Critical Review Form
Therapy

PGY-3

Shackelford SA, Del Junco DJ, Powell-Dunford N, et al. Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival. JAMA. 2017 Oct 24;318(16):1581-1591.

Objectives: **"to evaluate US military experience with prehospital blood product transfusion on MEDEVAC aircraft in Afghanistan, directly addressing the deficiencies in the literature." (p. 1582).**

Methods: **This retrospective observational study was conducted by reviewing the records of casualties in Afghanistan undergoing MEDEVAC rescue between April 1, 2012 and August 7, 2015. Members of the US military with at least one established criterion for prehospital transfusion (1 or more limb amputation with at least 1 located above the knee or elbow, or shock defined as SBP < 90 mmHg or HR > 120) who survived at least until MEDEVAC rescue were eligible for inclusion. The exposures of interest were initiation of prehospital transfusion of blood products (RBCs or plasma) and minutes from MEDEVAC rescue to first blood product transfusion.**

The primary outcomes were 24-hour and 30-day survival. Secondary outcomes included 3-day survival in those who survived the first 24 hours, and prevalence of shock (SBP < 90, HR > 120, or a shock index > 0.9) at hospital admission. As this was a non-randomized study, patients were balanced between groups using frequency matching based on 5 factors: 1) mechanism of injury (gunshot vs. explosion); 2) presence of prehospital shock; 3) type and severity of limb amputations; 4) hemorrhagic torso injury; and 5) severity of head injury. Patients who received transfusion were classified into 26 strata and those did not receive prehospital transfusion were matched to each stratum, such that the ratio of recipients to nonrecipients varied across strata. Using additional confounders (age, minutes from injury to MEDEVAC rescue, year in which injury occurred, transport team, and tourniquet use), regression modeling was employed to further balance the study groups.

During the study period, there were 502 casualties meeting inclusion criteria; the median age was 25 years and 98% were male. Of these, 55 received a prehospital blood transfusion and 447 did not. Of those patients who did not receive a transfusion, 345 were frequency matched to prehospital transfusion recipients.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. This was an observational study with data obtained from the Department of Defense trauma registry, the prehospital trauma registry, and the Armed Forces Medical Examiner System Database. The decision to transfuse blood products in the prehospital setting was made by the clinicians caring for the patient. Frequency matching and regression analysis were employed in an attempt to control for known baseline confounders.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	N/A
3.	Were patients analyzed in the groups to which they were randomized?	N/A. This was not a randomized trial. Instead, patients were analyzed according to whether or not they actually received a prehospital transfusion.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Prior to frequency matching, patients who received prehospital transfusion were more likely to have suffered an explosive injury (84% vs. 68%), had higher rates of multiple or proximal amputations (22% vs. 8%), higher rates of multiple proximal amputations (29% vs. 7%), higher rates of hemorrhagic torso injury (56% vs. 37%), and much higher rates of tourniquet use (84% vs. 45%). These imbalances remained significant following the use of frequency matching. Similar rates of prehospital shock were seen between the unmatched groups and matched groups.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes, though this is likely of little significance. This was not a randomized study and was not blinded, so patients would theoretically know if they were being given a blood transfusion. It is unlikely, however, that this would contribute to any performance bias on the part of the patients.
2.	Were clinicians aware of group	Yes. Again, the study was not blinded. However

	allocation?	given the retrospective nature of the study, clinicians would not have known that they were being studied and hence should not have been guilty of performance bias.
3.	Were outcome assessors aware of group allocation?	Uncertain. The authors make no mention of blinding outcome assessors and chart reviewers. Given that the outcomes were very objective (i.e. death), observer bias should not have affected the outcomes.
4.	Was follow-up complete?	No. One transfusion recipient and 13 nonrecipients were excluded due to missing data.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• Prior to matching, death at 24 hours occurred in 5% of transfusion recipients and 19% of nonrecipients (ARR -14%, 95% CI -21% to -6%). Death at 30 days occurred in 11% of transfusion recipients and 23% of nonrecipients (ARR -12%, 95% CI -21% to -2%). • Following frequency matching, death at 24 hours occurred in 5% of transfusion recipients and 20% of nonrecipients (ARR -15%, 95% CI -22% to -7%). Death at 30 days occurred in 11% of transfusion recipients and 23% of nonrecipients (ARR -12%, 95% CI -21% to -2%). • In the adjusted survival analysis using the matched cohorts, prehospital transfusion was still associated with increased survival at both 24 hours (adjusted HR 0.26, 95% CI 0.08-0.82) and 30 days (HR 0.39, 95% CI 0.16-0.92). • The adjusted survival analysis looking at survival to 30 days among those who did not die in the first 24 hours revealed no association between prehospital transfusion and survival (HR 0.84, 95% CI 0.18-4.00).
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	No. This was a cohort of members of the military suffering wartime injury, including high-velocity gunshot wounds and explosive injuries. A large number of subjects (73% of prehospital transfusion patients and 26% of nonrecipients) suffered a traumatic amputation, which is much more rare among those patients seen in our ED with significant

		hemorrhage from trauma. In addition, MEDEVAC transport is quite different from EMS transport. It is quite likely that the effects of early transfusion on survival in these patients, under these circumstances, would be quite different than the effects on patients in our EMS system and institution (external validity).
2.	Were all clinically important outcomes considered?	No. The authors considered the most important outcomes (i.e. 24-hour and 30-day survival), but did not consider several other important outcomes, such as the amount of blood product required, transfusion-related adverse events (e.g. anaphylaxis, TRALI), ICU LOS, time on the ventilator, and functional outcomes.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This study was understandably not randomized, but the observational nature of the study makes it very difficult to draw any firm conclusions. Despite the use of frequency matching and adjustments for known confounders, the two groups being compared in this study (prehospital transfusion recipients and nonrecipients) are clearly very different from one another. Selection bias may have had a more profound effect on who did and did not receive prehospital blood than any attempts to adjust for baseline risk could account for. Additionally, the study setting, patient population, and mechanisms of injury are so vastly different from what is encountered in our environment that it would be impossible to generalize the results to a non-military setting.

Limitations:

1. **This was not a randomized controlled trial. The decision to administer blood products may have been influenced by confounding factors, but may also have been related to the capability of transport teams, as "the capability to transfuse was not known with certainty for transport teams serving nonrecipients." (p. 1582). Prehospital transfusion recipients were more likely to be transported by the US Air Force Pararescue and the UK Medical Emergency Response Teams, which are equipped with higher levels of than the more common US Army MEDEVAC aircraft platforms.**

2. **Despite the use of frequency matching and adjustments for known confounders, the two groups being compared in this study (prehospital transfusion recipients and nonrecipients) are clearly very different from one another. Selection bias may have had a more profound effect on who did and did not receive prehospital blood than any attempts to adjust for baseline risk could account for.**

3. **The study setting, patient population, and mechanisms of injury are so vastly different from what is encountered in our environment that it would be impossible to generalize the results to a non-military setting (external validity).**

4. **Of the nonrecipients matched to recipients, 112 survived longer than 24 hours without any transfusion, casting doubt on their eligibility for prehospital transfusion.**

Bottom Line:

This military study conducted in Afghanistan suggests that prehospital administration of blood products in select trauma patients was associated with increased survival at 24 hours (adjusted HR 0.26, 95% CI 0.08-0.82) and 30 days (HR 0.39, 95% CI 0.16-0.92). This was a retrospective study limited by selection bias and by the fact that the ability of medevac teams to administer blood products in the nonrecipient cases. Despite the use of the statistical techniques to match patients based on prognostic factors, unknown confounders are still likely to have played a role in influencing the results. Unfortunately, given the nature of the injuries seen in this study, and differences between military evacuation transport and urban/rural EMS services, it would be difficult to apply these results to patients in our institution (external validity).