

In the last issue of this newsletter, I covered many of the basics of the massive transfusion protocol (MTP). In this issue, I'll cover some more advanced topics that many trauma centers may not have yet fully considered. And remember, the "science" of blood transfusion has evolved dramatically over the past decades, if not for centuries. You can be certain that many of these "facts" that we hold dear now will be shown to be incomplete or downright wrong in the very near future.

What Is The Ideal Blood Product Ratio?

Let's dive in with the ratio question. Back in the day, when a massively bleeding patient came in, we gave crystalloid. And frequently, a lot of crystalloid. The books said slam in two liters of saline or lactated Ringer's solution. It was believed that there was little downside to crystalloid. Consequently, quite a bit of it was given before we ever thought about blood products.

And there were no systems in place to standardize how blood was requested, what was sent, or how much was used. We generally started off with a bunch of packed red cells. Yes, every now and then we might remember to ask for some plasma, and even less commonly some platelets or cryoprecipitate. Ratios? We didn't really pay attention. In reality, there were probably four red cell packs to one unit of plasma, on average. And the ratio to platelets was so low it was hard to even measure!

INSIDE THIS ISSUE

- 1 **What Is The Ideal Blood Product Ratio?**
- 2 **TEG And Your MTP**
- 3 **MTP and TXA**
- 3 **The History Of Fractionated Blood Components**
- 4 **Use Of Whole Blood For Massive Transfusion**

TRAUMA MEETINGS

49TH ANNUAL WESTERN TRAUMA ASSOCIATION

LOCATION: WESTIN SNOWMASS RESORT, SNOWMASS, CO
MARCH 3-8, 2019

SPEAKING ENGAGEMENTS

TEXAS HEALTH 21ST ANNUAL TRAUMA SYMPOSIUM

LOCATION: OMNI FORT WORTH HOTEL, FORT WORTH, TX
APRIL 4, 2019

By now, we have plenty of data showing that this crystalloid-heavy resuscitation contributed to coagulopathy and poor outcomes. We've adopted a more balanced concept of resuscitation, which of course we call "**balanced resuscitation.**" What does this term mean? Basically, it's a combination of restricted crystalloid use, more optimized ratios of blood products, and some degree of permissive hypotension in select patients.

Before we dive more deeply into ratios, let's agree on the nomenclature. You may hear people talking about a 1:1 ratio, or 2:1:1, or even 1:1:2. Which product is which? Always read the paper or text carefully, as there is no real standard here. Typically, if only two numbers are specified, RBCs are first and plasma second. But when three are given, **you** must determine whether the red cells are first or last. Here are the most common configurations:

RBC : plasma : platelets

Plasma : platelets: RBC

Many papers have been written examining the ratio puzzle. Mortality, complications, renal or lung injury, deep venous thrombosis and pulmonary embolism, lengths of stay, transfusion reactions (of all types), and much more have all been investigated.

The most helpful literature covering administration ratios are systematic reviews. The main focus seems to be finding the magic ratio of red cells to everything else. The old-time higher ratios (1?:4) were generally considered to be inferior, so most research has

focused on comparing 1:1:1 to 1:1:2. Here are the main factoids, and all keep to the plasma:platelets:RBC format:

- There was **no discernible difference in 24-hour or 30-day mortality** between groups with ratios of 1:1:1 or 1:1:2
- Patients with a 1:1:1 ratio received significantly more platelets and plasma than the 1:1:2 patients
- Giving cryoprecipitate or fibrinogen concentrate early had no effect on mortality

Although systematic reviews try to make up for shortcomings of individual studies, they introduce their own problems. However, they seem to **indicate that the “magic” ratio lies between 1:1:1 and 1:1:2**. Most centers strive for the former, but due to many reasons (e.g. no thawed plasma, delivery issues) realistically try to stay under the latter.

Bottom line: Think about the logistics in your own trauma center, and design your massive transfusion protocol so that you can maintain a ratio somewhere between 1:1:1 and 1:1:2.

Reference: Optimal Dose, Timing and Ratio of Blood Products in Massive Transfusion: Results from a Systematic Review. Transfus Med Rev 32(1):6-15, 2018.

TEG And Your MTP

Thromboelastography (TEG) and its fraternal twin rotational thromboelastometry (ROTEM) are relatively new toys in the trauma community. They allow for (somewhat) rapid assessment of clotting function, and allow the trauma professional to surmise what products might push abnormal clotting characteristics back toward normal.

Many trauma centers already own this technology due to use by non-trauma services. But there have been several research presentations on the topic over the last five years, and many centers are clamoring to buy these units for use in their MTP.

But new technology is usually expensive, and isn't always all it's cracked up to be. TEG and ROTEM require a (often-times) new machine and a never-ending supply of disposable cartridges for use, like your ink jet printer. Some hospitals are reluctant to provide the funds unless there is a compelling clinical need.

Surgeons at the University of Cincinnati compared the use of TEG with good, old-fashioned point-of-care

(POC) INR testing in a series of major trauma patients seen at their Level I center.

Here are the factoids:

- This was a retrospective review of 628 major trauma patients who **received both TEG and POC INR testing using** an iSTAT device over a 1.5 year period
- **Median ISS was 13**, and there were many sick patients (20% in shock, 21% received blood, 11% died)
- **INR correlated with all TEG values**, with better correlation in patients in shock
- Both INR and TEG correlated well with treatment with blood, plasma, and cryoprecipitate
- Processing time was **2 minutes for POC INR vs about 30 minutes for TEG**
- Charges for POC INR were **\$22,000 vs \$397,000** for TEG(!)

Bottom line: Point of care INR testing and TEG both correlated well with the need for blood products in major trauma patients. But POC INR is much cheaper and faster. Granted, the TEG gurus will say that you can tailor the products administered to meet the exact needs of the patient. But in all my travels, I have never visited a center that has fully, effectively, and contemporaneously incorporated TEG or ROTEM into their massive transfusion protocol from start to finish.

The area where TEG and ROTEM are most helpful are in the “mop up” phase at the tail end of the MTP. These tools allow trauma professionals to determine exactly which products are needed to normalize parameters, and they frequently diverge from the 1:1:1 to 1:1:2 ratios at that point.

If you don't have one of these toys yet, make sure that you have a very good clinical reason to do so. If you do, think very carefully about how you can meaningfully incorporate it in the massive transfusion process and write it into your protocol.

Reference: All the bang without the bucks: defining essential point-of-care testing for traumatic coagulopathy. J Trauma 79(1):117-124, 2015.

MTP And TXA

Tranexamic acid has been in use for decades, just not for trauma. **The CRASH-2 trial** was a massive multi-country study showed that there was a slight mortality reduction from 16% to 14.5% in trauma patients who

had or were at risk for “significant hemorrhage.” Moreover, there was no difference in vascular occlusive events, blood product transfusions, or need for surgery. Sounds great, right?

The MATTERS trial was initiated by the US military and tried to address some of the perceived shortcomings of CRASH-2 and found an absolute mortality reduction of 6.7%. But it also showed DVT rates that were 12x higher and PE rates 9x higher when this drug was given.

Since those two studies, a significant number of critiques have been published, as well as some additional research. Unfortunately, this has only served to cloud the picture. **TXA is very inexpensive and readily available**, so there has been a significant move to adopt both in the trauma center, as well as during pre-hospital care prior to arrival.

The trauma group at Denver Health published a study of 232 patients with a 20% mortality rate from their injuries. They identified three subsets of patients based on their fibrinolytic response upon presentation to the hospital: physiologic fibrinolysis (49% of patients), hyperfibrinolysis (28%), and fibrinolytic shutdown (23%). They found that **mortality significantly increased in those receiving TXA who were physiologic or hyperfibrinolytic, but unchanged in those in shutdown**. They cautioned that giving this drug before the patient’s fibrinolytic status was known could contribute to mortality.

Bottom line: So confusing! And most centers already include TXA in their massive transfusion protocol. Most have not seen unexpected mortality after giving the drug, so the jury is not in yet. Each trauma center should weigh the currently known pros and cons, and decide whether they are “believers” or not. Carefully review all mortalities and thrombotic complications after administration to see if there was any relation to the use of TXA.

References:

1. *Massive transfusion protocols and the use of tranexamic acid. Current Opinion Hematol 25(6):482-485, 2018.*
2. *Tranexamic Acid is Associated with Increased Mortality in Patients with Physiologic Fibrinolysis. J Surg Res 220:438-443, 2017.*
3. *CRASH-2 Study of Tranexamic Acid to Treat Bleeding in Trauma Patients: A Controversy Fueled by Science*

and Social Media. J Blood Transfus Article 874920, 2015.

The History Of Fractionated Blood Components

How is it that we are even debating the use of blood component therapy vs whole blood? Most living trauma professionals only remember a time when blood components have been infused based on which specific ones were needed.

Prior to about 1900, blood transfusion was a very iffy thing. Transfusions from animals did not go well at all. And even from human to human, it seemed to work well at times but failed massively at others. In 1900, Landsteiner published a paper outlining the role of blood groups (types) which explained the reasons for these successes and failures. With the advent of blood storage solutions that prevented clotting, whole blood transfusion became the standard treatment for hemorrhage in World War I.

When the US entered World War II, it switched to freeze-dried plasma because of the ease of transport. However, it quickly became clear that plasma-only resuscitation resulted in much poorer outcomes. This led to the return to whole blood resuscitation. At the end of WWII, 2000 units of whole blood were being transfused per day.

In 1965, fractionation of whole blood into individual components was introduced. This allowed for guided therapy for specific conditions unrelated to trauma. It became very popular, even though **there were essentially no studies of efficacy or hemostatic potential for patients suffering hemorrhage.** The use of whole blood quickly faded away in both civilian and military hospitals.

The use of fresh whole blood returned for logistical reasons in the conflicts in Iraq and Afghanistan. A number of military studies were carried out that suggested improved outcomes when using whole blood in place of blood that has been reconstituted from components. That leads us to where we are today, rediscovering the advantages of whole blood.

Use Of Whole Blood For Massive Transfusion

So why doesn’t component therapy work so well for trauma? Refer to the diagram at the bottom of the page. Although when mixed together the final unit of

reconstituted blood looks like whole blood, it's not. Everything about it is inferior.

Then why can't we just switch back to whole blood? That's what our trauma patients are losing, right? Unfortunately, it's a little more complicated than that. The military has been able to use fresh warm whole blood donated by soldiers which has been stored for just a few hours. That is just not practical for civilian use. We need bankable blood for use when the need arises.

This ultimately means that we need to preserve the blood, and this requires a combination of preservatives to prevent clotting and keep the cellular components fresh, and refrigeration to avoid bacterial growth. This is not as simple as it sounds. Adding such a preservative to whole blood dilutes it by about 12%. And there are concerns that cooling it may have effects on platelet function. **Recent data suggests that platelet function in cooled whole blood is preserved, but platelet longevity is decreased.**

There are other issues with the use of whole blood as well. It contains a full complement of white blood cells, and this may be related to reports of venous thrombosis, respiratory distress, and even graft vs host disease. Unfortunately, removing the white cells (leukoreduction) also tends to remove the platelets, and there is little literature detailing the safety of this practice.

Another problem is the plasma component in whole blood. Universal donor (type O) whole blood may contain significant amounts of anti-A and anti-B antibodies. For these reasons, most blood banks limit the number of whole blood units transfused to a handful. A recent paper from OHSU in Portland details a massive transfusion in which 38 units were given to one patient. There was no transfusion reaction, but platelet counts dipped precipitously. All centers currently using whole blood utilize only low-titer anti-A and anti-B units.

So does whole blood work as expected in the civilian arena? The data is still incomplete, but the total transfusion volume appears to be decreased in patients without severe brain injury. **With the increased interest and use of whole blood, it is imperative that more safety and efficacy studies are forthcoming.**

Here are some tips on getting started with your own whole blood program:

- **Develop a relationship with a supplier of whole blood.** Hammer out the details of the exact product (product age, leukoreduction, titer levels, returnability if not used).
- **Obtain approval from your hospital's Transfusion Committee!** Obviously.
- **Work with your blood bank to develop processes to ensure proper availability and accountability.** What is the maximum number of units that can be used in a patient? When should units be returned to the general pool to ensure they are not wasted?
- **Decide where whole blood will be available.** Obviously, the blood bank will house the majority of the product. But should you have it in an ED refrigerator? On air or ground EMS units? These situations demand several extra layers of oversight and add greatly to complexity.
- **Educate, educate, educate!** Make sure everyone involved, in all departments, are familiar with your new MTP!

References:

1. *Whole blood for resuscitation in adult civilian trauma in 2017: a narrative review. Anesth Analg 127(1):157-162, 2018.*
2. *Massive transfusion of low-titer cold-stored O-positive whole blood in a civilian trauma setting. Transfusion, Epub Dec 27, 2018.*

