Blood in the Pump: Pain or Gain?

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Hemoglobin and hematocrit (Hgb/Hct) are poor surrogates for both oxygen carrying capacity and tissue oxygen delivery. Yet, they have been worshipped as easily obtained laboratory values from which medicine has largely driven "transfusion triggers". Historically, the trigger of 10gm/dl (100gm/L) was utilized form the 1940's to 1980's. Besides being "round numbers" these levels had little evidence of utility either in preventing tissue ischemia or improving outcome for patients. On a personal note, when I began my career in cardiac anesthesiology 10gm/dl was the DE novo transfusion goal for all patients either during or after CPB. Approximately 60-80% of patients were transfused in the 1960-1980 years and "pump lung" was described. Today the transfusion utilization for "routine" (we can argue what that means) CPB is between 20-45% with some centers standing out wherein their utilization of transfusions is at 10% or below. Pediatric patients, especially neonates, presenting for congenital heart surgery present "special" circumstances in that they have a small circulating volume, immature liver functions and are hemodilution challenged.

The thought process vis-à-vis red cell transfusion as a prime, into or while on bypass is fraught with assumptions. The first assumption is that by solving the oxygen content equation we therefore have an assessment of oxygen delivery. This lecture will review that equation but look into how oxygen gets from erythrocytes to tissues and it will make that point that the oxygen content equation is of use only for larger arterial content. The microcirculation is carefully regulated both for its Hct, oxygen extraction speed of red cell transit and number of capillaries open per gm of tissue (functional capillary density). The homeostasis for oxygen delivery to the microenvironment is beautifully regulated by Mother Nature, and what we prime into the pump may or may not affect that. Therefore, worship any transfusion trigger is wrong. Yet transfusion trigger is still both in our lexicon and it is how researchers report their data.

Historically, again, reports of a case series of three pulmonary failures after CABG surgery in the 1980's noted that the only common denominator was "an unusual or allergic reaction to blood or blood transfusion"! Pump-lung, then today we call it TRALI (Transfusion Associated Lung Injury) and it is the number one cause of deaths and major morbidity after transfusion. The incidence of TRALI in heart surgery can exceed 1%. In over 16,000 cases at the Cleveland clinic postoperative lung dysfunction (respiratory distress) was dramatically associated with transfusion (4.8% v. 1.5% $p<0.001$). So it also is with renal failure, immunosuppression, heart failure and use of inotropic agents (potentially vasoplegia). Yet data exist and publications note that low Hct is associated with renal dysfunction/failure and adverse neurologic outcomes. But, when reading all of this data one cannot always separate when patients have had permissive low oxygen carrying capacity, when they were anemic to start and when transfusion utilization (a linked therapy to low Hct and anemia) as a response. If transfusion is a result of anemia (either chronic or acute due to hemodilution, and transfusion is fraught with serious outcome mechanistic side effects, shouldn't we the researchers ferret out the effects transfusion v. low oxygen delivery.

DeFoe and Surgeoner did that to some respects in two papers from 2007 and 2009. In those two papers out of the Norther New England Cardiovascular Outcome Consortium. I the first paper by DeFoe the

question was asked at what point does mortality increase when anaemia is encountered on pump. There was a doubling of mortality at approximately 21% Hct. But there was no discussion of transfusion, the therapy that was triggered by low Hct. Surgenor some years later looked at the same database (w9th a number of new patients) and found that the question is convoluted and complex. Anemia is bad and related to many morbidities but transfusion is linked to a 16% increase in mortality per unit of blood utilized. Of interest the patients that did the worse in both short and long term outcome were those who were anemic to start and the "team" decided to prime the CPB machine with banked blood.

Recently comparisons of bypass conduct "down under" - The Australian and New Zealand Collaborative Perfusion Registry- ANZCPR v. Perfusion Measures and outcomes PERForm registry are showing that methods are very different. Specifically for this discussion the use of transfusion, triggers, as well as a number of patient blood management techniques are quite different. Lowest Hct on bypass was quite different as was autologous blood harvest, retrograde autologous prime and I suspect (not reported) transfusion triggers. That is fascinating in that Australia has national guidelines for transfusion and the institution of patient blood management in Western Australia has been a huge success. Data form Western Australia has shown a reduction in blood utilization with their institution of PBM program, a $140 million plus cost savings and improvement in outcomes, but this is for all types of surgery and not specifically alone on cardiac surgery. In the Virginia Cardiac Surgery Quality Initiative (VCSQI) when the STS/SCA-AmSECT guidelines were instituted in 11 of 17 hospitals blood transfusion utilization decreased, length of stay, renal dysfunction, pulmonary dysfunction, infection, myocardial failure and very importantly re-admission to hospital all dropped (readmission within 30 days decreased by 50%). These hospitals in that participated had an estimated 49 million US dollars savings.

The biology of transfusion is well studied and a wide range of inflammatory mediators are present in allogeneic blood as it ages. Much has been made of 2, 3 DPG depletion in banked blood as it ages. The entire question of older v. fresher blood is a complex question but suffice it to say that no matter how long blood has been on the shelf in the blood bank it is not a patient's own fresh native red cells. The fact that the change in 2,3 DPG, even though those changes can be found 3 days after transfusion in the recipient, may not change tissue oxygen delivery goes back to the beginning of this abstract- we do not in fact fully understand oxygen delivery, especially in the critically ill patients. We have made historical assumptions and perhaps bio-complexity is such that each incremental change is hard to tease out and follow. But we do know that either when studies have randomized patient groups (cardiac as one) or in aggregate to lower transfusion triggers those patients receiving less blood (6 of 9 trials) showed no worse outcomes and 3 of 6 trials had better outcomes. This lecture will review in some small detail some of the biology of aged red cells as well as ask the question whether that inflammatory soup put into the pump primes the pump for even worsening inflammatory stress.

Treatment of anemia prior to surgery is becoming more and more a standard. In places where anemia is approached as a disease in itself and it is tackled prior to surgery transfusions have decreased and outcomes are better. Shander has discussed in great detail, is it the anemia or the transfusion that causes the adverse outcomes. It turns out it is both and the two cannot be separated unless one studies large numbers of Jehovah's Witness or bloodless medicine patients. The lowest recorded Hgb of which I am aware was in Japan were a patient survived 0.6gm/dl after heart surgery. This cannot be advocated and certainly extremes of hemodilution will reveal more deaths but it begs the question, again form the beginning her, do we know what we are doing and do the assumptions we have historically made make sense? Indeed, it has been predicted and advocated that pre-operative anemia in elective surgery will

someday become a reason to postpone a case as too risky, just the way we postpone full stomach or those that have not received beta-blockade or pre-operative antibiotics.

So we have to transfuse and yes anemia at some point does become limit of oxygen delivery. The pediatric literature will be explored wherein pump prime with blood is often performed. The literature does have considerable numbers of case series wherein this is avoided and wherein other techniques such as splitting units, trying to minimize exposures and patient blood management techniques have been applied to neonatal cardiac surgery. Of interest a "belief" that FFP usage to replete coagulation factors into the pump prime is good has been refuted as well. Arguments for usage of fresh whole blood have and can be made but still the data in randomized trials or level 1 research are missing to say that even in the neonatal critical patient that such "abnormal" behavior is not by itself worthy of generalization. Again, the use of pre-operative pump prime is local and based upon local history and preference. Transfusion for heart surgery is "tribal"!

Utilization of products, adoption of guidelines, embracement of patient blood management is all dependent upon leadership in different heart centers. Variability of transfusion trigger (as bad a physiologic indicator as it is) is never the less still almost universally accepted as a guide for centers regarding when they utilize blood. That fact (the tremendous variability) should signal that we still do not know what we are doing with regards to oxygen delivery. The fact also that the transfusion trigger has crept down but variability and lack of adoption of guidelines is the rule not the exception says that physicians, teams and even perfusion groups cannot embrace evidence based medicine or reach consensus. In the end, there is no single point at which a transfusion is necessary, required or will definitely improve outcome! Yet many espouse that they know exactly when "their patients" should get blood. This lecture will try to put some science behind triabalism!

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