Critical Review Form
Therapy

PGY-4

Perel P, Clayton T, Altman DG, et al; PROGRESS Partnership. Red blood cell transfusion and mortality in trauma patients: risk-stratified analysis of an observational study. PLoS Med. 2014 Jun 17;11(6):e1001664.

Objectives: **"to evaluate the association of RBC transfusion with all-cause mortality at 28 days (or hospital discharge) according to predicted risk of death at hospital admission. The secondary objective was to evaluate the association of RBC transfusion with fatal and non-fatal vascular occlusive events." (p. 2)**

Methods: **This retrospective observational study was conducted using data previously collected in the CRASH-2 trial. In this study, trauma patients from 274 hospitals in 40 countries with, or at risk of, significant bleeding within 8 hours of the traumatic event were randomized to receive tranexamic acid or placebo. The current study used the collected to data to compare outcomes between those who received at least one unit of RBCs and those who did not receive any RBC transfusion. The primary outcome of interest was all-cause mortality at 28 days. The secondary outcome was fatal or non-fatal vascular occlusive events (myocardiacl infarction, cerebrovascular accident, DVT, and pulmonary embolism).**

In order to adjust for baseline risk of death, a previously derived model (Perel 2010) was used to risk stratify patients in four prespecified strata : <6%, 6-20%, 21-50%, and >50% risk of death. This model used several predictors to assess baseline risk, which were Glasgow Coma Scale (GCS), age, heart rate (HR), systolic blood pressure (SBP), time since injury, type of injury (blunt vs. penetrating), and geographical region. Odds ratios were then calculated comparing RBC transfusion to no RBC transfusion for each risk stratum. The authors also made these comparisons separately for each of four geographical regions, and performed a sensitivity analysis which excluded patients who died on day "0" in order to account for potential survival bias.

Out of a total 20,127 patients enrolled in CRASH-2, 10,227 (50.8%) received a RBC transfusion. Factors associated with increased likelihood of RBC transfusion were:

1. **Enrollment in a high-income country**
2. **Arrival at the hospital > 3 hours after injury**
3. **Lower SBP**
4. **Lower GCS**
5. **Higher HR**
6. **Blunt injury**

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. While this data came from a randomized, controlled trial, the current analysis compares outcomes in patients receiving RBC transfusion to those who did not receive transfusion. Decision to transfuse patients was not random, but was made at the discretion of the treating clinicians at the various enrollment sites.
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?	No. This was a retrospective look at prospectively collected data from a randomized, controlled trial. The intervention being assessed (transfusion of RBCs) was not a part of the randomization process. Patients were evaluated based on whether or not they received a RBC transfusion.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. As noted by the authors, patients who received a blood transfusion were more likely to be enrolled in a high-income country, had lower SBP and GCS, had higher HR, and were more likely to be suffering from a blunt mechanism of injury. Overall, it is not surprising that these patients were at higher risk not only of all-cause death, but of developing vascular occlusive events during their subsequent hospitalization (selection bias). While the authors did further risk stratify patients (based, unfortunately, on a predictive model that was derived from this very cohort) they do not provide a further breakdown of other potential confounding factors between the two groups within these strata. It is therefore difficult to know if there were further baseline differences between the groups within the strata (which there likely were) that would have affected the risk of death or vasoocclusive events.
B.	**Did experimental and control groups retain a similar prognosis after the study**	

	started?	
1.	Were patients aware of group allocation?	Yes. Blinding to transfusion was not employed as this was not the intervention being studied in the initial study.
2.	Were clinicians aware of group allocation?	Yes. Blinding to transfusion was not employed as this was not the intervention being studied in the initial study.
3.	Were outcome assessors aware of group allocation?	Yes. Not only were clinicians who cared for the patient and made diagnoses (including diagnoses of vascular occlusive events) not blinded to transfusion status, but the authors do not mention any blinding of investigators who assigned the specific cause of death among patients (observer bias).
4.	Was follow-up complete?	Mostly yes. Of 20211 patients randomized, 4 withdrew consent (3 in the TXA group, 1 in the placebo group). A further 80 patients had no follow-up data (33 in the TXA group, 47 in the placebo group. Follow-up data was therefore available for 20127 (99.6%) of the enrolled patients.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• All-cause unadjusted mortality was more likely among patients receiving RBC transfusion: 19.8% vs. 10.7%, OR 2.06 (95% CI 1.91-2.24).
		  ○ Deaths from bleeding, multi-organ failure, myocardial infarction, and all other causes were more frequent among those who received a RBC transfusion.
		• Vascular occlusive events were also more common among those who received a transfusion compared to nonrecipients: 2.6% vs. 1.0%, OR 2.58 (95% CI 2.05-3.24).
		• Among patients at baseline predicted risk of death of <6% and 6-20%, all-cause mortality was higher among patients who received a RBC transfusion. Among patients at 21-50% predicted risk of death, there was no different in mortality between the groups. Among patients at >50% predicted risk of death, mortality was higher among patients who did NOT receive a transfusion.
		  ○ 6% risk: 6.4% vs. 1.2%, OR 5.40 (95% CI 4.08-7.13)
		  ○ 6-20%: 15.1% vs. 7.2%, OR 2.31 (95% CI 1.96-2.73)
		  ○ 21-50%: 31.6% vs. 33.5%, OR 0.92 (95% CI 0.78-1.08)
		  ○ >50%: 59% vs. 70.8%, OR 0.59 (95% CI

		0.47-0.74) ○ Adjustment by propensity score did not have any significant effect on mortality differences between groups at any risk stratum. Similarly, adjustment for use of platelets, FFP, and cryoprecipitate and for country did not result in any significant change in outcomes. ○ Excluding patients who died on day 0 did not have any significant effect on mortality differences, except for patients with a predicted risk >50%, for whom a slightly higher mortality among nonrecipients was observed, but this time did not achieve statistical significance (OR 0.80, 95% .062-1.02). • Vascular occlusive events were more common among patients in all 4 predicted mortality risk groups, with the caveat that statistical significance was not achieved in the >50% risk group. ○ 6% risk: 1.5% vs. 0.3%, OR 4.92 (95% CI 2.80-8.65) ○ 6-20%: 2.1% vs. 1.3%, OR 1.66 (95% CI 1.13-2.46) ○ 21-50%: 4.8% vs. 2.7%, OR 1.80 (95% CI 1.16-2.80) ○ >50%: 5.3% vs. 3.4%, OR 1.58 (95% Ci 0.93-2.68)
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. Of the total cohort, only 2711 (13.5%) were enrolled in Europe or North America, none of which came from the US (external validity); the vast majority of patients were enrolled in Asia, Africa, and Central or South America. Differences in practice pattern (i.e. more sophisticated resuscitation measures) clearly had a significant effect on mortality and blood product administration. The availability of vascular interventional radiology (VIR) alone as a means to stop bleeding following trauma would have significant impact on the use of transfusion and on mortality.
2.	Were all clinically important outcomes considered?	No. In terms of outcomes, the authors assessed all-cause mortality, mortality due to a variety of individual causes, and vascular occlusive events. They

		did not evaluate other significant adverse events due to blood product transfusion (anaphylaxis, TRALI, ARDS), length of stay, cost, or functional outcomes.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study suggests that patients at low baseline risk of death had worse outcomes if they were administered RBCs, while patients at high risk had improved outcomes, these results do not necessarily suggest an opportunity to change management. In addition to several methodological limitations (including the very high risk of selection bias, the use of a prediction rule that was derived in this very patient population, and the risk of external validity), this study does not prove that patients who were administered RBCs did not truly need to be given blood products. While this study suggests an associated between transfusion and mortality in high and low-risk patients, it does not prove that there is any actual causation. For now, the decision to administer RBCs following significant trauma should follow previous practice patterns.

Limitations:

1. **The initial study's inclusion criteria were very subjective, limited to patients felt to be at high risk of hemorrhage. Despite this criterion, only about half of the enrolled patients actually received any blood products, and only 5% had bleeding as their cause of death.**

2. **This study used previously collected data in a retrospective fashion to look at the effect of a therapy (RBC transfusion) not initially being studied. As a result of the nature of the initial study and the therapy being evaluated here, there is a very high risk of selection bias, which can only partly be attenuated by the statistical methods used here. Other important clinical factors, such as injury severity score, should have been included in their attempts to control for baseline risk of death.**

3. **No patients were enrolled in the US, and only 13.5% were enrolled in Europe or North America (external validity).**

4. **The predictive model used to risk stratify patients into strata of baseline mortality risk was derived from this very cohort, and has only been validated retrospectively in a single cohort of additional patients.**

Bottom Line:

This retrospective analysis of data from the CRASH-2 trial suggests that patients at low baseline risk of death who receive blood transfusion are at higher risk of death than nonrecipients, while patients at high risk of death who receive blood are at

lower risk than nonrecipients. Unfortunately, this is based on a retrospective analysis and hence is likely influenced by selection bias, despite attempts to control for certain confounders. This study demonstrates an association between blood transfusion and mortality, but does not prove causation. As a result, it would be difficult to recommend any changes in practice based on the results.