Hurts So Good: Uncovering the Relationship Between Blood Transfusions and Allograft Outcome

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See Clinical Research on Pages 986 and 1041.

The concept that blood has curative qualities dates back to ancient times. The poet Ovid (43 BC–17/18 AD) wrote of the rejuvenation of Aeson by "letting out the old blood" and replacing it with a restorative tincture.[1] Accounts of Roman spectators hoping to gain the strength of slain gladiators by drinking their blood are well detailed by the philosopher Pliny the Elder. But it was not until 1829 that James Blundell, the father of modern blood transfusion, published the first successful case of human-to-human blood transfusion, saving the life of a young woman experiencing postpartum hemorrhage by transfusion of 8 ounces of blood (∼240 ml).[2] However, many of Blundell's other patients did not survive transfusion, presumably due to ABO incompatibility and the resulting hemolysis. Recognizing both the benefits and detriments of

transfusion, Blundell cautioned that transfusions be limited only to the severely ill.

Fast-forward to the present where pretransfusion testing and infectious disease screening have markedly improved the safety profile of transfusion. Nevertheless, blood transfusions are still associated with adverse events, the most common being transfusion reactions (e.g., allergic, febrile, respiratory, etc.).

Among individuals who receive ongoing transfusions, such as those with end-stage renal disease (ESRD), one risk/consequence of transfusion of particular concern is alloimmunization to human leukocyte antigens (HLA antigens). In the context of ESRD, HLA alloimmunization from transfusion can increase a patient's level of panel reactive antibodies and preclude transplantation of kidneys expressing 1 or more of the corresponding HLA antigens.[3]

After transplantation, the effects of transfusion in transplant recipients have been incompletely characterized. In particular, whether the posttransplant transfusion of blood products places the recipient at risk of antibody-mediated rejection, delayed graft

function, decreased graft survival, or a combination of these, has not been established in randomized controlled studies. While some studies report transfusions to be risk factors for acute rejection and poor graft survival,[4] others conclude that transfusions are not associated with increased allograft risks.[5] In this issue of *Kidney International Reports*, 2 new studies further investigate the role of blood transfusion in the outcome of kidney allografts.[6,7]

Massicotte-Azarniouch et al.[6] and Daloul et al.[7] independently examined the risks of posttransplant blood transfusions on renal allograft outcomes. They came to the same conclusion, namely, there are no differences in outcomes among renal transplant recipients who received blood transfusions compared with those who did not. This would lead readers to conclude that transfusions can be administered after transplant without concern for increased adverse events to the donor allograft.

However, to determine the (possible) effects of transfusion in ESRD patients, confounding factors must also be considered. ESRD patients are prone to anemia, which is multifactorial (i.e., decreased production of erythropoietin, iron deficiency, anemia of chronic disease, and blood loss secondary to dialysis). As such, when studying transfusion in this population, it is critical to control for morbidity and account for potential reverse causation, where outcome actually leads to exposure. Logically, it makes sense that the sicker the patient, the more likely the patient will need a transfusion. Similarly, logic dictates that "sicker" transplant recipients would have poorer allograft outcomes. Thus, when the exposure of a study is transfusion

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and the outcome of that study is rejection or graft loss, ensuring that outcome results from exposure and not baseline morbidity is problematic.

Massicotte-Azarniouch et al.[6] and Daloul et al.[7] both put forth considerable effort to account for confounding factors to conclude that the exposure (transfusion) was chiefly responsible for the outcomes of interest. To reduce the possibility of reverse causation, Massicotte-Azarniouch et al.[6] used varying lag times of red blood cell transfusion between exposure and outcome. Given that elicitation of an immune response may take days to weeks after exposure, the authors performed analyses using lag times of 3, 7, 10, and 14 days. They also used a negative control group (osteoporotic fracture or osteoarthritis) in an attempt to control for morbidity, because osteoporotic disease would be considered an indicator of a comorbidity not caused by transfusion. Unfortunately, the authors found a positive association between transfusion and the negative control group. This unexpected result could be due to persistent indeterminable confounding, underscoring the difficulty in teasing out comorbidity from outcomes associated with transfusion.

Daloul et al.[7] also attempted to account for confounders. Firstly, their study population was limited to nonsensitized renal transplant patients receiving a first transplant. This approach decreased the number of recipients who met the inclusion criteria, and only nonsensitized recipients were examined, thereby removing the confounder of a preexisting HLA antibody that could contribute to posttransplant outcomes. Hence, antibodies detected after transplant in their patient cohort would be attributable to the transplant allograft or the posttransplant transfusion donors, or both.

Secondly, Daloul et al.[7] also wanted to ensure that exposure led to outcome. To this end, the authors sought to limit immortal time bias, which, in their study, could overestimate the role of exposure on outcome. Specifically, outcomes were only analyzed from day 30 posttransplant, thereby excluding early deaths and outcomes that could have been confounded by postsurgical complications. Analytic measures using inverse probability of treatment weighting were specifically applied to deal with confounding. In simple terms, inverse probability of treatment weighting studies populations in which covariates and treatment (transfusion) are independently assigned, as would be expected under randomization. This approach modeled the relationship between covariables and cause or exposure and was based on a logistic regression that predicted probability of transfusion as a function of 25 covariables (e.g., age, race, hypertension, diabetes mellitus, sex, cytomegalovirus status, immunosuppression, etc).

Although the painstaking analyses in the 2 reports were admirable, there were missed opportunities to study the immune responses beyond rejection and graft survival. First, neither group examined compliance to immunosuppressive regimens, which alone could greatly influence graft outcomes.

Second, the authors did not fully study HLA antibody profiles of their study cohorts after transplant. In fact, Massicotte-Azarniouch's group[6] never evaluated recipient HLA antibodies to monitor for development of de novo donor-specific antibodies (DSAs), and whereas Daloul's group did look for posttransplant DSAs, it was only done for cause. Given the low mean fluorescence intensity cutoff of 1000 in their study, patients with subclinical antibody-mediated rejection may have had DSAs that went undetected. Additionally, a strict numerical cutoff would not account for DSAs with lower mean fluorescence intensity due to distribution of antibody targeting a common epitope shared among multiple target beads. Predetermined testing intervals for HLA antibody would be one way to study the evolution of an immunologic response in these transfused individuals.

When the immunologic consequences of blood transfusion posttransplant are the main objectives of a study, then thorough characterization of blood donor characteristics, especially determining their HLA types, is warranted. Indeed, Hassan et al.[4] obtained the HLA typings of a subset of blood donors in their retrospective review of adverse outcomes of blood transfusion on renal transplant recipients, allowing the identification of transfusion-specific antibodies, which were then compared with DSA specificities. Interestingly, they determined that recipients with transfusion-specific antibodies and DSAs of identical specificity were at increased risk of antibody-mediated rejection and graft failure.

Data such as these support transfusion algorithms that avoid supplying blood products from donors with similar HLA types to the allograft donors. In light of the current interest in HLA epitope analysis, future studies may want to address epitope mismatches among the recipient, blood donor(s), and allograft donor to evaluate whether immunogenic epitopes portend poorer outcomes.

An additional consideration not addressed in either article is the

role that inappropriate blood use could play in allograft outcomes. Although Massicotte-Azarniouch *et al.*[6] referred to presumed adherence to transfusion guidelines, there was no systematic audit of blood use. Of note, retrospective audits of transfusion find that only a fraction of transfusions are considered appropriate.[8] These audits should be used to develop blood management programs that decrease transfusion use and optimize patient care by minimizing exposure and associated transfusion-related risks. Possible risks of transfusion in the post-transplant setting (including allosensitization and rejection) may be mitigated by reducing blood use and adhering to guidelines established on evidence-based medicine.

Inarguably, the history and evolution of transfusion has been one of the great advances in medicine, saving the lives of countless anemic and acutely bleeding patients. However, transfusion is a double-edged sword. Despite major benefits, there are inherent risks. Transfusion medicine literature indicates that the overall risks of transfusion often outweigh the benefits.[9] Even after controlling for confounding factors, data demonstrate that red blood cell transfusions are independent predictors of death, associated with nosocomial infections, and place recipients at increased risk to develop multiorgan dysfunction and acute respiratory distress syndrome. To quote the novelist Alice Hoffman:

> *"I really feel like the gift is also the curse. It's always half-and-half. Whatever brings you the most joy will also probably bring you the most pain. Always a price to pay."*

Independent of transplant status, the medical community should take heed to Blundell's warning to only transfuse when absolutely necessary.

DISCLOSURE

Both authors declared no competing interests.

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