Transfusion: The impact of Patient Gender and Storage Age of Red Cells

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Morbid outcomes related to red blood cell transfusion during heart surgery have not been studied with large randomized controlled trials. Thus controversy takes place ad nauseum. Three contingents participate in this controversy: blood bankers, industry scientists and marketers, and physicians like cardiac anesthesiologists and surgeons who care for patients at high risk for transfusion.

Each contingent has its own bias and conflict of interest profile. The blood bankers focus on efficiency and safety of the procurement, storage, and administration. Industry seeks scientific bases support to substitution of expensive manufactured alternatives to red blood cell and component transfusion. Clinicians look for ways to smooth hospital courses and free one patient at a time from morbidity and mortality.

The contingents all profess to evidence based process-design and clinical decision-making. The gold standard for such evidence is the RCT, the randomized controlled trial.

Unfortunately the magnitude and expense of RCTs in this field is extremely high because the event rates are relatively low and the confounding variables are many, large scale RCTs are rare to non-existent. What we are left with are a variety of meta analyses, and analytic manipulations of existing clinical or administrative databases, which use constructs such as propensity matching to create what amount to “virtual” control groups where none exist in reality.

With that caveat in mind, let us proceed to consider a sampling of some recent analyses of the effects of patient female gender and duration of storage on morbidity and mortality outcomes.

In 2006 Koch et al published an analysis of 11,963 isolated CABG patients from the Cleveland Clinic Foundation database. She determined that 48% of these patients were transfused. Risk adjustment was performed for a large number of variables, and then a statistical model was created to assess the incremental impact of red blood cell and blood component transfusions on this risk adjusted outcomes measure. She found that transfusion of red cells was associated with the following statistically significant increases in adverse outcomes:

Mortality  x2.06
Prolonged vent support x1.79
Serious infection  x1.76
Cardiac complications x1.55
Neurological events x1.37

Koch was also able to demonstrate that each unit of red cell transfusion incrementally increases these risks.

In terms of understanding the risk adjustment factors predisposing to red cell transfusion, Shetata et al reviewed the literature (2461 citations from 1966-2005) to determine that the strongest risk factor for transfusion (4x to 8x) was urgent/emergent surgery, followed by increased age (1x-3x) and female gender (2x). His findings are supported by numerous similar publications.

Age is an easily understandable factor, but what about female gender? Rogers et al performed a cohort study on the Michigan Medicare CABG patient database, finding that red blood cell transfusion were more frequent in women (88% vs 66%). They also found that transfused patients were (13% vs. 4.5%) more likely to have infection. Patients who were transfused were 5.6x more likely to die in the 100 days following surgery.

Interestingly in this population of older men and women, there was a 13% higher unadjusted mortality rate in the women, but this gender difference was abolished by modeling an adjustment for transfusion. The obvious conclusion therefore is that it is not the gender but rather the gender-related increase in transfusion rates which are responsible for the mortality differential.

Now on to storage duration of Red cells. As you can appreciate, and data purporting to show that fresh blood is safer than old blood gets the blood bankers very concerned, as a major push in their literature is toward ways to extend even further the acceptable storage durations. Recently the use of anaerobic techniques seems promising for extending the shelf life of RBCs.

But Colleen Koch published in a 2008 NEJM article that dichotomizing storage to “under” and “over” 14 days (means 11 and 20 days for the two groups) was not good for patients. She showed in a cohort of 2872 patients (8802 units transfused) that in-hospital mortality, intubation beyond 72 hours, renal failure, and sepsis were all significantly increased with the >14 day storage. When she combined the complications, older blood was associated with a 25.9% serious adverse outcome rate vs. 22.4%, (P=0.001) for the fresh blood group.

Naturally the letters to the NEJM editors flew in from the Blood bankers, with most of them complaining that this was not an RCT, plus they had excellent data on red cell safe viability within the 42-day storage limit.

Dzik from MGH wrote in Transfusion Medicine a specific rebuttal to Koch’s analysis. His assessment can be synopsized: Numerous substantial flaws in data analysis and presentation may have led to an erroneous conclusion about the effect of blood storage age and perioperative mortality. Dzik concluded that” Given the fundamental importance
of a safe and adequate blood supply to national healthcare, the question of the proper storage age for blood should be studied using a prospective study design.”

So what are we, who are on the front lines, to do with this data and opinion about the need to avoid transfusion in our patients, especially in the females? Should we be looking at the expiration dates and picking the freshest blood? I have started doing this and am considering encouraging my perfusion colleagues to do the same, because we often are transfusing only one or two units to our female patients, but generally have 4 units set up. At the my hospital, the blood bank is unenthusiastic about sending fresh units to the cardiac ORs, and in fact, because we are one of the highest utilizers, they actually send us the oldest blood because they can be quite certain that we will use most of what we order. Their incentive is to get the old blood used before it expires.

For me, the primary thing is do is to include a more detailed transfusion discussions with my female patients as I go through my anesthesia consent process. Secondly, I am now using aggressive warming technologies on all women, and the surgeons and perfusionists no longer actively cool. Thirdly, I am seeking pharmacologic blood sparing strategies to offer to women, in particular women undergoing resternotomy. Now that we no longer have access to aprotinin, such strategies for me involve plasminogen stabilization with EACA, and some form of “platelet anesthesia”. By way of disclosure, EACA is not approved for use in cardiac surgery, and neither is my favorite platelet anesthetic PGE1.

As with RCTs which are probably not going to happen because no one is motivated to fund them, so it will be with rigorous studies of pharmacologic approaches which involve “off patent” or “orphan” drugs. Manufacturers of orphan drugs will loose their protected status if they increase the number of doses used per year above some fixed number, so they are not interested in studying new applications. The NIH generally does not fund drug studies.

So we are left with mining our clinical and admin databases as Colleen has done so well, to look for rationales to support transfusion decisions. We will be open to Dzik-type criticism. Working out personal / team based practice strategies can be useful. Behavior modification by way of practitioner specific feedback systems may also be applicable, since transfusion trigger decisions are so multifactorial.

In any case, as we continue to learn more about the dangers of transfusion, we should work as individuals, teams, and within our professional societies to support and encourage industry to develop new technology, institutions (hospitals, insurers, government agencies) to conduct studies which are powered appropriately, and for our selves to work on transfusion behavior analysis and feedback within or peer review processes.


