Red blood cell non–ABO-identical transfusions are harmful: really?

Prevention of ABO-incompatible red blood cell (RBC) transfusion is of utmost importance in the practice of transfusion medicine. While every effort is made to provide ABO-identical blood, donor RBCs that are ABO compatible but not ABO identical (e.g., group O donor to a group A, group B, or group AB recipient) are transfused when ABO identical donor units are not available, in emergencies, or to avoid wastage of outdated blood. Based on immunologic considerations, provision of ABO-compatible blood should not put the patient at risk of transfusion reactions. However, the possibility remains that in ABO-nonidentical transfusions, the plasma in the RBC units may contain ABO-incompatible antibodies (e.g., anti-A or anti-B) that can target recipient ABO antigens on RBCs, causing hemolysis. Since platelets (PLTs) also express ABO antigens, the anti-A/B in non–ABO-identical RBC transfusions may target the corresponding ABO antigens on PLTs, possibly leading to their activation and clearance. These anti-A/B can also potentially interact with the free soluble circulating ABO antigens present in donor or recipient plasma, forming immune complexes that have been implicated as the drivers of adverse events in non–ABO-identical plasma transfusions. Since RBCs contain minimal plasma (<30 mL), the risk of adverse events due to passive transfer of incompatible ABO antibodies or soluble ABO antigens is deemed very low. Nevertheless, in an observational study of 4241 trauma patients previously published, those receiving ABO-matched blood had a lower mortality rate than patients who received uncrossmatched (universal donor group O) transfusions. The authors concluded that the increased mortality was not due to uncrossmatched RBCs itself but rather “a surrogate marker for acute, active bleeding” in patients for whom there is no time to perform a crossmatch.

In a separate multihospital Canadian registry study of 18,843 non-group O patients published in this issue of TRANSFUSION, a significant increase in in-hospital mortality was associated with ABO-nonidentical RBCs compared to ABO-identical RBC transfusions only among blood group A recipients. A strength of the study is that the analyses controlled for a number of confounders including age, creatinine, hemoglobin, in-hospital intervention, the number of units transfused and their storage age, and year of admissions. The finding that transfusion of group O units increases the risk of in-hospital deaths in group A recipients, but not group B or AB, argues against donor group O RBC itself being the culprit since you would expect to see this adverse effect equally in all non-group O recipients including group B and AB. When trauma patients were excluded from the analyses, transfusion of ABO-nonidentical blood increased the risk of in-hospital deaths in group A, but reduced it in group B patients. The detrimental effect of receiving universal group O RBCs only in group A recipients is likely due to patient-specific characteristics and the authors speculate that factors present in group A recipient plasma (identity unknown) rather than donor plasma (e.g., high-titer anti-A) may be the instigator of the adverse events associated with receipt of group O RBCs. Possible biologic reason(s) for why transfusion of group O RBCs to group B patients may be protective against in-hospital death in trauma patients are not discussed.

This article presents a considerable amount of research analyses and results. The breadth and effort in examining this research data notwithstanding, we would like to address some of the limitations and how they may impact the findings. One major limitation is that group A has a substantially greater number of patients with a broader distribution of medical diagnoses, thereby, allowing for a more comprehensive examination in A than in groups B and AB. Although there were significant interaction terms for blood group and exposure to non-identical blood, the stratified analyses by groups B and AB did not have sufficient sample size for the majority of disease categories to calculate hazard ratios. This shortcoming makes it difficult to fully compare the effects in the three groups.

The receipt of PLTs, plasma, and cryoprecipitate, which could potentially indicate disease severity, was also not factored in the analyses and as such the question remains as to whether the higher risk of in-hospital death in group A recipients was due to severity of disease in this patient group. Furthermore, it is unclear whether these products were ABO identical or not. Patients receiving ABO-compatible, but non-identical, plasma have been reported to have higher mortality and increased complications, including respiratory distress syndrome and sepsis, compared to patients who received ABO-identical plasma. Thus, controlling for ABO type of plasma products that patients may have
received is an important confounder that was not included in the present study. Due to the high plasma content in PLT products, transfusion of ABO-nonidentical PLTs may have also affected the outcomes of the study. In vitro, it has been shown that exposure of group A or B PLTs to group O plasma results in impaired PLT function, suggesting that mismatched donor or recipient PLTs may become dysfunctional in ABO-mismatched transfusion with potential to compromise normal hemostasis in the recipient. In centers that have adopted the policy of only issuing ABO-identical PLTs and cryoprecipitate, statistically and clinically significant reductions in febrile and allergic reactions and RBC alloimmunization have been reported. In contrast, in a secondary analysis of the PLT dose (PLADO) trial, a large randomized, prospective study in hematology-oncology patients, the clinical complications including risk of severe bleeding as well as febrile and allergic reactions were not increased in recipients of ABO major-mismatched PLT units despite lower PLT count increments in this patient group compared to those who had received ABO-identical units or ABO minor-mismatched PLT transfusions. Despite these conflicting data regarding the detrimental effects of ABO-mismatched PLT transfusions, this study would have further benefited if receipt of PLT transfusions as well as their ABO status was also included as a confounder in the analysis.

Another limitation is that despite controlling for a large number of confounders, some potential sources of variation were not sufficiently addressed. The analyses included data from several hospitals, but did not stratify per center or include it as a confounding factor. Differences in the level of patient care between hospitals can present as a source of variation that may bias the estimate effect being observed for in-hospital mortality. In-hospital intervention is included as a confounding factor in analyses and it is shown to be implemented similarly across the three blood groups. However, the exact nature of the intervention is unclear and the effectiveness of the intervention can potentially differ, thereby affecting risk of in-hospital death. Race/ethnicity is not mentioned but if that data point is retrievable, examining study sample characteristics by race/ethnicity would be informative. Some analyses include sex as a covariate while other analyses do not. Without exclusion of the additional potential sources of variation and lack of information on the process of selection for some of the variables, it is difficult to fully assess the validity of the risk effect on nonidentical blood in-hospital mortality.

As the authors point out, this study will require further confirmatory studies. Larger sample sizes for group B and AB patients will be needed to yield more precise risk estimates of the effects of non-ABO-identical transfusion, as well as to generate hazard ratios by diagnosis for group B and AB patients. Improved modeling by including additional relevant confounders, for example, ABO status of other blood products, will be important for more precise results. As the authors suggest, understanding why nonidentical RBCs might increase mortality will be important and perhaps a logical starting point would be to examine the role of the recipient immune characteristics at the time of transfusion. However, further analysis minimizing the potential sources of variation in this retrospective study is central to being able to decide whether it is better to pursue the mechanism or patient prospective studies. Clearly, fine-tuning the current analyses in addition to corroborating the findings in independent studies will be needed before we even begin to contemplate how to manage our blood supply and blood inventory to solely provide ABO-identical transfusions.

**CONFLICT OF INTEREST**

The authors have disclosed no conflicts of interest.

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