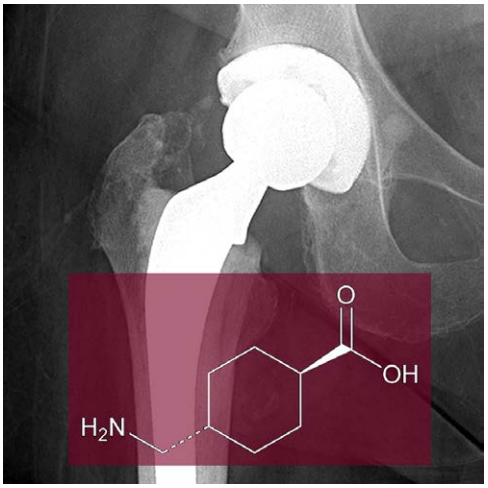
Tranexamic Acid in High-risk Arthroplasty Patients: How Will We Adapt to Evolving Evidence?

Douglas A. Colquhoun, M.B., Ch.B., M.Sc., M.P.H., Brian R. Hallstrom, M.D., Sachin Kheterpal, M.D., M.B.A.

"Let's step outside to settle this." While this pugilistic phrase is most commonly seen in Hollywood movies, it is rarely heard in the professional confines of an operating room. However, just a decade ago, one of us found themselves uttering it during a dialogue with a new orthopedic surgeon recommending the use of tranexamic acid for an elective hip replacement. This was a medication the anesthesiologist knew well from their liver transplant patient population but had never administered for a joint replacement. It seemed inappropriate to have this discussion in front of an awake patient. While only 4% of patients undergoing elective lower extremity joint replacement in 2011 received tranexamic acid,[1] nearly three quarters were receiving it in 2016,[2] and it is now recommended routine practice in consensus guidelines.[3]



"…opinions and biases are less reliable than well-conducted retrospective cohort studies, which use rigorously collected and validated data."

In this issue of Anesthesiology, Poeran *et al.*[2] advance our knowledge in a critically understudied area: tranexamic acid administration in "high-risk" lower extremity arthroplasty patients. These data demonstrate three important concepts for the readers of this journal: (1) lower extremity arthroplasty patients with a history of myocardial infarction, atrial fibrillation, or renal disease that receive tranexamic acid had a lower rate of transfusion without a measurable difference in adverse events than patients who did not receive the medication; (2) robust analyses of rigorously collected and validated observational data can advance daily practice beyond clinician bias and preference when we lack randomized controlled trial data; and (3) anesthesiologists must become facile at assessing the quality of a variety of study data, methods, interpretations, and conclusions.

Tranexamic acid has been identified by the World Health Organization as an essential medicine given its ability to treat life-threatening hemorrhage in trauma, traumatic brain injury, and obstetrics.[4–6] The agent was developed and reported in 1962 by Utako Okamoto and has found renewed interest across a range of surgeries. Early literature using national administrative data from hundreds of hospitals evaluated the association of transfusion and tranexamic acid administration in lower extremity arthroplasty.[1] However, very few high-risk patients with a history of coronary artery disease, congestive heart failure, or neurologic disorders received tranexamic acid due to concerns of adverse events. As a result, while the overall population did not demonstrate a risk of adverse events associated with tranexamic acid administration, the issue of high-risk patients and their risk/benefit balance remained unanswered because this group has been systematically understudied.

In the current work, Poeran *et al.*[2] extend their previous analyses and evaluate the risk/benefit of tranexamic acid administration in three distinct high-risk patient groups receiving tranexamic acid compared to similar high-risk patients not receiving the drug: (1) more than 12,000 patients with a history of myocardial infarction; (2) more than 22,000 patients with a history of renal disease; and (3) more than 22,000 patients with a history of atrial fibrillation. In each of these groups, there was a nearly 70% adjusted relative reduction in transfusion from a baseline of more than 15 to 23% to 5 to 9%. In addition, there was no measurable increase in venous thromboembolism, myocardial infarction, ischemic stroke, or transient ischemic attack. These data suggest that previous concerns about administration of tranexamic

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acid in these high-risk populations may be overstated. Administration of tranexamic acid was associated with a lower rate of erythrocyte transfusions, which have their own risks and costs. However, no single study is definitive. In contrast to the large number of patients with myocardial infarction, renal disease, or atrial fibrillation, relatively few patients with other comorbidities in this data set received tranexamic acid and were available for study (only 178 patients with a history of deep venous thrombosis, 52 patients with pulmonary embolism, 83 patients with ischemic stroke, and 614 patients with seizures). These high-risk patients remain an importantly understudied population with no reliable evidence to guide practice. We must continue to cautiously observe and reevaluate the use of tranexamic acid in these patients; the current data cannot be used to establish safety in these populations. Ideally, high-quality prospective randomized controlled trials of tranexamic acid in these populations will be performed. Perioperative clinicians must ensure we do not repeat the mistakes of the aprotinin era, plagued by the absence of high-quality unbiased evidence and a lack of data transparency.[7] However, combined with a recently published meta-analysis of tranexamic acid randomized controlled trials in many different surgical groups,[8] the data presented by Poeran *et al.*[2] do provide a degree of reassurance that current patterns of use of tranexamic acid in specific high-risk lower extremity arthroplasty patients are not associated with harm.

When left with individual clinician biases due to the absence of randomized controlled trial data, prospective registries and administrative data can be used to advance the perioperative medicine evidence base if collected and analyzed with transparent declarations of their limitations. Many essential perioperative clinical trials evaluating choice of fluid resuscitation, fluid balance, anesthetic adjuncts, and anesthesia technique inform daily care.[9–12] However, many questions remain unanswered. In joint arthroplasty, observational data can inform the role of tranexamic acid, the risk of concurrent bilateral knee replacements, the benefits of home discharge, and identify specific implants at high risk of failure. One such collaborative quality initiative and data registry is the Michigan Arthroplasty Registry Collaborative Quality Initiative. The registry has abstracted standardized and validated patient comorbidities, operative information, implant data, and outcomes since 2012 for nearly 50,000 lower extremity joint replacements a year. Rigorously validated, highly scrutinized data overcome some of the limitations and concerns of retrospective cohort studies.

We must use the full breadth of reliable, reproducible, and peer-reviewed data to advance care. In many situations, we must be ready to shed our biases or historical practices when new evidence is presented. Through collaborative efforts across surgery and anesthesiology, we can collect data, evaluate practice, and disseminate information.[3] Robust trials and subsequent meta-analyses of such studies remain the pinnacle of trusted evidence. However, in the absence of such evidence, the anesthesiologist is left weighing retrospective cohort studies against expert opinions and their own biases; these opinions and biases are less reliable than well-conducted retrospective cohort studies, which use rigorously collected and validated data. The work by Poeran *et al.*[2] in this issue highlight one such situation. The reality is that we cannot be mesmerized by any one article. We must demand reproducible science, regardless of the underlying methods. As scientists trained in the field of anesthesiology, we must adhere to words often ascribed to Keynes: "When the facts change, I change my mind. What do you do?"

Competing Interests

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Correspondence

Address correspondence to Dr. Kheterpal: sachinkh@med.umich.edu

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