Welcome to the Anesthesiology journal podcast, an audio interview of study authors and editorialists.

Dr. James Rathmell: Hello. I’m Jim Rathmell, Professor of Anesthesia at Harvard Medical School and one of the executive editors for Anesthesiology. You’re listening to an Anesthesiology podcast designed for physicians and scientists interested in the research that appears in our journal.

Today, we’re going to talk to the author of a publication that appears in the July 2016 issue of the journal. Helping me with today’s podcast is BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University. Dr. Sweitzer, thank you for helping me today.

Dr. BobbieJean Sweitzer: Thank you, Dr. Rathmell, for inviting me to join this conversation.

Dr. James Rathmell: With us today is Dr. Frédérique Hovaguimian from Division of Anesthesiology at the University of Zurich, in Zurich, Switzerland. Dr. Hovaguimian is the first author on a publication titled, "Restrictive versus Liberal Transfusion Strategy in the Perioperative and Acute Care Setting: A Context-specific Systematic Review and Meta-analysis of Randomized Controlled Trials. This article appears in the July issue of the journal. Dr. Hovaguimian, welcome, and thank you for being willing to talk with me today.

Dr. Frédérique Hovaguimian: Hello, Dr. Rathmell. Thank you very much for giving me the opportunity to discuss with you today.

Dr. James Rathmell: Also with us today is Dr. Hovaguimian’s co-author, Professor Paul Myles, who is Director of the Department of Anesthesia and Perioperative Medicine at Alfred Hospital and Monash University in Melbourne, Australia. Dr. Myles, welcome, and thank you for being willing to talk with me today.

Dr. Paul Myles: Good to be here, Dr. Rathmell.

Dr. James Rathmell: Dr. Myles, I thought we’d start with you, as senior author on this paper. Can you start by telling us a little about so-called restrictive versus liberal transfusion strategies? How are they defined, and why are these strategies important? And what questions did you set out to answer by conducting this systematic review?

Dr. Paul Myles: Well, the concept of restrictive and liberal transfusion strategies is really to determine whether a lower hemoglobin or hematocrit threshold, limiting blood transfusion, might provide additional benefit by avoiding some harms of transfusion, and perhaps be otherwise equally safe in accepting a slight reduction in the oxygen-carrying capacity of the blood, challenging the traditional view that a hemoglobin threshold of around about 10 milligrams per deciliter, or 100 grams per liter, is necessary. And there’ve been quite a few randomized trials over the last 10 to 15 years, both in the critical care and surgical setting, that have tested this hypothesis.

Now, what interests me in this is, as a cardiac anesthesiologist, I’m concerned about the potential limitation of oxygen supply, particularly to, for instance, the heart. We know, for instance, in basic physiology, that there’s maximal oxygen extraction in the heart, and the only way of increasing blood oxygen delivery in that setting is to increase flow; and therefore, a lower hemoglobin threshold could provide some additional risk, at least in that cardiovascular setting. And therefore, we investigated the literature and identified all the randomized trials addressing this subject in different types of surgery, and also the critical care setting, and pooled them in a meta-analysis to try and determine whether or not a restrictive regimen was safe or if it also provided additional benefits in some settings.

Dr. James Rathmell: Dr. Hovaguimian, how did you get involved in conducting the study with Professor Myles?

Dr. Frédérique Hovaguimian: Actually, it’s quite simple. We conducted this study while I was completing a master degree of clinical research methods at Monash University in Melbourne. As for the topic, transfusion strategies always appealed to me, maybe because working in different hospitals made me realize how policies can drastically differ, even in a small country like Switzerland.

Dr. James Rathmell: Have you had a long interest in transfusion medicine?

Dr. Frédérique Hovaguimian: Yes. I think it’s really relevant in our everyday practice.

Dr. James Rathmell: And you’re a practicing anesthesiologist as well?

Dr. Frédérique Hovaguimian: Yes, I am.

Dr. BobbieJean Sweitzer: I’d like to ask you to explain just how you conducted the study and what you set out to find. You tell us in the paper that you used a context-specific approach to conduct a systematic review to quantify the effects of transfusion strategies. What exactly is a context-specific approach, and what specific questions did you use to help you answer this question about transfusions?

Dr. Frédérique Hovaguimian: Well, it all started when we realized that in previously published meta-analysis, data were combined even if they were coming from very different populations or contexts—say, children with elderly, or cardiac surgery with a postpartum setting. As a clinician, I found these risk estimates difficult to interpret, since a young woman that just had a C-section would probably better tolerate anemia than an 85-year-old with ischemic heart disease and hip surgery. In other words, populations with a different risk to develop adverse events were pooled together.

You certainly heard of the expression, mixing apples with oranges, which is a common criticism of meta-analysis. Here, it’s a bit more subtle. It would be more like combining green apples with pink ones. And that’s what we call clinical heterogeneity.

Now, the problem with mixing green and pink apples is that you lose the information related to their color. And in this previous analysis, the information related to the patient’s risk to develop adverse events was lost. This is problematic because then you don’t know if the observed effect—for instance, the lack of harm observed with restrictive transfusion strategies—is truly the result of the intervention itself or of the fact that heterogeneous populations were combined together, or of both. And our goal was thus to preserve that bit of information about the patient’s risk to develop adverse event throughout the analysis, which led us eventually to use a context-specific approach.

Dr. James Rathmell: That’s perfect. That’s a wonderful explanation.
Dr. Frédérique Hovaguimian: [Laughter].

Dr. James Rathmell: So, I get it. When you’re approaching a young woman having a peripartum hemorrhage, you’re going to think very differently, or you may think very differently, than someone who has advanced cardiovascular disease…

Dr. Frédérique Hovaguimian: Exactly.

Dr. James Rathmell: …where it’s appropriate to transfuse. And that makes sense in everyday practice. But then when you go to do a meta-analysis, the tendency is to lump everything together, and you lose all of those subtleties—the different colors of the apples.

Dr. Frédérique Hovaguimian: Exactly. And when clinicians…

Dr. James Rathmell: Well, then…

Dr. Frédérique Hovaguimian: …look for evidence, you know, they look for meta-analysis, and then they end up with those patients pooled together even if it doesn’t make any sense in the clinical setting.

Dr. James Rathmell: Well, that’s something we really need to guard against. I give talks on this and I talk about, it’s like a budget, right? It’s all about the assumptions. And when you lump everything together, you may be treating individual populations or sub-populations inappropriately. And that’s what you did so nicely here.

Dr. Frédérique Hovaguimian: Absolutely.

Dr. James Rathmell: Well, can you describe the number of trials that were involved in this study, and how exactly you group them into these context-specific strata? You talked about two of them, but I think there are many more in this study.

Dr. Frédérique Hovaguimian: So, the idea was to obtain homogeneous strata in terms of risk to develop adverse events; or, in other words, strata with low clinical heterogeneity. To form this strata, we used criteria that are known to affect clinical heterogeneity, such as patient age, comorbidities, concomitant medication, or clinical settings.

We eventually included 31 trials and regrouped them into five strata. The first included eight trials conducted in patients with cardiovascular disease undergoing cardiac or vascular procedures. The second included nine trials conducted in elderly population undergoing orthopedic surgery. The third included ten trials conducted in a mixed surgical and medical population admitted to an acute care facility. The fourth included two trials conducted in a younger, less comorbid population, admitted for acute traumatic brain injury or subarachnoid hemorrhage. And the fifth included two trials: one connected anemic women in the postpartum phase, and one in thrombocytopenic middle-aged patients with hematologic cancer.

Dr. BobbieJean Sweitzer: And what did you find in your analysis?

Dr. Frédérique Hovaguimian: So, we found that restrictive transfusion strategies were associated with an increased risk of complications in situations combining high-risk patients with major surgery. Those with cardiovascular disease undergoing cardiac or vascular procedures seemed to have more event reflecting inadequate oxygen supply, higher mortality rates, or both.

In the elderly orthopedic population, a restrictive policy led to a 40% increase in ischemic events or acute kidney injury. These findings were, however, not reproducible in critically-ill patients. As for the risk of infection, only orthopedic patients assigned to a restrictive policy seemed to have less septic events. We believe that the lack of protective effect in cardiac surgery patients might be related to the fact that these patients were more systematically exposed to non-erythrocytes blood products such as fresh frozen plasma or platelets which are, by the way, also known to impair the immune response.

Dr. BobbieJean Sweitzer: So, in these two groups of high-risk patients—those undergoing cardiac and other vascular procedures—restrictive transfusion strategies seemed to increase the risk of mortality. But that was not true for the critically ill patients and you saw no difference in rates of infection associated with either transfusion strategy. But what were the limitations of your study?

Dr. Frédérique Hovaguimian: First, there are limitations related to the residual heterogeneity in the included data: variability in outcome definitions; variability in outcome reporting; scarcity of data; variability in event rates, or variability in study size. We can try our best to minimize the effect of these sources of heterogeneity, and I think that’s really what we did here. But we also have to accept that a certain degree of heterogeneity will always remain. Maybe this is not such a bad thing, since it allows us for a wider applicability of the findings.

Then there is the problem of subjectivity. For instance, to capture the full spectrum of effects related to transfusion strategies and to improve statistical precision, we used arbitrarily-defined outcome categories because we thought they were biologically well-founded. But by doing so, we left aside the analysis of each individual endpoint. It could be that these individual components differ in clinical importance. For instance, having a postoperative stroke could be for a patient more relevant than having an acute kidney injury, and these questions cannot be adequately addressed when outcomes are merged into categories.

Dr. James Rathmell: So, neither patient groups nor the magnitude of impact of specific outcomes in individual patients can really be gotten at in this type of an analysis.

Dr. Frédérique Hovaguimian: Yes, that’s correct. When you merge categories together—when you choose to do that—you usually obtain better estimates of the effect, because it’s more statistically stable or it’s more precise; but you lose these subtle differences in terms of; what does it mean for the patient? If I am going through high-risk surgery and I get a stroke because I’m anemic, and no one gave me blood, I would find it more relevant because—if I can get an infection. But that’s my personal idea of it. And when we perform such big data or such big groups analysis, this patient-related point of view doesn’t really come out, and that’s something that’s related really to the methodology.

Dr. James Rathmell: That’s superb. So, it’s really still very important for us to apply these things in a meaningful way to each of the patients we care for.

Dr. Frédérique Hovaguimian: Absolutely.

Dr. James Rathmell: Dr. Myles, the confidence intervals around the odds ratios for these differences in mortality come pretty close to straddling unity, meaning there’s no demonstrable statistically significant differences. With what degree of certainty can we conclude that these are true differences? And even if they are true differences, how significant are they in the clinical care of our patients?

Dr. Paul Myles: The good thing about a meta-analysis is, with a lot larger numbers you have more study power, and the estimates of risk are obviously accompanied with the 95% confidence intervals. And...
that, to me, is a good measure of the certainty of the results. And if we look at the spread of those estimates, the point estimate of risk is in excess of one; so, demonstrating or suggesting excess mortality. But the confidence intervals do straddle the unity value of one, and therefore not quite statistically significant in the cardiac setting. It was so in the orthopedic setting with elderly patients. So, what that tells us is, there is a strong signal suggesting harm. But of course, it’s not a definitive result. It’s really, I think, a wake-up call both for clinicians in general in their practice to be perhaps more cautious until more data is published, or a more definitive large, randomized controlled trial is done.

Dr. James Rathmell: Anesthesiologists are keenly aware of the risks and the benefits of transfusion, yet much confusion remains about best practices. How have the findings of your study changed your own transfusion practices?

Dr. Paul Myles: For all doctors, the first thing, of course: first, do no harm. So, I think we have to be cautious about changing practice or adopting techniques where the evidence is not yet sufficient to prove absolute benefit, and certainly to reduce any concerns of harm. And our findings, I think, are pointing towards a possible harm of a restrictive transfusion practice, and in my practice I therefore am a little bit more liberal of transfusing in patients with known or suspected coronary artery disease. I would not, for instance, use a transfusion threshold anything less than about 85 or 90 in that setting. I think that’s the important finding for the here and now, until further studies are done to guide us further in our practice.

Dr. James Rathmell: You say 85 or 90—translate that into hematocrit, for those of us on the other side of the ocean.

Dr. Paul Myles: [Laughter]. Well, in terms of hematocrit, again, it depends slightly, of course, on a few factors; but that’s typically in the range of about 24 to 26 as hematocrit.

Dr. James Rathmell: What are some of the questions that remain unanswered about how and when we should use transfusion in the perioperative period, and are you pursuing any ongoing studies in this area?

Dr. Paul Myles: Well, of course, there’s a lot of other types of research going on around blood transfusion—both efforts to try and reduce bleeding, with both surgical technique, antifibrinolytic drugs and other blood-sparing agents, and of course the avoidance of excessive IV fluid administration, which of itself, of course, causes a direct hemodilution effect. And each of these relatively simple approaches can reduce unnecessary transfusion; but at the same time, of course, we don’t want to go to a level that starts to create some stress or harm to organ systems. My big area of interest relates around antifibrinolytic drugs, particularly tranexamic acid, in the cardiac surgery setting. I do know of many other studies happening in orthopedic, spine and other types of surgery.

Dr. James Rathmell: I hope today’s discussion will be of interest to many of our listeners, and spur you to read the article in the July 2016 issue of Anesthesiology. We’ve also created an infographic to highlight the key findings in this study and make it easy to interpret.

I want to thank Dr. Hovaguimian and Myles for discussing their new research with us today. You’re both to be congratulated for taking a disciplined and systematic approach to combining the many trials on transfusion and attempting to answer the very important question about the best strategy for transfusion. It seems there still are no absolute answers.

Thank you, and I wish you well as you continue efforts to answer meaningful questions for everyday anesthesiologists that improve the safety of anesthesia for our patients.

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