

Erythrocyte Transfusion

Remedy or Poison?

IN this issue of ANESTHESIOLOGY, Karkouti *et al.*¹ use population-based administrative healthcare databases to estimate the impact of erythrocyte transfusion on postoperative outcomes after elective hip or knee replacement surgeries. They demonstrate that there is a major discrepancy in the estimation of the impact of erythrocyte transfusion according to the approach used to analyze the data. By using an approach based on logistic regression comparing transfused and not transfused patients, they observed that erythrocyte transfusion was deleterious; in contrast, using an alternative approach based on characteristics of the centers studied, erythrocyte transfusion was found to have no impact on mortality. These contradictory results require further discussion. Our focus in this editorial is to try to better understand the causes of this discrepancy and to evaluate how these findings might impact our actual clinical management of these patients and the consequences for further research.

What More Do We Really Need to Learn about Erythrocyte Transfusion?

There is a large body of research already written on perioperative transfusion, so we may first ask whether there is really a need for more studies in this field. It has been observed that erythrocyte transfusion is associated with worse outcomes in most of the observational studies.²⁻⁴ Furthermore, some randomized controlled trials suggest that a restrictive strategy of erythrocyte transfusion is at least as effective as, and possibly superior to, a liberal transfusion strategy in critically ill patients.⁵ However, some studies provide contrasting results suggesting that transfusion might not be as deleterious in critically ill patients.⁶ In fact, there is a lot of contradictory



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the medical history of the patient considered. Furthermore, some treatments, such as β -blockers, seem to modulate this tolerance to anemia.^{7,8} As a matter of fact, the question of defining markers allowing clinicians to determine whether a patient will benefit from an erythrocyte transfusion remains a real research topic.⁹ Consequently, there is no doubt that we still have a lot to learn about erythrocyte transfusion. The current study by Karkouti *et al.*¹ contributes to improving our knowledge on this topic.

Are Large Administrative Databases Appropriate for Transfusion Research?

The strength of administrative databases is that they include a large number of patients allowing for powerful statistical analyses. They also include coded comorbidities using well-established rules from the International Classification of Diseases codes (ICD-9 or ICD-10). These precise and accurate classifications associate each subtype of pathology

evidence regarding erythrocyte transfusion in the literature; therefore, there is a clear need for studies in the field of perioperative medicine. Indeed, the need for erythrocyte transfusion remains a daily clinical question for most anesthesiologists, because the optimal strategy for managing patients with low hemoglobin is not well established. Even the definition of what constitutes a low hemoglobin level remains controversial. This leads to a major discrepancy not only between transfusion strategies used between centers but also between anesthesiologists. In fact, the search for a universal threshold for hemoglobin level requiring erythrocyte transfusion is probably not the most accurate way to predict the need for transfusion. Tolerance to anemia is highly variable depending on

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to a code. Nevertheless, the collection of the patients' data is directly linked to the knowledge of the codes by the clinicians who collect the data. In fact, the strengths of these codes are probably their main weakness for clinical use. Indeed, the number of codes needed to accurately describe the preoperative comorbidities of a patient is huge. Consequently, the precision of the description of the pathology is not as good as we would expect.

These databases are not collected to respond to the specific clinical questions of anesthesiology; consequently, some variables of great interest may be lacking. For example, preoperative hemoglobin would have been a useful piece of data in the current study.¹⁰ Another concern in the use of these databases for anesthesia research is how missing data are managed. There are few tools available to correct for the over- or under-declaration of comorbidities. This is of particular concern in patients presenting with major outcomes such as postoperative death. In these cases, data are frequently more meticulously collected, whereas for the patients with positive outcomes, this collection may have been more superficial. The result is the overestimation of some predictors as a result of this collection bias.

Although administrative databases present some weaknesses, clinical databases, which have the benefit of including all the relevant variables for study, also present some limitations. The total number of patients in a clinical database must be extremely large to generate an adequate number of patients presenting with the outcome of interest. Because this is difficult to achieve in a clinical database, they are rarely large enough to produce robust consistent models, based on few observed patients with the actual endpoint of interest (*i.e.*, mortality). Nevertheless, we have to be cautious with the significance attached to the variables included in the administrative databases and recognize the impact of the unmeasured variables on the results of such studies.

Which Variables Are Predictive for Erythrocyte Transfusion?

In this observational study, Karkouti *et al.*¹ hypothesize that some unmeasured confounding factor may have unduly influenced the impact of erythrocyte transfusion reported in previous observational studies. It is common sense that those patients requiring transfusion are also the same who bleed and are often also sicker patients and thus they would be expected to have the worst postoperative outcomes. The question of capturing and isolating these confounding influences is more complex. Which variables would be able to predict the need for transfusion? Bleeding is obviously one of them, but the same amount of bleeding would not be associated with the same probability of transfusion if the preoperative hemoglobin levels were different. Furthermore, even if the preoperative hemoglobin levels were the same, particular medical histories may still influence the probability of transfusion. In other words, to predict erythrocyte transfusion according to variables available in administration databases

is not that easy. The consequences are that regression models might be biased because of the unmeasured variables and/or the complex interactions between the available variables.

Karkouti *et al.*¹ used an alternative approach to estimate the impact of erythrocyte transfusion based on the rate of transfusion observed in each center (66 centers with transfusion rates ranging from 10.3 to 57.9% were included in the analysis). Although they observed a strong relationship between transfused and not transfused patients with respect to outcomes, they did not identify the significant differences between the centers classified according to their transfusion rates and how this would influence the outcomes of transfused and not transfused patients.

How can we interpret this difference? Which analyses should be considered conclusive regarding the impact of erythrocyte transfusion on postoperative mortality? The comparison between transfused and not transfused patients might seem less biased, but the characteristics of the database used are probably of major importance in the interpretation of these results. As a matter of fact, the only preoperative variables available in the database used in this study are: surgical procedure, age, sex, socioeconomic status, and comorbid disease. However, anesthesiologists do not give erythrocyte transfusions based only on these preoperative variables. Indeed, preoperative hemoglobin, perioperative bleeding, and hemoglobin nadir are of major importance in the decision-making process. When we do not take these variables into account, the definition of "erythrocyte transfusion" does not make any sense because these unmeasured variables are missing. Consequently, this variable named "erythrocyte transfusion" describes a complicated process comprising many individual variables such as excessive bleeding (caused by surgical complications or by preoperative treatments or conditions) and/or low preoperative hemoglobin. Is it really plausible that "erythrocyte transfusion" could be independently associated with a worse prognosis? What is the real impact of the "actual" erythrocyte transfusion in this? When the variables used to clinically decide to transfuse or not to transfuse a patient are not taken into account in the models, this direct approach consisting of creating two balanced groups according to the preoperative variables produces biased results, which could promote a suboptimal strategy for the management of these patients. As a matter of fact, there is no reason to assume that the complex procedures would have been distributed equally in these two groups. On the contrary, all the evidence tends to include them in the group of patients receiving transfusion, creating a large imbalance in the groups regarding the unmeasured variables.

Which Approach Is the Most Relevant to Estimate the Impact of Transfusion?

Karkouti *et al.*¹ suggest in their work that the wide interhospital variability in transfusion rates might be used to estimate the impact of erythrocyte transfusion. The idea is that for two patients presenting with the same preoperative comorbidities, the probability of being transfused is different between two centers. There is a major discrepancy in the rates of transfusion

observed in the 66 centers included in this study. It remains hard to believe that one anesthesiologist would be five times more likely to give an erythrocyte transfusion based only on local transfusion strategies. This might have an impact on the rates of transfusion, but it should not be that large. The alternative explanation is that this generalized classification of the centers causes us to lose information about the complexity of the surgical procedures, and the mean bleeding associated with these procedures according to center.

Whatever are the respective parts of these two confounding factors, when we use this alternative approach, the variable we named “erythrocyte transfusion” is more likely to reflect consequences of the “actual” erythrocyte transfusion than it was with the previous approach. Consequently, we might think that this approach provides a better estimation of the true impact of erythrocyte transfusion than the one given by the first logistic regression. The results presented by Karkouti *et al.*¹ are then of major importance not only for research methodology but also for clinical practice. Nevertheless, although interesting, these results remain only preliminary. We still have no accurate unbiased estimation of the impact of erythrocyte transfusion.

What Could Be the Next Step in Transfusion Research?

The determination of a hemoglobin threshold to define patients requiring erythrocyte transfusion allows a simple rule to predict transfusion. Nevertheless, it is unlikely that all patients have the same threshold. This is already taken into account when considering young healthy pregnant women or elderly patients with coronary artery disease. That being said, which patients require transfusion? The level of evidence for the potential markers of transfusion requirements remains low. Some approaches using markers of imbalance between oxygen needs and consumption seem to be promising,⁹ but there is a clear need for more research on this subject. In fact, hemoglobin thresholds are useful and should be taken into account, but it seems that this strategy might not be optimal, and we need to also define physiologic markers for the need of transfusion. One of the next steps in transfusion research could be to better define the patients requiring erythrocyte transfusion, because although erythrocyte transfusion is a remedy when needed, it could be a poison when unnecessary, given that it is not a “risk-free” treatment modality.

Considering the uncertainty about the impact of erythrocyte transfusion, the approaches aimed at reducing the need for erythrocyte transfusion should not be neglected. Three main groups of strategies should be considered: (1) increasing the preoperative hemoglobin levels (*i.e.*, preoperative iron or erythropoietin therapy); (2) retransfusion of salvaged cells; and (3) reduction of bleeding using antifibrinolytic drugs. For all these strategies, there is evidence that they produce a reduction in the need for transfusion; however, the safety of some of these strategies remains poorly described.¹¹ The demonstration of the safety of transfusion-saving strategies could also be one of the future areas of transfusion research.

Finally, Karkouti *et al.*¹ demonstrate the difficulty of the interpretation of the results in the field of perioperative erythrocyte transfusion research. Although no clear recommendation for clinical practice could be drawn from only these results, we should consider that better interpretation of the results from studies might transform the apparent impact of a treatment, as it is the case for erythrocyte transfusion in this study.

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