Host: Welcome to the *ANESTHESIOLOGY* journal podcast, an audio interview of study authors and editorialists.

Dr. James P. Rathmell: Hello. I'm Jim Rathmell, Professor of Anesthesia at Harvard Medical School and Chair of the Department of Anesthesiology, Perioperative and Pain Medicine at Brigham and Women's Hospital. I'm one of the Executive Editors for *ANESTHESIOLOGY* and you're listening to an *ANESTHESIOLOGY* podcast that we've designed for physicians and scientists interested in the research that appears in the journal.

Today we are going to talk with the lead author of an original research article that appears in the February 2021 issue. With us today is Dr. Faraj Abdallah. Dr. Abdallah is an Associate Professor of Anesthesiology and Pain Medicine at the University of Ottawa in Ottawa, Ontario, Canada.

Dr. Abdallah is the senior author on an article that appears in the February 2021 issue of the journal and it's titled, "Perineural Liposomal Bupivacaine is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia: A Systematic Review and Meta-analysis." Dr. Abdallah, thank you for joining us.

Dr. Faraj W. Abdallah: Thank you, Jim, for this valuable opportunity to deliver our research findings to a wider audience.

Dr. James P. Rathmell: We also have with us today Dr. Mary Ellen McCann. Dr. McCann is Senior Associate in Perioperative Anesthesia in the Department of Anesthesiology, Critical Care and Pain Medicine at Boston Children's Hospital and Associate Professor of Anesthesia at Harvard Medical School.

Dr. McCann authored an editorial that accompanies Dr. Abdallah's meta-analysis in the February 2021 issue of the journal and it's titled, "Liposomal Bupivacaine: Effect, Cost-effective, or (Just) Costly?"

Dr. McCann was the Acting Chair For the FDA Anesthetic and Analgesic Drug Products Advisory Committee that was held on February 14th and 15th in 2018 which advised on the supplemental IND application for expanded indications for liposomal bupivacaine for nerve blocks. Dr. McCann, welcome and thank you for joining us.

Mary Ellen McCann: Thank you for inviting me. It's a real pleasure.

Dr. James P. Rathmell: Dr. Abdallah, congratulations on the publication of your study. Let's start by setting the stage and describing your study for listeners. Liposomal bupivacaine is useful for infiltration and field blocks and it's said to provide extended postoperative analgesia for up to 72 hours after various surgical procedures.

The US Food and Drug Administration just approved liposomal bupivacaine for perineural use in interscalene nerve blocks of the brachial plexus, but the evidence of clinical effectiveness of perineurally applied liposomal bupivacaine as in extending the duration of postoperative analgesia peripheral nerve block is not definitive.

Your group set out to systematically review the available studies. Can you tell us your original hypothesis and how you went about conducting this study?

Dr. Faraj W. Abdallah: Sure. Liposomal bupivacaine has been promoted as being capable of prolonging the postoperative analgesia of peripheral nerve blocks up to 72 hours. If this is true, then its benefits should certainly outlast those of plain bupivacaine whose duration of action does not exceed 24 hours at best.

The outcome that has been used in the initial trials to capture the benefits of liposomal bupivacaine was an area under the curve of pain scores; that is, pain severity over time. For this reason we also picked the same measurement as our primary outcome.

We extracted and statistically pooled the data from studies that compared the effects of liposomal versus plain bupivacaine nerve blocks on postoperative pain using (inaudible) techniques and we sought to demonstrate the superiority of liposomal bupivacaine.

Dr. James P. Rathmell: So, you found nine randomized trials that included 619 patients and you used these in the analysis. All of them were evaluated in the effectiveness of peripheral nerve block analgesia that compared liposomal bupivacaine to nonliposomal local anesthetics.

The primary outcome was the difference in the area under the curve of the pooled 24-to-72 hour rest pain severity scores and then there were a number of secondary outcomes including postoperative analgesic consumption, time to first analgesic request, incidence of opioid-related side effects, patient satisfaction, length of hospital stay, liposomal bupivacaine side effects and functional recovery.

You interpreted area-under-the-curve pain scores in light of a minimal clinically important difference. What did you learn?

Dr. Faraj W. Abdallah: Well, let me first very briefly explain where this 2.0 cm · h things came from. For a single assessment of postoperative pain at a single time point, it's generally accepted that one unit or one centimeter on a numerical rating scale is the least that could be considered clinically meaningful.

That is, this is the least improvement in pain severity that could be detected by a patient experiencing postoperative pain when the treatment for this pain is offered.

Now, for multiple measurements of pain over the 24-to-72 hour periods that were performed in our study, this one unit per assessment translates into 2.0 cm · h value. So, that is what we considered as the minimum that's clinically important.

As for our findings, we found that the difference in the area under the curve of postoperative pain over the 24-to-72 hours period between liposomal and pain bupivacaine was only 1.0 cm · h which is less than what is considered then clinically important. In other words, the modest benefit that we observed is probably undetectable by the patient.

And there were no differences in any of the other outcomes that you had mentioned, so no differences on the secondary outcomes and for the primary outcome a difference that is modest and probably undetectable.

Dr. James P. Rathmell: So perineural liposomal bupivacaine provided a statistically significant but not a clinically important improvement in the area under the curve of postoperative pain scores compared to plain local anesthetic.

Dr. Faraj W. Abdallah: Indeed. Statistical testing showed some benefit but the clinical interpretation of this benefit indicates that it's not important because its magnitude during the 24-to-72 hours is too small.

To contextualize this, if we were looking at another outcome, say our ability to perceive temperature and our skin allows to discern a 1 degree Celsius difference in temperature, then this would be like a quarter of a degree or half a degree, meaning a difference that we do not notice when it occurs, i.e., undetectable.

So, when the benefit is undetectable, I wonder if this is considered any justification for using this intervention.

Dr. James P. Rathmell: What were the limitations of your study and what did you conclude?

Dr. Faraj W. Abdallah: Our main conclusion is that for pain control liposomal bupivacaine is not different from plain bupivacaine and this lack of difference undermines the justification for using it as an alternative to plain bupivacaine and peripheral nerve blocks.

The identifiable limitations primarily relate to the heterogeneity involved when we pool different surgical populations having different surgical procedures who receive different types of peripheral nerve blocks.

Now, luckily in our situation this did not translate into statistical heterogeneity which kept our results robust, probably because most of the studies

pointed in the same direction; that is, liposomal bupivacaine was not more effective or it was not superior to plain bupivacaine.

Dr. James P. Rathmell: Dr. McCann, I want to turn to your editorial that also appears in the February 2021 issue of the journal. The editorial is titled, "Liposomal Bupivacaine: Effect, Cost-effective, or (Just) Costly?"

You discuss Dr. Abdallah's meta-analysis and a narrative review that also appears in the February 2021 issue by Dr. Brian Ilfeld and that's titled, "Clinical Effectiveness of Liposomal Bupivacaine Administered by Infiltration or Peripheral Nerve Block to Treat Postoperative Pain."

You do a terrific job of explaining the FDA's Advisory Panel's review process for analgesic drugs and putting these articles in perspective. Can you explain the criteria that the FDA uses when approving new analgesic drugs? And specifically, what comparators are used in most analgesic clinical trials and what limitations does that pose?

Dr. Mary Ellen McCann: Well, Dr. Rathmell, traditionally the FDA has approved drugs with only placebo comparators, meaning that the new drug just has to show efficacy over placebos.

This paradigm for drug approvals for opioid analgesics was somewhat changed in 2018 when the FDA enacted an Opioid Plan for Action. With this plan, the FDA relies more heavily on advisory panels and considers the public health ramifications of new opioid drug applications rather than just the efficacy over placebos. However, this action plan has not been extended to other classes of analgesics or drugs, for that matter.

So, placebo drug trials are simpler for both the FDA and the drug manufacturer to evaluate. The only question that the studies have to answer is, do they work over placebo? Comparator trials are more difficult because both the new drugs as well as the comparator need to be administered in effective doses.

However, the chief limitation of placebo drugs—as was discussed in the editorial—is that some new drugs are ultimately very costly and can be improved without any studies or few studies demonstrating their benefit over existing less expensive drugs.

Dr. James P. Rathmell: Well, unfortunately Dr. Ilfeld is not with us today. Could you start by briefly describing his narrative review and findings, the concerns that it raises when interpreting published studies, and what you conclude from his analysis?

Dr. Mary Ellen McCann: Well, his paper was an exhaustive review of 76 randomized controlled trials involving liposomal bupivacaine. Some of these trials compared infiltrated liposomal bupivacaine with placebo, infiltrated liposomal bupivacaine with other infiltrated local anesthetics, infiltrated liposomal bupivacaine with local nerve blocks, liposomal bupivacaine nerve blocks with local anesthetic nerve blocks, and at least one epidural study.

So, it's really an exhaustive review of what's out there in terms of liposomal bupivacaine. By far the most commonly used comparator for active comparative trials was regular bupivacaine followed by ropivacaine.

The outcome measures of these studies tended to be some type of postoperative numeric pain scale or morphine rescue equivalents. They evaluated, which I thought was the most interesting part of this paper, each study using the Cochrane Risk of Bias Version 2 tool which consists of five domains that look at bias: so, bias from the randomizing process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of outcome.

The authors found that 30% to 40% of the studies they looked at were at concerning or high risk for bias. They also looked at conflicts of interest, meaning were these studies funded by the manufacturer or were some of the researchers receiving some sort of compensation from the manufacturer of liposomal bupivacaine and they found almost one half of the studies exhibited some type of conflict.

So, they ultimately concluded that studies that exhibited bias or possible conflicts of interest were much more likely to show superiority of liposomal bupivacaine over comparators compared with nonbiased or conflicted studies and they ultimately concluded that liposomal bupivacaine was not an improvement over regular bupivacaine.

Dr. James P. Rathmell: So, a really close look at studies that aren't used in FDA registration, exactly those comparator studies that you were talking about that are not used in the FDA registration process.

So, let's turn to Dr. Abdallah's systematic review and meta-analysis. Can you briefly summarize your interpretation of his study?

Dr. Mary Ellen McCann: Dr. Abdallah looked at, I believe, 12 studies comparing the clinical effectiveness of liposomal versus regular bupivacaine for peripheral nerve blocks with the primary outcome measure being the 24-to-72 hour differences in rest pain scores between the two study groups.

He found that although there was a slight difference between the groups favoring liposomal bupivacaine, this difference did not meet the specified difference that was chosen before the meta-analysis was done to meet the definition of clinically relevant difference in pain scores.

Dr. James P. Rathmell: You tell us in your editorial that this shouldn't come as a surprise based on the dossier that was submitted for initial FDA approval of liposomal bupivacaine for local infiltration. Can you explain?

Dr. Mary Ellen McCann: Well, in 2006 the manufacturer of liposomal bupivacaine submitted their first new drug application for approval of this drug for wound infiltration. They submitted five Phase II active comparator controlled trials with regular bupivacaine as the comparator and three active controlled trials. And none of these studies demonstrated a clinical or statistical difference between the two formulations of bupivacaine.

The manufacturer ultimately withdrew the application because the FDA had some safety concerns; they needed more studies to determine the safety of the new formulation.

Then in 2009 they submitted two new Phase III placebo controlled trials that did show efficacy—that shouldn't be a surprise there—and the drug was approved for wound infiltration, for bunionectomy, and hemorrhoidectomy in 2011.

They then, in 2014 and 2017, submitted four more placebo controlled trials for an indication of postsurgical analgesia by nerve block. Of these four trials, only one trial met both criteria of decreased postsurgical pain at rest by pain scores as well as time to opioid rescue.

So, you can see the placebo trials all showed efficacy but the early trials that they did were comparator trials and they did not show any superiority. And so, it was approved because the FDA can approve drugs as long as they show some efficacy, but it shouldn't be a surprise that the findings found in 2020 are not different from the original trials.

Dr. James P. Rathmell: Now, no doubt the FDA approval process does have its limitations, but if a new drug is at least as efficacious as an existing drug, shouldn't that be reason enough for approval?

Dr. Mary Ellen McCann: Well, there are always other considerations. Of course one of the paramount considerations is drug safety; and, in fact, is one of the reasons that the Food and Drug Administration was created. There was a tragedy in, I believe, 1937 where over 100 people died after receiving sulfanilamide that had an excipient of diethylene glycol. So, there are other considerations.

However, cost has not traditionally been considered in evaluating new drugs but maybe it should be a consideration going forward. There are scenarios that you could imagine where a new drug may be approved even if it's not as efficacious as an existing drug.

I'm thinking, for example, in a hypothetical new analgesic drug that has no addiction potential and is safe but is not quite as efficacious as exists in opioids. Obviously, this new drug could be an adjunctive opioid sparing medication and thus would be useful yet not quite as efficacious as drugs

out there. So there are a lot of considerations that go in to approving new drugs.

Dr. James P. Rathmell: Yes. In fact, tramadol is a drug just like that: less efficacy but less addictive potential. So, what did you conclude from this analysis? What's the take-home message for practicing anesthesiologists?

Dr. Mary Ellen McCann: Well, the take-home message for me is to trust the science. These very early studies demonstrate the lack of superiority of liposomal bupivacaine over regular bupivacaine, but somehow hospital formularies and medical practices still opted to treat their patients with the new expensive drug.

And I think we all need to be critical thinkers when we opt to change our existing practice to a practice of using new medications. And I also think that it would be very helpful for the cost to be more transparent to providers. For instance, the single dose of 266 milligrams of Exparel brand liposomal bupivacaine costs over $300 versus $3 for regular bupivacaine. And I had to actually do some digging to determine the cost of the liposomal bupivacaine.

So, your regular practitioner really doesn't have access to all the costs and I think that would be very helpful and I'm not sure how that can be done; maybe through hospital pharmacies or insurance companies, but I think more transparency in terms of costs would be helpful, too.

Dr. James P. Rathmell: Dr. Abdallah, I'm going to ask you the same question. What did you conclude from this analysis? What is the take-home message from your standpoint for practicing anesthesiologists?

Dr. Faraj W. Abdallah: The pooled results of trials of effectiveness versus current care standards were negative. For practitioners, if they intend from using liposomal bupivacaine in nerve blocks as temporal pain control, these findings undermine the justification to use liposomal bupivacaine instead of plain bupivacaine.

Dr. James P. Rathmell: I know you've done a number of other studies specifically in examining liposomal bupivacaine. Maybe you could describe some of those and then tell me what comes next for you and your research team. You've been very, very active in the area of regional anesthesia and really looking systematically at the published results.

Dr. Faraj W. Abdallah: We have been working as a research group to try and find means to prolong the duration of nerve blocks so that we can extend their benefits beyond the duration of local anesthetics. And liposomal bupivacaine set our expectations very high and we have been looking at its uses in the various areas where it has been approved, namely surgical field infiltration, periarticular infiltration, and perineural application in peripheral nerve blocks.

The paper in *ANESTHESIOLOGY* that we're discussing now examined the potential benefits in peripheral nerve blocks and showed no difference compared to plain bupivacaine. Last month another paper was published in another journal comparing liposomal to plain bupivacaine in periarticular infiltration for a total knee replacement and, again, the results were similar.

The third paper that is now in press compares liposomal to plain bupivacaine in surgical field infiltration and the results were consistent in that we could not find differences between liposomal and plain bupivacaine. So, this seems to be consistent across all three uses of this product.

And it doesn't take much to conclude that the underlying rationale or theory behind liposomal bupivacaine is nice and appealing, but unfortunately the practical applications are in a different place. They do not deliver the promised effect.

Hopefully, something could be done to maybe prolong the duration using different techniques and it seems at the moment that peripheral nerve catheters and adjuncts are the most promising approaches.

And our group currently is also working and experimenting with different adjuncts and examining the various administration routes to find ways to maximize the duration of single-injection nerve blocks and improving their analgesic effect.

Dr. James P. Rathmell: I hope today's discussion will lead many of you listening to read this new article that appears in the February 2021 issue of *ANESTHESIOLOGY* where you can learn more about the limited clinical utility of liposomal bupivacaine for training acute postsurgical pain.

Dr. Jon Wanderer from Vanderbilt and I also created an infograph that appears in the same issue and it's titled, "Bursting the Liposomal Bubble: Sustained-release vs. Plain Bupivacaine" where we highlight the primary findings of all of the articles we discussed today.

Drs. Abdallah and McCann, thank you for joining me today and for your terrific explanations.

Dr. Faraj W. Abdallah: Thank you, Jim, for having us.

Dr. Mary Ellen McCann: Thank you for inviting me.

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