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 the journal.

Today, we’re going to talk with the authors of a publication that appears in the May 2017 issue of the journal. With us today is Dr. Abdullah Terkawi. He’s currently a resident in anesthesiology at the University of Virginia, and he worked with Dr. Ed Nemergut, Professor of Anesthesiology at the University of Virginia, and Dr. Dan Sessler, Chair of the Department of Outcomes Research at the Cleveland Clinic. Dr. Terkawi is the first author on an article titled “Pain Management Modalities after Total Knee Arthroplasty: A Network Meta-analysis of 170 Randomized Controlled Trials.” Dr. Terkawi, thank you for joining us.

Dr. Abdullah Sulieman Terkawi: Thank you.

Dr. James Rathmell: Also with us today is Dr. Colin McCartney. He’s Professor of Anesthesiology and Pain Medicine at the University of Ottawa in Ontario, Canada. Together with Dr. Brian Ilfeld of the University of San Diego, Dr. McCartney authored an editorial view that accompanied Dr. Terkawi’s article entitled “Searching for the Optimal Pain Management Technique following Knee Arthroplasty: Analgesia is Just the Tip of the Iceberg.” Dr. McCartney is going to share some of the perspective that their editorial brings to this new research. Dr. McCartney, welcome, and thank you for your willingness to share your insights.

Dr. Colin J. L. McCartney: Thanks for the opportunity, Jim. It’s a pleasure to be here.

Dr. James Rathmell: Dr. Terkawi, congratulations on the publication of your work. Now, it’s quite an achievement for anesthesiologist in training. Tell us a little bit about your background. Do you have advanced training in statistics or clinical research, or some other area of research?

Dr. Abdullah Sulieman Terkawi: I started my anesthesia (inaudible) in Saudi Arabia. While in Saudi Arabia, I collaborated with Drs. Pamela Flood and Steve Shafer, doing a genetic research project that required time series modeling in obstetric anesthesiology. Their mentorship inspired me to come to the United States for anesthesia training. I moved to University of Virginia in 2013 and did two years of a clinical research fellowship, which included training in statistics. I enjoy doing statistics and using novel statistical methods. I started my residency in 2015 at University of Virginia and I am currently a CA1. My long-term goal is fellowship in pain management followed by an academic position that will allow me to investigate anesthesiology in general, and pain management specifically.

Dr. James Rathmell: So, set the stage for us. We already know a lot about managing pain after total knee replacement. What did you set out to learn from this new look at the existing literature?

Dr. Abdullah Sulieman Terkawi: So, having done anesthesia in several countries and institutions, I’ve seen the range of anesthesia practice, and since I have a personal interest in pain management, I noticed how pain management after total knee arthroplasty differs markedly across institutions. I also noticed how strongly various anesthesiologists believe that their practice was optimal, often in the absence of evidence.

On a personal note, I conducted a randomized clinical trial in 2013 comparing epidural analgesia to combined femoral and sciatic nerve block, and when I submitted the work for publication I was surprised when the editor-in-chief responded that he was uninterested in my study, since he had a good personal success with periarticular infiltration. As it happened, I was learning about network meta-analysis at the time, and recognized that analgesia for total knee arthroplasty would be a great topic for network meta-analysis.

Dr. James Rathmell: So, you set out to combine and compare the many published original research articles in an effort to figure out which technique provides the best pain control after knee replacement. But you wanted to go beyond the simple meta-analysis, and indirectly compare techniques that had never been directly compared, using what’s called a network meta-analysis. Can you tell us how you carried out the study and explain, in simple terms, how a network meta-analysis works?

Dr. Abdullah Sulieman Terkawi: Sure. I think Dr. Ilfeld and Dr. McCartney nicely summarize the network meta-analysis in their editorial. Network meta-analysis is a relatively new methodology that expands the concept of traditional meta-analysis to produce pairwise comparisons and relative treatment effect across a range of interventions through both direct and indirect comparisons. Importantly, the method allows comparisons among treatment modalities that have never been directly compared. The end result is a relative ranking of all modalities, while properly accounting for correlations between effect sizes from multi-arm trials.

For example, if one randomized clinical trial demonstrates that treatment “A” is superior to “B,” and a second RCT provides evidence that treatment “C” is superior to “A,” then by networking the two we have evidence that treatment “C” is superior to “B” even though these two interventions were not directly compared. Nowadays, many experts consider network meta-analysis to be the best method for summarizing and evaluating available evidence, and many consider it to be the highest level of evidence in treatment guidelines.

Dr. James Rathmell: Well, we’re going to come back to that with Dr. McCartney, because he really had an elegant explanation, and this idea of network meta-analysis is kind of new, so I want listeners to get ahold of that. But let’s go on to your trial. You included 170 trials and you assessed 17 different treatment modalities for controlling pain after total knee replacement. What did you find? Which are the best techniques and which are the poorest techniques?

Dr. Abdullah Sulieman Terkawi: Based on the available evidence, we found that combinations of multiple nerve block, especially combined femoral and sciatic blocks, perform better than other modalities in terms of better analgesia, less opioid consumption, and larger range of motion in the first 72 hours after surgery. In a word, two is better than one, and one is better than none.

Interestingly, epidural analgesia, which is often considered a standard, appears inferior to multiple peripheral nerve block, and even selective femoral nerve block, in most outcomes. In contrast, patient-controlled analgesia—PCA—and specific opioids alone were worse than virtually every other approach. Thus, I would strongly encourage...
Anesthesiologists to provide their patients with whatever possible adjuvant pain management modality might be available; and if nerve block cannot be provided for some reason, the surgeon should at least provide periartricular local anesthetic infiltration.

Dr. James Rathmell: So, what are the limitations of this study?

Dr. Abdullah Sulieanm Terkawi: So, I think our study has some unique features. First, we defined the optimal modality as one that the best balanced low pain scores, low opioid consumption, and large knee range of motion, and we also measured them at multiple timepoints up to 72 hours. We were able to rank the treatment modalities for each outcome—used something called surface under the cumulative ranking curve values, and rankogram, to present the hierarchy of intervention for each outcome.

But, of course, every study has limitations and in our case they include, number one, by the nature of meta-analysis our results are limited by the quality of available studies. Many included studies had small sample size and high or unclear risk of bias. We were limited to available studies. Many important comparisons have never been studied, and network meta-analysis is only a partial substitute for comparisons that have never been attempted. Some comparisons were based on spurious results and thus lacked power, thus having wide confidence intervals and uncertain ranking. And finally, rehabilitation remains poorly studied, and we therefore restricted our analysis to range of motion only.

Dr. James Rathmell: So, on some of these limited outcomes regional anesthesia, particularly combinations of nerve blocks, adds to analgesia in the short term, but we don’t know much about the longer-term effects of these.

Dr. McCartney, the title of your editorial view is “Searching for the Optimal Pain Management Technique following Knee Arthroplasty: Analgesia is Just the Tip of the Iceberg.” I want to start by reading a terrific explanation of network meta-analysis from your editorial, because I think it explains the concept very nicely. You tell us, traditional pairwise meta-analysis combines the results of multiple randomized controlled trials, or RCTs, that all investigate the direct comparison of two, and only two, interventions to produce an estimate of the relative net benefits of these interventions. In contrast, network meta-analysis synthesizes the results of multiple RCTs that do not necessarily include one common intervention, but various possible treatments. Using a process similar to geometry’s transitive property of equality, this technique allows indirect comparison of diverse modalities that might themselves never have been directly compared.

For example, if one RCT demonstrates that treatment “A” is superior to “B” and a second RCT provides evidence that treatment “C” is superior to “A,” then, networking the two, we have evidence that treatment “A” is superior to “B” even though these two interventions were never directly compared. That’s nicely said.

Now, can you put Dr. Terkawi’s network meta-analysis in perspective for us? The study clearly ranks the treatment modalities covered in their analysis. As you ask yourself in the editorial, will there then finally be widespread consensus regarding the optimal post-total knee arthroplasty analgesic technique with this new analysis?

Dr. Colin J. L. McCartney: Thanks, Jim. Just wanted to start off by congratulating Dr. Terkawi on his very— and colleagues, on their very elegant study and their very elegant methodology—and also acknowledge the significant contribution to the editorial of my colleague, Dr. Brian Ilfeld.

When it comes to consensus, and what widespread consensus is found, I think what the study tells us is what we probably already know, which is that peripheral nerve blocks are very good for pain control, they’re very good for reducing opioid consumption, and they’re very good for improving passive rehabilitation.

We now need to move past those things, I think, to focus on, you know, what is widely now called the triple aim, which is a combination of patient experience, the overall cost of care, and the effects of an intervention on population health. I think, you know, with total knee arthroplasty, what are the factors that impair not just passive rehabilitation but, probably more importantly, active rehabilitation?

And the factors that I’ve seen in my practice are that, number one, pain is a major limitation to active rehabilitation, and that’s very important when it comes to providing best pain control after knee replacement. Then the other factors include symptom control, some of them related to opioid consumption, like nausea and vomiting, dizziness, and in fact motor block as well, which is not as commonly just caused by the peripheral nerve block, but is also caused by the surgical incision itself and the muscle split that is done whenever you do a total knee arthroplasty. So, there’s a fine line to tread between providing best analgesia and also facilitating best rehabilitation for the patient.

Dr. James Rathmell: So, it’s important for readers to understand that this study was heavily weighted toward the examination of the influence of postoperative analgesic modalities on just a few factors—pain scores, opioid use, and passive range of motion—because most of the studies lacked much information about any other factors. You tell us, while these factors are important, they don’t reflect the full range of priorities of the many stakeholders involved in total knee replacement surgery. What do you mean by stakeholders, and how are others likely to influence the selection of the analgesic treatment regimen selected by a specific joint replacement program?

Dr. Colin J. L. McCartney: Well, I think we have to take this back to the triple aim again. So, we look at the triple aim. We look at patient experience, we look at efficiency and cost of care, and we look at overall population health. That gives you your stakeholders there.

I think the patient, of course, is central to all that we do in medicine, and needs to remain at the core of what we do. I think when we look at other stakeholders and other people who are very invested in patient care, we need to look at the anesthesiologist, the surgeon, the nursing staff, the physiotherapist, and also society in general. In every healthcare system, somebody has to pay for that procedure, and whether that’s a government-funded system or whether it’s a private-funded system, the payer also is a significant stakeholder. So, that’s who I would regard as the stakeholders.

Dr. James Rathmell: So, there’s a lot more to putting a program together, where all of the individuals that have something to say about how the entire progress from decision to undergo joint replacement, through rehabilitation, are going to fall into place. You know, in fact, here in Boston, the majority of our joint replacement programs abandoned the use of continuous peripheral nerve block some years ago in efforts to facilitate early ambulation, rightly or wrongly. What do you think the take-home message from this study is for practicing anesthesiologists, and those of us who are on these teams that try and facilitate joint replacement, but really have a foodness for regional anesthesia?

Dr. Colin J. L. McCartney: I think you hit the nail on the head with your expression, “team.” You know, I think the key thing is building a team with your surgical, physiotherapy and nursing colleagues to facilitate rehabilitation after surgery. And when you do that, and you focus on one common aim that we’re all focused on, which is usually active rehabilitation for the patient, and that includes concern of the patient, concern of the surgeon, and other—the anesthesiologists and other staff that are looking after the patient, that all aims at one target. And when
you do that, you can start assessing the factors that impair that target. And like I say, in the past, that was – or in past and present, I still do many joint replacements on a monthly basis. Those factors are pain, nausea, dizziness, and motor block. If you can balance all of those things to reduce all of those things to a level where patients can actively rehabilitate, you’ll facilitate quality and ability to rehabilitate in a fast manner.

I think, in order to do that, you need to build a local culture of collegiality and of working together, and you can only do that by respect for one another, and focusing on goals that we all seek. We need to consider standardization of care, because without standardization it’s very hard to measure outcomes and determine standardized outcomes. And then, you know, there are other ways of feeding back outcomes to providers as well. I think, you know, in my own institution, the thoracic surgeons here and thoracic anesthesiologists have worked very well with feeding back outcomes on an anonymous basis to providers, and looking at positive deviance, to raise the overall standard of care for all – that all providers provide to their patients.

Dr. James Rathmell: You also tell us that Dr. Terkawi’s study is important in that it points us exactly where there are gaping holes in our existing knowledge. What are the top two or three research questions in this arena that need to be better addressed in order to guide our clinical care?

Dr. Colin J. L. McCartney: I think you can split them into two areas. One is the actual topics of research, and number two is the methods by which we answer these questions. I think when we’re looking at our areas of study, some of the key areas that have not really been looked at in the last many years is, number one would have to be knowledge translation. You know, when we look around North America, for example, despite the fact that there are many studies that demonstrate the benefits of neuraxial anesthesia for total joint arthroplasty, only about 25% of patients actually get a neuraxial block. And what that tells us is, translating knowledge into practice takes a long time and we need to look at ways of more effectively translating our knowledge into practice.

The second key area would be ways of optimizing rehabilitation outcomes after major surgery like total knee arthroplasty. Not just in hospital but also at home, because we’re discharging these patients faster and faster after surgery, and we have a lot of data about what happens in hospital but very little data about what happens at home, and how we can actually do a better job of making sure that patients, when they go home, they’re in comfort and symptom-free, so that we can continue their rehabilitation in as fast a manner as possible.

When it comes to the methods, I think Dr. Terkawi’s study, you know, focuses on randomized controlled trials. And randomized trials in themselves are a very good way of examining specific questions. But we have to realize – and for anybody that’s done a randomized trial, they’ll realize that only about 20% of patients in any population are able to be recruited into that trial. So, whether they’re actually representative of the total population or not is a good question.

The other aspect that we haven’t seen a lot of in joint research is qualitative research to look at the patient experience around the joint replacement.

And finally, as I mentioned earlier, standardization of outcomes is going to allow us to put studies together in the way that Dr. Terkawi and colleagues have done to look – you know, for example, one of the limitations that they recognize in their study was the lack of active rehabilitation measures, and that really undermined their ability to look at the impact of some of those procedures on rehabilitation.

And I should say one more thing: that, as we started to look at better ways of examining some of these interventions, I think large-scale, pragmatic randomized controlled trials, which sacrificed the quality of the overall methods, but with the ability to randomize larger numbers of patients across institutions, so that you have the same amount of power but hopefully be able to recruit larger numbers of patients from any one population, so that the final result was more representative of the population under study.

Dr. James Rathmell: Real-world data. Dr. Terkawi, what comes next for you in your research? Are there specific questions your group is addressing as a result of this meta-analysis?

Dr. Abdullah Sulieman Terkawi: I think, first, network meta-analysis has multiple potential applications in our field, and it’s probably the best way to present the full range of current evidence in context, thus guiding both clinical care and future research.

Second, I think scientists need to continue exploring selective nerve blocks that will provide excellent analgesia with preserving motor function.

Dr. James Rathmell: I hope today’s discussion will lead many of you listening to read this new article and the accompanying editorial view that appear in the May 2017 issue of ANESTHESIOLOGY, to learn more about what we know and what we don’t know about pain management after total knee arthroplasty. Drs. Terkawi and McCartney, thank you for joining us, and for the terrific explanations. I wish you well as you continue your efforts to better understand the role that choosing the optimal pain management modality might play in improving outcomes after total knee arthroplasty.

Dr. Abdullah Sulieman Terkawi: Thank you.

Dr. Colin J. L. McCartney: Thank you very much, Jim.