Discussion of 2021-1772

IMPACT OF INCORPORATING WHOLE BLOOD INTO HEMORRHAGIC SHOCK RESUSCITATION: AN ANALYSIS OF 1377 CONSECUTIVE TRAUMA PATIENTS RECEIVING EMERGENCY RELEASE UNCROSSMATCHED BLOOD PRODUCTS

**DR JUAN C DUCHESNE** (New Orleans, LA): In their work, the authors prospectively analyze the impact of whole vs component therapy in patients with hemorrhagic shock. Their ultimate goals were to provide good scientific evidence on why whole blood should be the first and maybe the only choice of resuscitation in this subgroup of patients. The reason I am emphasizing “good scientific evidence” is because whole blood is nothing new in the armamentarium of resuscitation. Whole blood was widely used during World War I, in World War II by Allied Forces, and was becoming standard of care for casualties during the Korean Conflict and the Vietnam War. Unfortunately, its use dissipated due to the blood banker’s industry, without any scientific data on fractionation of whole blood into its components. This transition occurred without any rigorous scientific support, and that is why we, as responsible scientists, are here today discussing this topic.

In their work, the authors hypothesize and conclude that in patients suffering hemorrhagic shock, whole blood transfusion is associated with both improved survival and decreased overall blood use.

Can you clarify whether the 840 patients who received whole blood were exposed to any component therapy? As you know, this can obscure the true benefit of whole blood.

Based on your results, is your institution going to get rid of component resuscitation and transition to only whole blood resuscitation?

Of interest, there was lower volume of resuscitation in the whole blood group. Is this finding by design, or is it truly a more hemostatic low-volume resuscitation?

Our institution demonstrated a similar finding in last year's Southern Surgical Association published papers, where the whole blood group had potentially decreased immune dysregulation with fewer ventilator days and lower incidence of acute respiratory distress syndrome. In your work, the whole blood group had a decreased incidence of sepsis. Do you think the cause for increased sepsis in the component therapy group might be related to the more diverse and wider immune exposure in the component therapy group vs in the whole blood group? In other words, should we start analyzing the impact in immunoregulation on outcomes in patients with "more donors" component therapy vs "fewer donors" in the whole blood group?

Although transfusion-associated circulatory overload (TACO) was not as common as expected for either group, how did your institution perform quality and performance improvement on this volume overload complication?

And finally, as it was demonstrated in your study, the whole blood group patients were in more shock than in the component therapy group–the reason is that your first responders preferentially pulled whole blood in this group of patients, giving them a survival advantage over those patients resuscitated with component therapy who, to begin with, were not as sick as the whole blood group. If it makes sense to our first responders, why do we need to keep banging our heads against the wall looking for evidence? It not only needs to make sense to our first responders, but it needs to make sense to all of us.

This important and greatly needed evidence will help move the pendulum of damage control resuscitation.

**DR NICHOLAS NAMIAS** (Miami, FL): Two decades of war and the need to provide blood in austere environments led to the reintroduction of walking blood banks by our military physicians. Speaking to those who were able to transfuse fresh, warm, whole blood reveals that the results of such treatment are nothing short of miraculous, leading to improved hemostasis and lower overall fluid requirements. This experience followed those surgeons home, where the concept of transfusing packed red blood cells, plasma, and platelets in a 1:1:1 ratio, to approximate whole blood, has been taking hold and adopted as routine in many trauma centers. To improve upon approximating whole blood, some areas, and notably Houston, have been leaders in transfusing banked whole blood. Dr Cotton and colleagues undertook an analysis or 3 years’ worth of trauma patients who received emergency release uncrossmatched blood at their institution and set out to compare those who received any whole blood (the whole blood group), to those who received no whole blood (the component group). Note that this does not mean the resuscitation in the whole blood group consisted entirely of whole blood, just that they received any whole blood. A total of 840 patients ended up in the whole blood group, and 547 patients were in the component therapy group. The patients were demographically remarkably well matched. In terms of severity of illness, patients in the whole blood group were sicker by multiple measures, which makes sense–there was something about those patients that led emergency medical services or the physician to give them whole blood. The authors set out to determine whether there was a survival benefit to whole blood and if there was a reduction in total amount of transfusion as the co‑primary outcomes. Secondary outcomes included transfusion reaction, acute renal failure, sepsis, respiratory failure, venous thromboembolic events, overall hospital‑free days, ICU‑free days, ventilator‑free days, and blood product use by patient location.

In Table 4, you provide the 24‑hour transfusions in the whole blood groups as a median (interquartile range) of 6 (0,18) and for component therapy as 6 (2,15) with a p value of 0.257. You then subject this to logistic regression, and in Table 5 show an odds ratio for transfusion volume of 0.38, when controlling for age in years, male sex, injury severity score (ISS), scene systolic blood pressure and arrival lactate. This is a remarkable difference from what we see in the univariate analysis for 2 groups that were very similar at baseline. Although I find this hard to conceptually grasp, and I would have liked to see you match some cohorts or perform a propensity score matching analysis and show actual volumes transfused between the 2 groups, I do find this result to be entirely plausible.

My bigger concern is the survival benefit you report based on being in the whole blood group when controlling for the same things we just mentioned. Am I to believe that even though the raw mortality was 75% vs 76% in the whole study population, somehow, when controlling for age, sex, blood pressure, ISS and lactate, there is a fourfold likelihood increase in survival when one is exposed to a unit of whole blood as opposed to only getting component therapy? Do you think this result could just be an artifact of the logistic regression not doing what it ought to do for this dataset? Over the years, the statisticians have debated on the merits of forward selection, backward selection, stepwise selection, and now, purposeful selection. This tells us non‑statisticians that logistic regression is not perfect. Given that the logistic regression performed here yields a fourfold likelihood of survival for the whole blood group, all other things being equal, does it make you wonder whether something is wrong with the model? The odds ratio must turn into real numbers in the reader’s mind to make it tangible, so what is a reader to think? This was a sick cohort, with a survival rate of approximately 75% in each arm. So, if the arms had been perfectly matched for severity of illness, would we have expected 80% survival for whole blood and 20 percent for component? 100% for whole blood and 25% for component? I cannot come up with a set of real-life numbers that are believable. Did you attempt or would you consider propensity score matching analysis?

This is a tremendous clinical experience from one of America's busiest and best trauma centers. They are leading the way with advances in transfusion science. I think if this paper is going to make an impact, there either must be a better explanation of why there is a fourfold survival benefit, or another analysis that would make the results more accessible to the non‑statistician, like propensity scoring. Ultimately, of course, if this data can lead the way to a prospective randomized controlled trial for whole blood in trauma, it will have been a great contribution.

**DR LEONIDAS G KONIARIS** (Indianapolis, IN): Could you comment on either 90‑day or 1-year survival in the groups? In other words, is there a long‑term benefit of having received whole blood?

**DR DAVID B LEESER** (Greenville, NC): I remember in 2004, when I was in Iraq, we were using whole blood resuscitation, but the science was not well controlled, so the current work is really important. Whole blood is a fresher product, due to its limited shelf life. It is not on the shelf as long as blood components. If we are thinking the whole blood effect is immune mediated, are the red blood cells and other components you are giving older than the whole blood? Older cells and products potentially have more cytokines which may incite inflammation. So, I would like to know how long the blood products in the patients who received component therapy had been on the shelf vs the patients who received whole blood therapy? I think that is an important question to answer, if we think the whole blood effect is partially immune-based.

**DR BARBARA A GAINES** (Pittsburgh, PA): Was this Rh-negative or -positive blood, did you give it to women, and what is your feeling about giving Rh-positive whole blood to women of childbearing age?

**DR JEFFREY UPPERMAN** (Nashville, TN): I’m a pediatric surgeon. Dr Cotton, I will not hold it against you for not testing the little people. Full disclosure, I am a member of the Scientific Advisory Council of the American Red Cross, but I'm speaking on behalf of myself. I do have a question regarding supply chain. I just received several emails that we are running out of O blood, and they are below severe levels. So, Dr Cotton, was there something special happening in the Houston Metro that you were able to get your hands on so much whole blood you could put it in helicopters? There is a shortage of blood products in general these days, so will this science meet the real barriers in a society where we will not be able to fulfill this need?

**DR JASON BRILL** (Houston, TX): Yes, the 840 patients in the whole blood arm initially received typically 1-2 units of whole blood and then went on to receive component therapy. There was a small percentage that only received whole blood because of either achieving hemostasis or they just did not require any further blood‑based resuscitation, but upwards of 85 percent continued with component therapy. I agree that is a confounder, but as was mentioned by several of the discussants, it is a matter of supply chain. I wish that I could have type‑specific whole blood for all trauma patients. In fact, I wish I could line healthy volunteers out the door ready to give fresh whole blood, but we are dealing with practicalities and reasonable approaches.

So, yes, the "whole blood" group in general received component therapy later. No one received more than 4 units of whole blood. Again, the typical number was 1-2 units.

As I already alluded to, I cannot get rid of component‑based resuscitation for trauma patients, due to the crossmatching issues alone, because we were using uncrossmatched blood. I think we have shown that the safety profile is very good, but the Association for the Advancement of Blood & Biotherapies is still recommending that type‑specific blood be used. I think it will take time to transition both the supply chain and the logistics, as well as the scientific community, to recognizing the benefits of whole blood in this population.

I do think that lower volume in the whole blood group is a result of the better hemostatic profile of whole blood. If you look at the coagulation factor concentration with a reconstituted unit of 1:1:1, we are talking about 65 percent of normal with most coagulation factors, probably better for the non‑labile factors than the labile, but the storage lesions are significant, especially when following fresh frozen plasma and turning it back into thawed plasma. In whole blood, based on rTEG and ROTEM studies, it appears that the coagulation efficacy (and effectiveness in the real world) is still there, on the order of 85 to 90 percent, even after 21 days of storage.

I think the issue of fewer donors is very significant. I think this shows up in the incidence of sepsis decreasing in the patients in the whole blood arm, and I agree that that should be incorporated into future studies looking at the number of donor exposures. The other issue is that with the reconstitution of that 1:1:1 in the massive transfusion protocol, it is not only exposure to more donors, but exposure to more anticoagulants and more additives. So, if you look at that one cooler, you are now talking about almost a liter of crystalloid‑based anticoagulant and other additives as opposed to a whole blood unit, which is somewhere on the order of 80 to 90 mL, depending on which anticoagulant it is stored in. Again, I wish I could use fresh whole blood for everyone, but the supply issues mean that we are going to have to add anticoagulant if we want to bank whole blood as we did throughout this study.

TACO is another important consideration. I think we have a very reasonable incidence. There is a suggestion that whole blood, in some instances, may be associated with an increase in TACO. We certainly did not see that in our study, and I think ongoing performance improvement is warranted and certainly education of both providers and nursing staff is something that we will continue monthly, through the regular trauma improvement channels.

Moving on to Dr Namias' questions regarding the ability to control for the differences between the 2 groups in the logistic regression analysis, I agree it is imperfect. What we are trying to do is show association, and I think the odds ratios here show the associations. I am not suggesting that there is an 80 percent decrease in mortality. A mortality rate of 25 percent is not a rare outcome. I cannot turn the odds ratio into a relative risk model, but I do think that there is a magnitude of effect that could be further elucidated with additional study.

We only looked at 30‑day survival. We could not go to 90 days or 1 year. As many people know, follow‑up in this group is not very good. The more blood we use, of course, the younger the blood becomes for the whole blood supply, typically 14 to 21 days. I will need to go back and look at the age of the packed red blood cells used in the component only group.

To address Dr Gaines' question about Rh status, Rh-negative blood was used exclusively for the first 4 to 5 months of the study and then, because of supply issues, we just could not come up with enough O-negative blood. We had to switch over to O-positive, and that is when our blood bankers informed us that we were not going to be able to give it to childbearing-age women. I will say that, at least in Houston, women are not injured as frequently as men in these cohorts. So, the risk of seroconversion, while present, is a very small proportion of our population. Of course, I cannot generalize that to all centers. I personally believe that it might be worth the risk, given the survival benefit that we saw, but that is grounds for further research and discussion.

Regarding the supply chain for O, certainly we have extremely good, knowledgeable, and safe blood bankers and a blood supply that is very robust. I know that does not exist in all locations. That said, the way that we use the O blood that was on the pre‑hospital units, specifically our helicopters, is after a certain number of days, if it had not been used on the helicopter, it was transferred back to the hospital for use in the hospital setting. That really decreased the amount of blood that could have been wasted and also made fresher, younger blood available on the pre‑hospital units.