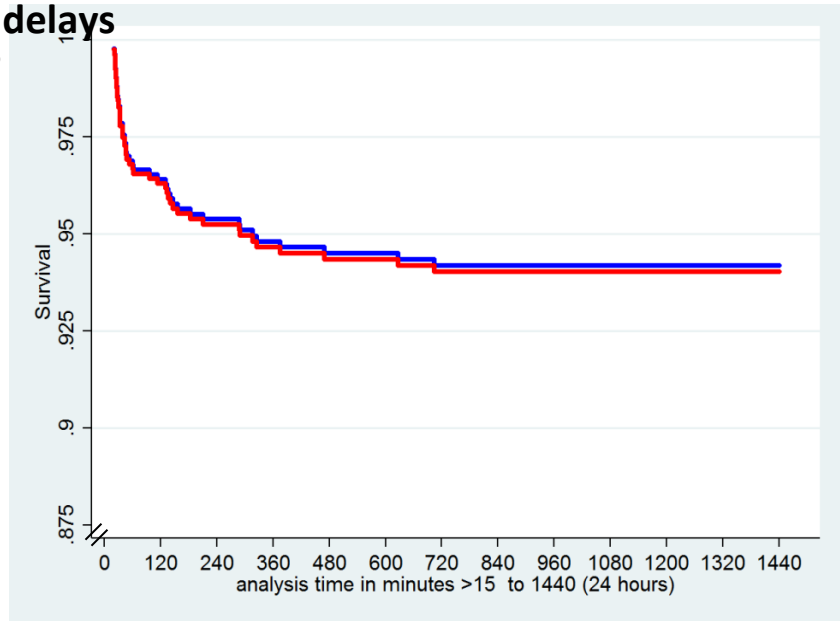
Adjusted Cox Proportional Hazards Models for 24 hour Survival

a. **Transfusion within 15* minutes vs. longer delays after MEDEVAC rescue from point of**



HR = 0.17 (95% CI = 0.04 – 0.73, *P*=0.017)

b. **Conditional survival among 16-minute survivors: Transfusion within 16-20 minutes vs. longer delays**



HR = 0.94 (95% CI = 0.41 – 2.17, *P*=0.887)

Earlier transfusion

Delayed transfusion

*Within a median of 36 minutes after injury occurrence (IQR 27,46)

Post-treatment characteristics and secondary outcomes - Unadjusted

Post-treatment Characteristics and Outcomes	PHT-Recipients (n=55)	Non-Recipients (n=345)	Unadjusted P values
Injury Severity Score (ISS): Median (IQR)	29 (17, 36)	17 (9, 33)	0.001*
Maximum AIS Score: Median (IQR)	4 (3, 5)	3 (2,5)	<0.0001*
Received Tranexamic Acid [TXA] (%)	48 (87%)	122 (35%)	<0.0001*
MEDEVAC transport time in Minutes: Median (IQR)	17 (15, 22)	(n=333) 16 (12, 23)	0.771
Minutes from injury occurrence to arrival at 1st surgical hospital: Median (IQR)	(n=54) 47.5 (37, 59)	(n=334) 45 (33, 60)	0.660
1st Surgical Hospital Level of Care Role 3 theater hospital vs. Role 2 resuscitative care (%)	48 (87%)	(n=304)† 164 (54%)	<0.0001
Documented shock (SBP<90, HR>120 or shock index >0.9) upon ED arrival (%)	42 (76%)	(n=299)† 162 (54%)	0.002*
ED base deficit: Median (IQR)	(n=52) -7 (-11, -4)	(n=249)† -3 (-7, -1)	<0.0001*
ED pH: Median (IQR)	(n=53) 7.28 (7.17, 7.38)	(n=257)† 7.36 (7.29, 7.42)	<0.003*
ED hemoglobin: Median (IQR)	(n=51) 12.4 (10.9, 13.7)	(n=261)† 14.3 (13.0, 15.3)	<0.0001*
ED INR: Median (IQR)	(n=34) 1.4 (1.2, 1.7)	(n=210)† 1.2 (1.0, 1.3)	0.006*
Total units of RBCs or whole blood within 24 hours of ED arrival: Median (IQR)	15 (8, 23)	(n=186)† 10 (4, 20)	0.001*
Total hospital days over the 30 days of follow-up among survivors at day 30 (IQR)‡	(n=48)‡ 30 (21, 30)	(n=265)‡ 18 (4, 30)	0.050

†Non-recipients who survived to the Emergency Department (ED) of the 1st surgical hospital (n=304)

‡Study patients who were discharged alive or survived at least through hospital day 30 (n=316, PHT-n=49, Non-Recipient-n=267)

Study Strengths

Capitalizing on unique and comprehensive research resources, this study was able to establish…

- At least a 4-fold sustained survival benefit from rapid transfusion (Number Needed to Treat ≤ 8).
- Timing is critical; benefit depends on starting transfusion within minutes of injury occurrence.
- Studies of advances in pre-hospital trauma care must include pre-hospital and early deaths.

Right Patient, Right Place, Right Time, Right Care

MEDEVAC PHT Study's Limitations

- A retrospective cohort design cannot overcome unmeasured, potentially important confounding (e.g., contra-indications for pre-hospital transfusion).

- Missing data values, especially for pre-hospital patient characteristics, diagnostic assessments, and intervention timing, remain a challenge.

MEDEVAC PHT Study

Conclusions…

our findings

1. Support blood product transfusion as far forward as possible
2. May help resolve conflicting findings and inform the design of future studies

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Questions