Conflict of Interest Statement

Dr Weksler is proctor for Intuitive Surgery and Speaker for AstraZeneca. Schumacher is a proctor for Intuitive Surgery. All other authors have nothing to disclose with regard to commercial support.

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Key Words: postoperative pain, minimally invasive surgery, randomized trial

Discussion

Presenter: Dr Benny Weksler

Dr Sudish C. Murthy *(Cleveland, Ohio)*. Dr Weksler and colleagues present a small but randomized trial of conventional versus liposomal bupivacaine as the primary or principal source of initial pain control for patients undergoing minimally invasive lobectomy: VATS and robotic lobectomy. This is a timely report given the urgency to develop more effective narcotics-sparing pain regimens for our patients. However, in the push to do this, there are cost-containment

issues that seem to run in a counter direction. Navigating both of these issues can be difficult given that they seem to be intersecting tangents, if you excuse that oxymoron, but that is critical. This is precisely where this study seems to fit. As pointed out, the cost of liposomal bupivacaine is, conservatively, 30 to 50 times more expensive than the non-liposomal equivalent. In fact, for many of us who work in high-volume thoracic surgery centers that have liberally used liposomal bupivacaine, it is almost certainly the highest of your elective pharmacy charges. It is easy to beat this study up on the size, which is unfortunate, and I'm not sure we can really hold the investigators too responsible for the fact that it poorly recruited or that there was a job change by a senior faculty during the study. I understand that, and I'm sure you know, that this was probably not initially powered accurately, and you had slightly larger ambitions and the audience needs to know that, but let's just take the data for the data and not worry so much about the power calculations. I will let others in the audience address this. I just have one question for you. You have superb results in both groups with a length of stay of 2 to 2.5 days, and I'm wondering whether there is something else you are doing from your operative technique or from your institutional ERAS programs that is reducing pain in these patients, and, consequently, the contribution of pain as a surrogate for length of stay? Could there be something that you can identify in your lobectomy technique or perhaps port placement that might be contributing to these surprisingly good results in both arms? With that, I will step back and listen to your answer. Thank you for the honor to discuss this.

Dr Benny Weksler *(Pittsburgh, Pa)*. I don't know that I can take credit for anything different that we do. During the study period, we did not use any ERAS protocol. The idea was to try to isolate the effect of liposomal bupivacaine. The majority of our cases were robotic. We put ports on 1 single intercostal space, and the assistant port is almost below the diaphragm. If that's a contributor or not, I don't know, but from what I've seen the majority of people are using similar port placement. I do want to comment briefly in regard to power—and those are the things that happen in randomized studies sometimes—so we took the last 20 patients before we initiated the trial, and they had a mean morphine equivalent dosage use of 27 mg $\pm$ 3. We needed 86 patients for the study to establish within 90% power a difference of 25%, which I thought would be reasonable considering the cost difference between the 2 drugs. So what happened is when we did the randomized study, the mean morphine equivalent dosage in the control group was 47 $\pm$ 5, which means—and that's not appropriate statistically, Dr Katie Nason is looking at me waiting for me to say it—but theoretically at this level this study would be powered to detect a 20% difference in morphine equivalent dosage. So yes, it's underpowered because we didn't plan it like that, but I would not dismiss it offhand.

Dr M. Blair Marshall *(Boston, Mass)*. Benny, I enjoyed your talk. In your slides, you showed at the early time point, the pain scores were higher in the liposomal bupivacaine group. We noticed the same in our study. Because of the delayed onset of action of liposomal bupivacaine, many institutions have started to mix liposomal bupivacaine with bupivacaine. When you compared bupivacaine with bupivacaine with epinephrine, the latter has a more durable effect. So, I'm wondering if we can not only mix liposomal bupivacaine with bupivacaine but also with epinephrine to get the maximal effect?

Dr Weksler. It's possible. My pharmacy people are going to have a stroke if I propose that.

Dr Marshall. It's very safe to mix liposomal bupivacaine with bupivacaine; that's all been published.

Dr Weksler. Yes, I know. I really don't have an answer to your comment. What I do know, and it's important to know, is it is possible that minimally invasive surgery changed some of those paradigms a bit, and in a manuscript that I think is in press in the *Journal*, the ERAS pain protocol did not make a difference in patients undergoing minimally invasive thoracic surgery. I don't know if we're talking as much about the bupivacaine or the fact that we're doing more and better minimally invasive thoracic surgery.

Dr Stephen G. Swisher *(Houston, Tex)*. It's an interesting observation. Our OB/GYN group recently did its randomized study, and they observed dramatic improvement with implementation of ERAS, but there was no difference when they randomize between these 2 cohorts. So this may be due to your minimally invasive or implementation of ERAS.

Dr Weksler. Thank you.

Dr Raphael Bueno *(Boston, Mass)*. Nice study. Question and a comment. The question is: Should pain score really be the primary objective of this comparison trial? Because as Dr Murthy pointed out, the real objective question is financial, and we might as well address that, and that is measured in length of stay. I wonder if that would give you a better answer and will help us give a better answer to the bean counters who are controlling the drugs. As far as the comment: I think you're significantly underpowered. With Dr Jaklitsch in our group, we developed a prospective database and we were put in the situation that Sid Murthy

discussed, and we looked at it, and it took 350 patients in each arm—and a prospective database not a randomized trial—to show a real significant difference in all those things. I worry about being underpowered, putting something underpowered out there, and that potentially adversely affecting one way or another how we practice without really having sufficient data to show where we are. The question is: Is the pain score a good primary objective?

Dr Weksler. Regarding your question, I think you could go either way. Morphine equivalent dosage is a surrogate of pain score because patients in this trial, and it's described in the manuscript, because of time constraint, I did not say it here—they all used PCA. So if they have pain they press the button. I believe that is a good surrogate. In regard to your comment, we were planning to get to 100 patients, and we didn't get there, but I would not dismiss our results, which are in line with some other retrospective studies in minimally invasive surgery. There is one on patients undergoing robotic surgery that was retrospective, granted, but didn't show any difference. There are studies on knee replacement that have not shown any difference, and others on mammoplasty. There are plenty of data that question how good this thing is. In the manuscript, I've also quoted a critical article on the approval process of liposomal bupivacaine in which the only studies that were used compared it with placebo and not with normal bupivacaine, so I think there are some problems.

Dr Linda W. Martin *(Charlottesville, Va)*. I didn't hear any description of your technique. When did you inject it, how many interspaces, did you go transcutaneous or transpleural? I think those things are extraordinarily important in assessing the effect. Second, I was curious as to why you only recorded pain scores and morphine equivalents until day 1 if your patients were there until day 2 or 3, and obviously we would think that the plain (nonliposomal) bupivacaine has to run out, and we're going to see those pain scores change. I think those pain scores for the entire hospital stay are interesting and important to report along with this, and it's not telling the whole story if that's not there. Last but not least, I think it's great that you never have to convert to open, but to the rest of us that happens every so often. Using the liposomal bupivacaine at the beginning of the case gives you that flexibility.

Dr Weksler. The way that we did that is properly described in the manuscript, and we injected the skin before incision. As soon as we got in the chest in robotic cases, we did it through the skin and intercostal nerve block from the second or third intercostal space all the way down to the diaphragm. In VATS cases, we did it through the chest with one of those big needles. VATS cases were the minority of the cases. I really can't take any credit for not converting. Those were the 50 that we didn't convert. That doesn't mean that I don't have conversions. But your point I think is more toward the fact that there is more evidence that the liposomal bupivacaine is more helpful in open cases. But again, no randomized trials. There was one more question that I forgot. I'm sorry.

Dr Martin. I was wondering why you only recorded your outcomes at day 1 and 2 weeks. What happens on days 2 and 3 when the plain stuff runs out and they start to hurt.

Dr Weksler. We recorded these on days 0, 1, and 2. We have data on day 3 as well, but there were not a lot of patients still in house on day 3. Our median length of stay was 2.5 days, which makes that data a little weaker. So we recorded it, but didn't present it here.

Unidentified Speaker. Were you using any other adjuncts? Ketorolac, intravenous acetaminophen, gabapentin, and were they distributed evenly between the groups?

Dr Weksler. The short answer is no. The only agent that could be used for breakthrough pain was ketorolac, and that was used in a few patients and was equally distributed between the 2 groups.

Unidentified Speaker. You said they had a PCA?

Dr Weksler. Everybody had a PCA.

Dr Katie S. Nason *(Pittsburgh, Pa)*. A good way to get at the comment that Blair brought up about the effectiveness of the liposomal bupivacaine being several hours after injection would be to look at when the most PCA use occurred over the time that they had the PCA. Did you look at that to see if it was highest where you know in the postanesthesia care unit or the nurses are giving them doses because they're in a ton of pain because they didn't have the effect of the bupivacaine occurring yet? And then it tapers off, or is it is it the same distribution of both groups? Because that may argue for a mixture and overall reduce in the morphine equivalents as opposed to looking equivalent, but maybe when they took them was not equivalent, we just weren't seeing. Because I've operated with you and I know you know a lobectomy is relatively quick in your hands. So you could get in and out before the liposomal bupivacaine would even be working.

Dr Weksler. No, I think it's a good question, Katie. I don't have the answer to your question. We did not look at the data. I don't have the distribution of the morphine only the total dose. I may be able to get a better sense as this paper goes through review. People ask me that question on pain scores distributed through the day through day zero. So it is possible that we can gauge that variance.