Critical Review Form
Therapy

Holcomb JB, Tilley BC, Baraniuk S, et al; PROPPR Study Group. 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. JAMA. 2015 Feb 3;313(5):471-82.

Objectives: **"to address the effectiveness and safety of a 1:1:1 transfusion ratio compared with a 1:1:2 transfusion ratio in patients with trauma who were predicted to receive a massive transfusion." (p. 472)**

Methods: **This pragmatic, multicenter, randomized controlled trial was conducted at 12 level 1 trauma centers in North America between August 3, 2012 and December 2, 2013. Patients aged 15 years or older brought directly from the trauma scene with a severe injury meeting criteria for the highest level trauma activation were screened for enrollment. Patients receiving at least 1 unit of any blood product prior to arrival or within one hour of arrival and predicted to require a massive transfusion (≥ 10 U or PRBCs within 24 hours) were eligible for inclusion. Patients predicted to expire within one hour of arrival, those requiring thoracotomy prior to receiving blood products, pregnant woman, patients with > 20% body surface area burns or inhalation injury, patients receiving > 5 minutes of consecutive chest compressions, and patients with a do not resuscitate order were excluded.**

Patients were randomized to receive either a 1:1:1 ratio of plasma, platelets, and PRBCs or a 1:1:2 ratio. For those receiving a 1:1:1 ratio, boxes contained 6 U of plasma, 1 dose of platelets (a pool of 6 U on average), and 6 U of PRBCs. For the 1:1:2 ratio group, odd-numbered boxes contained 3 U of plasma, no platelets, and 6 U of PRBCs; even-numbered boxes contained 3 U of plasma, 1 dose of platelets, and 6 U of PRBCs. Transfusion in all patients continued as long as clinically indicated and all other interventions were at the discretion of the treating clinicians.

The primary outcomes were 24-hour and 30-day mortality. Secondary outcomes included time to hemostasis; number and type of blood products transfused (both until hemostasis achieved and from time of hemostasis to up to 24 hours postadmission); any of 23 predefined complications; hospital-, ICU-, and ventilator-free days up to 30 days; major surgical procedures; and functional status at discharge or 30 days (whichever came first).

Of a total 14313 highest-level trauma activations during the study period, 78% were screened and 680 patients were randomized (338 to the 1:1:1 group and 342 to the 1:1:2 group). Randomized blood products were transfused in 669 patients. The median injury severity score (ISS) was 26. The majority of patients were male (78% in the 1:1:1 group and 83% in the 1:1:2 group) and the median age was around 34.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized to receive either a 1:1:1 or 1:1:2 ratio of blood products using permuted blocks stratified by study site.
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?	Yes. "Treatment assignment labels, generated by the Houston Data Coordinating Center (HDCC), were kept in secure files at each clinical site's blood bank." (p. 5, Baruniak 2014).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. In the primary analysis, patients were analyzed according to the group to which they were randomized (intention to treat analysis). A secondary per protocol analysis was conducted in which patients who received blood products out of order were excluded.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, race, baseline vital signs, GCS score, mechanism of injury (blunt vs. penetrating), injury severity score, and baseline lab values.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes. Although no attempt was made to blind patients, these were critically ill patients undergoing multiple life-saving interventions and hence were likely not truly aware of group allocation. It is very unlikely that any performance bias on the part of patients would have affected outcomes.
2.	Were clinicians aware of group allocation?	Not entirely. While it was not entirely possible to blind clinicians to treatment group due to the nature of the intervention, the initial container of blood products was sealed in order to blind the treating physician during the early period of resuscitation.
3.	Were outcome assessors aware of group allocation?	No. For the primary outcomes, "death was adjudicated by a clinician blinded to group assignment and external to the trial site and 1 or more causes of death were assigned." (p. 473)

4.	Was follow-up complete?	Yes. Primary outcome data was available for 100% of patients at 24 hours and 99.4% of patients at 30 days.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• There was no statistically significant difference in all-cause mortality between the 1:1:1 group and the 1:1:2 group at 24 hours (12.7% vs. 17.0%; ARR -4.2%, 95% CI -9.6 to 1.1%) or at 30 days (22.4% vs. 26.1%; ARR -3.7%, 95% CI -10.2 to 2.7%).
		  ○ Excluding patients who were given blood products out of order (per protocol analysis), there was still no difference in mortality at 24 hours or 30 days.
		  ○ The predominant cause of death within 24 hours was exsanguination, which occurred less frequently in the 1:1:1 group than the 1:1:2 group (9.2% vs. 14.6%; ARR -5.4%, 95% CI -10.4 to 0.5%).
		• Hemostasis was achieved more frequently in the 1:1:1 group than the 1:1:2 group (86.1% vs. 78.1%, p = 0.006).
		• The 1:1:1 group and 1:2:1 groups received similar overall amounts of blood products during the intervention period (median 16 U vs. 15 U), but patients in the 1:1:1 group received fewer blood products in the post-intervention period (median 1 U vs. 2 U). Oddly, patients in the 1:1:1 group received more total blood products in the 24 hours following admission compared to the 1:1:2 group (median 25.5 U vs. 19 U).
		• There was no significant difference in ICU-, ventilator-, or hospital free days up to 30 days between the two groups.
		• There was no difference in any of 23 complications at 30 days.

2.	How precise was the estimate of the treatment effect?	See above. Unfortunately, despite a 4.2% difference in 24-hour mortality and 3.7% difference in 30-day mortality, this difference did not achieve statistical significance.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. This study was conducted at 12 level 1 trauma centers in North America, which would presumably see patients similar to those seen at our institution.

		Patients were fairly evenly split with regards to blunt vs. penetrating injury, suggesting a similar pattern of injury to what we see. The median ISS was 26, suggesting a high degree of polytrauma.
2.	Were all clinically important outcomes considered?	Yes. The authors considered several key outcomes, including survival (short-term and long-term), functional status, ICU-free days, and ventilator-free days, and hospital-free days. They did not assess cost, quality of life, or patient satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. There was a trend towards decreased mortality with the use of a 1:1:1 transfusion ratio, suggesting that this is not only safe (compared to a 1:1:2 ratio), but may actually result in improved outcomes.

Limitations:

1. **Unfortunately, despite a 4.2% difference in 24-hour mortality and 3.7% difference in 30-day mortality, this difference did not achieve statistical significance. This suggests the study lacked sufficient power to detect a potentially clinically meaningful difference in outcomes.**

2. **Due to logistical constraints, clinicians were not truly blinded to group allocation, resulting in the unlikely possibility of performance bias affecting the outcomes.**

3. **Only 78% of potentially eligible patients were screened for potential enrollment (selection bias). No attempt was detailed to compare these patients to those who were screened to ensure that there was no large, systematic difference.**

Bottom Line:

This multicenter, randomized, controlled trial comparing a 1:1:1 blood transfusion ratio to a 1:1:2 ratio for severe trauma requiring massive transfusion found a trend toward improved mortality at 24 hours (ARR -4.2%, 95% CI -9.6 to 1.1%) and 30 days (ARR -3.7%, 95% CI -10.2 to 2.7%), though these outcomes did not achieve statistical significance. No difference in ICU-, ventilator-, or hospital-free days was observed, and there was no difference in adverse events. This study suggests that a 1:1:1 ratio is at least as safe as a 1:1:2 ratio and may actually improve outcomes.