Can Blood Transfusion Be Not Only Ineffective, But Also Injurious?

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Transfusion of blood components has been a cornerstone of hemodynamic management during the perioperative period. From the early twentieth century the development of blood banking techniques has been credited, despite little controlled data, with saving the lives of thousands of bleeding patients who would have otherwise most likely died. Since then, many types of asanguineous fluids have been added to the repertoire of clinicians in the operating rooms and wards, reducing the reliance on donated blood. Nonetheless, these simple fluids often fall short of providing a comprehensive replacement for numerous functions of blood beyond simple volume expansion. As a complex tissue with various cells and components, blood is tasked with carrying and supplying oxygen and nutrients to maintain acid-base and electrolyte balance, supporting macrocirculation and microcirculation with appropriate osmotic and viscosity characteristics, as well as providing coagulation and hemostasis. As such, blood has remained as the unrivalled and ultimate fluid of choice for hemodynamic management of bleeding patients. Unchallenged, red blood cell (RBC) transfusion has long been considered to be a safe and effective procedure for rapidly increasing patients' hemoglobin level and to improve oxygen delivery and hemodynamic.

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Inherent complexities of allogeneic blood components (and the complexity involved in collecting, preparing, storing, and transfusing them) also become their Achilles' heel as safe and reliable therapeutics. The residual plasma and white blood cells present in a unit of RBC contain a host of inflammatory mediators, free radicals, macromolecule oxidation products, dead and broken cells and vesicles, deranged electrolytes, and other components related to "storage lesions" in addition to loads of foreign antigens present in allogeneic blood, potentially creating unknown and unfavorable consequences of their own [1, 2]. Measures such as leukoreduction and improved storage solutions have generally been able to help with this situation, albeit to limited extents [3, 4].

Allogeneic blood transfusions have been rightfully likened to "organ transplantation"—certainly not a matter to be taken lightly. Hence, it is no surprise that an ever increasing body of evidence has raised questions about adverse patient outcomes related to injurious consequences of blood transfusion, in addition to casting doubt on the effectiveness of routine blood transfusions. In this issue of *The Annals*, the study by Paone and associates [5] adds to the pool of evidence. Arguing that transfusion of 1 to 2 units of blood during hospital stay is an indirect indicator of "discretionary and potentially avoidable" transfusions, the researchers collected data on 16,835 adult patients who underwent coronary artery bypass graft surgery from 2008 to 2011 at 33 hospitals under the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC). They compared the data of patients who did not receive any RBC transfusions with data of patients who received 1 to 2 units of blood transfusion. After adjustment for a number of confounders, they showed that transfusion of 1 to 2 units blood was associated with increased mortality and morbidity in their patient population [5]. A glance over the baseline characteristics of the cohorts (Table 1 of Paone and colleagues [5]) reveals differences that give the edge to patients who were not transfused (eg, younger age, higher body mass, higher preoperative hemoglobin level, lower prevalence of various comorbidities, more elective procedures, and higher ejection fraction). This revives the old question of whether transfusion is an independent cause of worse outcomes or just a marker of increased burden of disease [6].

Apart from a handful (and slowly growing) number of randomized clinical trials [7], the landscape of reports on the impact of allogeneic blood transfusions on patient outcomes is heavily dominated by retrospective studies. Even those few randomized controlled trials conducted to date have predominantly focused on comparing various transfusion strategies, rather than on comparing the outcomes of transfused patients versus untransfused ones. Controlled clinical trials are commonly performed to evaluate safety and efficacy of new treatments (or new indications of existing treatments). But when the key question being considered is about the risks (eg, whether smoking causes cancer or thalidomide causes congenital deformities), running a trial and exposing patients to the suspected risk factor leads to issues for Institutional Review Boards, and in these situations, data from observational studies and other evidence such as animal studies become paramount. While retrospective studies have provided us with invaluable evidence in many fields [8, 9],

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they can suffer from issues such as confounders that blur the causal relationships, keeping the observations within the bounds of the realm of association [6, 10].

This problem is not new or unique to transfusion medicine. Half a century ago, acknowledging the ethical issues of running a randomized clinical trial to establish the health risks of smoking, Bradford Hill [11] put forward nine criteria to aid in bridging the gap between observed association and underlying causation: availability of experimental evidence, strength of association, temporality, biologic gradient (dose-response relationship), biologic plausibility, coherence, consistency, analogy, and specificity. The same principles can be applied to transfusion medicine when evaluating the evidence from observational studies [12]. The data from multitudes of studies on outcomes of transfusion fit most of these criteria, leaving little doubt on the causal relationship between allogeneic blood transfusions and unfavorable clinical outcomes.

Not only do confounders make it difficult to prove causation, they also interfere with quantifying the effect size. Quantifying the dose-response effect is often a case in point. In the Paone and associates [5] cohorts, a patient receiving 1 to 2 units of blood was on average 2.44 times more likely to die, compared with a not-transfused patient. To adjust the risk of unfavorable outcomes attributed to transfusion for other confounders in their study, they used propensity scoring. In this approach, the investigators first construct a regression model to predict the risk or propensity of the patients being transfused (or more accurately, a model predicting the probability of the patients ending up in the transfused versus not-transfused cohorts). The model is used to calculate the transfusion probability or propensity score for each patient (a number between 0 and 1 depending on the way the dependent variable is coded). The patients can then be matched between the transfused and not-transfused cohorts based on their propensity scores, or alternatively, as done in the study by Paone and colleagues [5], the propensity score can be entered as an independent variable into the regression analysis alongside with transfusion to adjust the effect of transfusion on the outcomes.

This approach is limited by the predictive value of the model used to calculate the transfusion propensity scores, which is in turn limited by the available baseline data. A transfusion propensity regression analysis is essentially an effort to understand and model transfusion decision making—a complex and often stochastic process—based on a relatively short list of parameters. Substantial variability in transfusion rates of more or less similar patients at different institutes (or even between different clinicians at the same center) illustrates the challenges faced in modeling transfusion practices [13]. Although it has been suggested that many perioperative transfusions can be explained by the level of hemoglobin and surgical blood loss, a large part of the variability, however, remains unexplained [14]. Paone and coworkers [5] did not report the predictive value or any other similar measures of the regression model used to calculate the propensity scores, and it is not known how much of the variation in transfusion is explained by their analyzed variables. Nevertheless, after adjustment for the transfusion propensity score, patients in the transfused cohort were still on average 1.86 times more likely to die than the not-transfused cohort.

A few other issues are likely to further undermine the reported odds ratio of unfavorable outcomes in the Paone study [5]. While meeting all nine Bradford Hill criteria is not an absolute necessity to deduce causation from association, some criteria, such as temporality, are more important than others. Logically, cause must precede the effect, which means that transfusion must occur before a complication to be able to consider the former the cause of the latter. In the Paone study [5], however, it seems that any transfusions occurring during the index admission and any postoperative complications have been considered, which could possibly result in a complication (other than death) taking place before the transfusion being attributed to the RBC. The observation that a sizeable number of transfusions are given in the postoperative period further upholds this concern [15].

Despite its importance, it must be noted that the rarity of mortality as an endpoint reduces the power of a study and could possibly prevent it from identifying the observed difference as statistically significant. Without venturing into retrospective power and sample calculations and just to illustrate the impact of the low-occurrence outcomes on the required sample size, more than 10,000 patients are needed per cohort to be able to detect a difference in mortality rate of 1% versus 1.5% in the cohorts with power of 90% and statistical significance level of 0.05 [16]. For reference, the overall mortality rate among the 5,951 patients who received 1 or 2 units of packed RBC in this study was about 1.3%, which suggests an underpowered study for the mortality outcome, comparing the subgroups with 1-unit and 2-unit transfusions. Nonetheless, Paone and associates [5] included morbidity outcomes in their main analyses. While we agree that mortality events must be included among the studied outcomes of any transfusion studies, reliance on them and ignoring other outcomes related to morbidity, quality of life, and resource utilization is likely to limit perspective, and one is bound to miss outcomes that are important for the patient [17].

Presence of a dose-response relationship is another often-cited Bradford Hill criterion, which was excluded by design from analysis in this study. Additionally, the investigators did not include transfusion of other allogeneic blood components (platelets, plasma, and cryoprecipitate) in their analysis. These components may not be transfused as commonly as packed RBCs, but given the relative rare occurrence of mortality and major morbidity outcomes, they can still play important roles and their potential impact cannot be ignored. Lastly, the impact of survival bias remains uncertain.

Despite the limitations of cohort studies, the evidence alleging allogeneic blood transfusion as culprit for worsening patient outcomes keeps accumulating. Recently, Hopewell and coworkers [18] systematically reviewed the