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

Dr. BobbieJean Sweitzer: Hello, I'm BobbieJean Sweitzer, an associate editor for Anesthesiology, and you are listening to an Anesthesiology podcast, designed for physicians and scientists interested in the research that appears in our journal. Today we are speaking with the author of a publication that will appear in the March 2022 issue of the journal.

With us is Dr. David H. Kim. Dr. Kim is the first author of an article titled "Interscalene Brachial Plexus Block with Liposomal Bupivacaine versus a Standard Bupivacaine with Perineural Dexamethasone: A Noninferiority Trial." Dr. Kim is an assistant professor in the Department of Anesthesiology, Critical Care and Pain Management at the Hospital for Special Surgery, Weill Cornell Medical College in New York, New York. Welcome, Dr. Kim.

Dr. David H. Kim: Thank you for inviting me.

Dr. BobbieJean Sweitzer: So, Dr. Kim, your title indicates that this is a noninferiority trial. Can you tell us what that is and why you chose to do this type of study?

Dr. David H. Kim: That's an excellent question. So a noninferiority trial is a study design that is used to compare new treatments with an active standard treatment. Its purpose is to show that the new treatment is not worse than the current standard treatment. I have used this method before on other studies, and I found that it's a good way of seeing what is new out there and comparing it to what we know works now.

Dr. BobbieJean Sweitzer: Got it. So why did you choose to compare liposomal bupivacaine to standard bupivacaine with dexamethasone versus just comparing liposomal bupivacaine to standard bupivacaine?

Dr. David H. Kim: So what we wanted to do is we wanted to look at all the known methods of prolonging our single-cell blocks. In our practice, we used preservative-free dexamethasone the most. It has become our standard method of prolonging the peripheral nerve block. And we wanted to see and compare it to the new treatment, liposomal bupivacaine, to our own current practice standards.

Dr. BobbieJean Sweitzer: I guess you answered that with that first question where you said you try to compare new treatments with your standard treatments. So I recall that you used a small amount of 0.5% bupivacaine along with the liposomal bupivacaine. Why did you do this rather than just use the liposomal bupivacaine alone?

Dr. David H. Kim: So when we designed the study, we wanted to compare the best representation of the additives being used to prolong the block. For perineural dexamethasone, four milligrams was seen as the optimal dose at the time. For liposomal bupivacaine, the manufacturer was recommending using an admixture of 10 ml of 133 milligrams of liposomal bupivacaine with 5 ml of 0.5% bupivacaine. It was believed that there was a delay in onset with the liposomal bupivacaine, so that 0.5% standard bupivacaine was used to offset any uncovered analgesic period.

Dr. BobbieJean Sweitzer: Got it. And so what was your hypothesis?

Dr. David H. Kim: So our hypothesis was that the average NRS pain scores at rest over 72 hours in patients receiving liposomal bupivacaine was not inferior to patients who were given perineural dexamethasone to prolong their block.

Dr. BobbieJean Sweitzer: So you thought the new treatment was going to be just as good as the old treatment.

Dr. David H. Kim: Yes.

Dr. BobbieJean Sweitzer: So can you tell us a bit about the patients in your study?

Dr. David H. Kim: So all our patients who were enrolled underwent ambulatory shoulder arthroscopic procedures. We did exclude patients that had any preexisting neuropathy, cervical pathologies, chronic pain syndromes, chronic opioid users, and people who had severe respiratory conditions. The patients that were enrolled in the study were mostly 50 years old, male, and with a BMI of 27.5.

Dr. BobbieJean Sweitzer: So I know you said these were arthroscopic shoulder surgeries, but were there different types of surgeries that these patients were having?

Dr. David H. Kim: Yes. So we left the criteria broad. So we included any patients who were having rotator cuff repairs, stabilizations, or labral repairs.

Dr. BobbieJean Sweitzer: And what were your primary and secondary outcomes?

Dr. David H. Kim: So our primary outcome was the average NRS pain scores at rest over three days. Our secondary outcomes were analgesic block duration, motor, and sensory resolution, opioid consumption, NRS pain scores at rest and with movement on post-op day one through four and on post-op day seven, patient satisfaction, PACU discharge readiness, and adverse events.

Dr. BobbieJean Sweitzer: A lot of outcomes. There have been a fair number of studies, I believe, looking at outcomes with regional anesthesia, especially for shoulder surgeries. Why did you think we needed this study?

Dr. David H. Kim: So regional anesthesia has gained a lot of attention, and main reason why is because we're looking for alternatives to opioids. And if we can prolong our blocks, we believe that we can decrease the amount of opioid consumption. So it's very important for us to compare the different methods of prolonging our blocks, and also, it's important to validate prior studies that claim to prolong the blocks.

Dr. BobbieJean Sweitzer: What do we already know about the effects of adding dexamethasone to an interscalene block?

Dr. David H. Kim: So we do know that it does add analgesic duration to a block by about six to eight hours. Now, if we're talking about bupivacaine blocks, it prolongs it up to 30 hours.

Dr. BobbieJean Sweitzer: Hmm. Were the patients and participants blinded to the drugs that were used?

Dr. David H. Kim: Yes. Yes, they were. Patients were blinded to the drugs. They were told during their consent for the study that the blocks may last as long as three days or early as one day.

Dr. BobbieJean Sweitzer: I believe about a third of the patients who you approached for this study actually declined to participate. That seems a bit high to me. Do you know the reasons why they declined?

Dr. David H. Kim: So I believe most patients declined to participate in the study because they don't like the uncertainty of not knowing what they actually received. Being blind and not knowing which additive they got, they are worried about how long the block's going to last. So I also don't believe that the patients like to be seen as guinea pigs, and for them, the word study or experiment is kind of a word that they don't want to relate to when they're having surgery.

Dr. BobbieJean Sweitzer: Yes, the challenges we have. Did you look at the differences in costs of these two techniques?

Dr. David H. Kim: So since we funded the study, we did look at the budget. We did look at the cost of both preservative-free dexamethasone and liposomal bupivacaine. The cost of a vial, a 10-milligram preservative-free dexamethasone, at the time was $0.56, and the cost of the liposomal bupivacaine vial was about $170.

Dr. BobbieJean Sweitzer: Wow. That's quite a difference.

Dr. David H. Kim: Yes, yes, it is.

Dr. BobbieJean Sweitzer: Hmm. What do we already know about liposomal bupivacaine?

Dr. David H. Kim: So we know that it was FDA approved to be used in interscalene nerve blocks in 2018, and there have been a few randomized control trials comparing liposomal bupivacaine to either placebo or standard bupivacaine. So one study did show that it was very safe and effective in reducing pain and opioid consumption over 48 hours when it was compared to saline. And another study actually was comparing it, liposomal bupivacaine, to standard bupivacaine, but the results was not definitive. The authors actually concluded that it may reduce pain and enhance patient satisfaction in the first post-op week.

Dr. BobbieJean Sweitzer: So you followed these patients for a week post-operatively I believe you said is one of your secondary outcomes. How often were you actually checking on them?

Dr. David H. Kim: So we had our research assistants perform follow-up phone calls. These are scripted interviews on post-op day 1, 2, 3, 4, 7, and 14 days. Now, if a patient was still numb, if the duration of block did not end on post-op day four, the research assistants will continue to call them until the block wore off.

Dr. BobbieJean Sweitzer: And how did you actually assess pain and patient satisfaction after the patients were discharged home?

Dr. David H. Kim: The pain scores at rest and at movement and as well the Brief Pain Inventory questionnaire were answered by the patients by a scripted telephone interview post-op day one to four and also on post-op day seven. Now, these scripted interviews had four questions. One question was "When did your pain relief from the block completely wore off?" Another was "When did your numbness completely resolve and return to normal?" Another one was "When did your arm or hand weakness resolve and return to normal?" And the fourth one was "On the side where your surgery was performed, did you have any numbness, tingling, or weakness in the hand or fingers?" And we asked that question on post-op day seven if we wanted to assess for post-op neurologic symptoms.

Dr. BobbieJean Sweitzer: Can you tell us a bit more about the Brief Pain Inventory you mentioned?

Dr. David H. Kim: Sure. So it is a self-administered questionnaire that specifically evaluates pain severity and the impact of pain on daily function. The questionnaire asks for pain severity by looking at the worst, least, average, and pain now using a pain scale of zero to ten, ten being the worst. It also assessed how pain interferes with daily function, like general activity, mood, walking, working, relationships, sleep, enjoyment in life using a scale of zero to ten, ten being complete interference. Each patient was given the short form on discharge, and during their phone interviews, they would actually read the questions and answer the point score with the research assistant.

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

Dr. David H. Kim: So what we found was that the Brief Pain Inventory pain interference scores were statistically significant lower with the liposomal group post-op day two, three, and four. However, this did not reach clinical significance. There's a big difference between statistical significance and clinical significance, and we found that none of the scores on the Brief Pain Inventory score reached clinical significance.

Dr. BobbieJean Sweitzer: Hmm. Interesting. Did the different mixtures that you used, the bupivacaine liposomal versus just the plain bupivacaine, did they seem to be different in the intraoperative effects, or did you assess that?

Dr. David H. Kim: So there was concern about the delayed onset with liposomal bupivacaine. So we did measure intraoperative opioid consumption, and what we found was that there was not this statistically significant difference between the groups, which also raised the question on whether the admixture that we used can be used as a surgical anesthetic.

Dr. BobbieJean Sweitzer: Um-hum [affirmative]. Were there any adverse effects?

Dr. David H. Kim: No, no. So on post-op day 14, none of the patients had any post-op neurologic symptoms. But on post-op day seven, six patients in the liposomal bupivacaine group did have post-op neurologic symptoms, like tingling, numbness, and three patients in the perineural dexamethasone group did have some numbness and tingling sensation as well. But all of that resolved by post-op day 14. Now, what we did find interesting was that on post-op day one, the liposomal bupivacaine group did have a statistically significant more incidence of hoarseness, 25 in that group versus 14 in the perineural dexamethasone group.

Dr. BobbieJean Sweitzer: Hmm. What are your thoughts on that?

Dr. David H. Kim: So, you know, it's one of those things that we wonder if the liposomal bupivacaine does have this delayed onset. And we wonder if that post-op day one period you see that the perineural dexamethasone group – maybe it's not starting to (sounds like: succeed), so the hoarseness is getting less, while the liposomal bupivacaine group, it still persists. Now, that's on post-op day one. Now, post-op day two and three and four, there was no difference. So it just might be there's a slight lag with the liposomal bupivacaine group.

Dr. BobbieJean Sweitzer: So this was a non-industry-sponsored study, and you mentioned earlier that it was paid for by, I believe, your department or hospital. And you discuss this actually in the paper itself, the non-industry-sponsored versus industry-sponsored studies. Do you want to tell our listeners a bit about that?

Dr. David H. Kim: So our study was completely funded by the clinical revenue generated by our practice. When we were designing the study, we were thinking about ways of making it as unbiased as possible. And we looked at all the prior systematic reviews, Cochrane reviews that looked at pharmaceutical-sponsored studies. And it is kind of surprising to see that when we're looking at the data, you had – you know, one study showed that there was 96.5% of industry-sponsored trials being more favorable with their results. So we wanted to make sure that the study was, I guess, free from any bias, and that's why our practice decided that we will just fund it ourselves.

Dr. David H. Kim: That's quite admirable. And no one had concerns over the cost of liposomal bupivacaine? Remind us again that difference of those two drugs.

Dr. David H. Kim: We did realize that it's a very expensive study, but we felt that the $170 per patient versus $0.56 per patient – that it was very important for us to look at and make that comparison between the new treatment and the old treatment and let everybody make their own decision on what product they want to use.

Dr. BobbieJean Sweitzer: So if you were to have shoulder surgery tomorrow, what anesthetic would you like to receive?

Dr. David H. Kim: My honest answer would be that I would gladly use either one. I do know that both are very safe, but if cost was the major factor, then I would pick preservative-free dexamethasone.

Dr. BobbieJean Sweitzer: I mean, even if cost isn't a factor or – I mean, is it ever not a factor? Someone has to pay for it, right? Again, back to this is a noninferiority trial, and you showed that liposomal bupivacaine was just as good as plain bupivacaine but not any better. Is there any reason to use liposomal bupivacaine?

Dr. David H. Kim: I think that really is the judgment or the practitioner, whether or not they feel more comfortable using liposomal or preservative-free dexamethasone. But knowing, you know, what the study showed and knowing what our practice uses mostly, I would probably prefer the preservative-free dexamethasone.

Dr. BobbieJean Sweitzer: I hope today's discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you, Dr. Kim, for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

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