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

Dr. BobbieJean Sweitzer: Hello. I’m BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University and 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 an author of a publication that appeared in the June 2019 issue of the journal. With us is Dr. Rebecca Y. Klinger. Dr. Klinger is the lead author of an article titled “Intravenous Lidocaine Does Not Improve Neurologic Outcomes after Cardiac Surgery: A Randomized Controlled Trial.”

Dr. Klinger is an Assistant Professor in the Department of Anesthesiology and Section Chief of Thoracic Anesthesia, Duke University Medical Center in Durham, North Carolina. Welcome, Dr. Klinger.

Dr. Rebecca Y. Klinger: Thank you, Dr. Sweitzer. I’m so pleased to be invited to do this podcast with you and I’m delighted to have the opportunity to discuss our study with you and the listeners.

Dr. BobbieJean Sweitzer: Excellent. So, let’s dive right in. So, I think many of us know, by this point, that postoperative cognitive dysfunction has become a very hot topic in the anesthesiology community and one of the highest risk populations appears to be patients that you take care of having cardiac surgery. Can you tell us how common this is, the cognitive dysfunction, and what type of adverse cognitive effects are typically seen?

Dr. Rebecca Y. Klinger: Certainly. So, postoperative cognitive dysfunction, or POCD for short, generally refers to a decline in cognition that is temporally associated with surgery. It’s important to remember that unlike postoperative delirium, POCD cannot be diagnosed unless the patient has undergone formal neuropsychological testing both before and after surgery, which typically doesn’t happen outside of a research setting. But based on the research that has been done and depending on the specific tests and criteria that are used, the incidence of POCD is around 10% to 40% at 6 to 12 weeks after surgery. The 10% incidence is typically seen when we use the rather strict threshold of a more than two standard deviation drop on cognitive testing from before to after surgery and the incidence closer to 40% is seen when using a slightly more liberal cutoff of greater than or equal to one standard deviation drop in cognitive testing from before to after surgery.

And POCD affects a number of cognitive areas or domains—as we refer to them—including memory, attention and executive function. But typically what patients report is a deterioration in their memory or difficulty multitasking and performing activities at home or at work that they did before surgery. And it may not even be apparent to them right away after surgery until they resume their normal activities.

Dr. BobbieJean Sweitzer: So, are these effects transient or permanent?

Dr. Rebecca Y. Klinger: That’s a great question and one that’s been difficult to address. We can’t really perform studies where we randomize patients to surgery versus no surgery, so we never have a true nonsurgical control group to compare patients to. Based on studies comparing surgical patients to otherwise normal age-matched persons, we’ve learned that the decline in cognition that occurs with POCD is much more rapid than in persons who haven’t had surgery. Similar studies following patients with POCD and persons who haven’t had surgery indicate that POCD lasts for weeks to months after surgery but by one year after surgery is similar in surgical versus nonsurgical persons.

Some studies have indicated that POCD after cardiac surgery predicts cognitive decline even out to five years after surgery, but other studies indicate that surgical and nonsurgical patients have similar cognitive trajectories over time.

So, the short answer is that most cases probably resolve within a few months after surgery, but at this point we’re unable to predict how long POCD might last for an individual patient or if the duration differs depending on specific factors underlying POCD, which it probably does.

Dr. BobbieJean Sweitzer: So, can you discuss the presumed underlying pathophysiology of this cognitive decline after surgery? And specifically in the context of cardiac surgery. And why is the risk so high in patients having these procedures compared to other equally sort of risky or stressful surgeries?

Dr. Rebecca Y. Klinger: Well, as I just alluded to, the exact etiology of POCD is not fully understood and it’s probably multifactorial and varies for different patients and for different kinds of surgery. Cardiac surgery has some specific risk factors that you don’t find in other surgeries, many of which relate to cardiopulmonary bypass. In the setting of cardiopulmonary bypass with aortic cannulation and cross-clamping, there are microemboli which are circulated to the brain and may cause injury. Contact of a patient’s blood with a bypass circuit causes an inflammatory response that is over and above the stress and inflammatory response to surgery in general and that may translate to inflammation in the brain.

During cardiopulmonary bypass, it’s also possible that the brain is being hypoperfused for periods of time, potentially causing ischemic damage. And then there are metabolic and temperature changes that occur during bypass that can be potentially damaging to brain tissue.

Genetic polymorphisms and platelet receptors have been associated with a risk for developing POCD after cardiac surgery; and, finally, hemodilution appears to increase the risk of POCD.

Dr. BobbieJean Sweitzer: Lots of different reasons and it sounds like kind of the perfect storm of cardiac surgery. So, let’s talk about your specific study. What did you do?

Dr. Rebecca Y. Klinger: So, our study looked at whether or not POCD after cardiac surgery could be reduced by the administration of intravenous lidocaine since lidocaine is known to have some nerve protective and anti-inflammatory effects.

So, we performed a randomized placebo-controlled study on a total of 478 cardiac surgical patients who either received a loading dose plus a 48-hour infusion of lidocaine or a placebo for the same period of time.

And we performed a neuropsychological test battery on those patients before surgery and then again at six weeks and one year after surgery to determine their level of cognitive change from baseline.

Dr. BobbieJean Sweitzer: Can you give us an overview of the neuropsychological testing that you did?

Dr. Rebecca Y. Klinger: Sure. So, we used a rather standard neuropsychological test battery and this involves a number of specific tests that are administered by a trained psychometrician.

Each test looked at different components of cognitive function and then we do statistical analysis of the scores on these cognitive tests with what is referred to as factor analysis.

And that essentially allows us to combine the results of the different tests, remove redundancy and produce scores related to different cognitive domains including things like verbal memory, visual memory, executive function and attention and concentration.

Dr. BobbieJean Sweitzer: About how long did it take to administer these tests to a patient?

Dr. Rebecca Y. Klinger: These tests take about two hours to administer in full.

Dr. BobbieJean Sweitzer: So, hence, that you mentioned earlier when rarely do we have this kind of information outside of an actual study. Can you give us a specific example of maybe one of the tests your patients underwent?

Dr. Rebecca Y. Klinger: Yes. So, one of tests that we use is called the Trail Making Test and basically the patient is given a sheet of paper that has 25 circles distributed over it; in the first part of the test within each circle there is a number from 1 to 25 and the patient has to draw a line to connect the circles with the numbers in ascending order, so from 1 to 2 and 3 and so on.

And then in the second part, the level of complexity increases such that in each circle there’s either a number or a letter and the patients have to connect the circles with alternating numbers and letters again in ascending order, so from 1 to A to 2 to B and so on.

So, what we’re looking for is the time that it takes to complete this test or the processing speed and the longer it takes a patient to complete this test, the greater their cognitive impairment.
Dr. BobbieJean Sweitzer: So, what kind of differences in cognitive functioning were you looking for to determine if the lidocaine actually made a real difference or not?

Dr. Rebecca Y. Klinger: Sure. So, we looked at cognitive function in two different ways based on the test battery that I mentioned. So, the first was the binary outcome of POCD; so, either yes or no the patient has POCD. And basically the patient scores on the neuropsychological test were combined into five different cognitive domains. If their test score declined by one or more standard deviations from baseline in one or more of the five domains, that was defined as POCD. So at six weeks and at one year we determined whether patients had POCD as a dichotomous outcome.

In the second method we combined the test scores together into a global cognitive index and then we looked at the continuous change in the patients’ global cognitive score from baseline and again to six weeks and one year postoperatively.

Dr. BobbieJean Sweitzer: So, you didn’t study these patients right away with these neurocognitive tests. The first test was administered at six weeks postop?

Dr. Rebecca Y. Klinger: Exactly.

Dr. BobbieJean Sweitzer: And that’s because like a lot of patients, especially after this kind of surgery, will maybe not do so well on some of these tests right away?

Dr. Rebecca Y. Klinger: Yes, certainly you want to allow some time for the patients to recover from the effects of anesthesia and from surgery and being hospitalized and being on various medications.

So, we generally wait until the patients have been discharged from the hospital and around six weeks is our first time to look at their cognitive functioning.

Dr. BobbieJean Sweitzer: So, I think you mentioned you had 478 patients? They all had care at Duke or what was the setting and can you maybe tell us a little bit more about the patients and the types of procedures? I know they were all cardiac, but what kinds of cardiac procedures?

Dr. Rebecca Y. Klinger: Right. So, this study was performed primarily at Duke Hospital; we did have some patients who were enrolled at Cornell Medical Center and then at Sentara Norfolk General Hospital as well.

Basically we included patients who were 50 years of age or older and who were undergoing either coronary artery bypass grafting, valve surgery or a combination procedure of CABG plus valve surgery.

And in the end about 60% of the patients had undergone valve surgery, 30% underwent CABG and then 10% underwent a combination of those two procedures.

Dr. BobbieJean Sweitzer: So, I think many listeners will be familiar with some of the known predictors of postoperative cognitive decline such as preexisting cognitive dysfunction and educational levels. But were there any major differences between your study groups and either these or other meaningful comorbidities that you studied?

Dr. Rebecca Y. Klinger: Yes. So, you’re exactly right that there’s a number of patient-related predictors that we know for POCD and we specifically accounted for known predictors, as you mentioned: advanced age, level of education, preexisting cognitive dysfunction.

Our randomization gave us actually quite well-balanced groups; we did have some variables that were statistically different between the two groups. Those included proportion of Caucasian patients, ejection fraction and level of education. But again, we went back and controlled for all of these factors in our final analysis.

Dr. BobbieJean Sweitzer: So, I know you mentioned—and maybe you can recap for our listeners as well—the effects of lidocaine and I think it was some of its anti-inflammatory, but there’s a lot of drugs that could sort of fit that profile. Why did you think that lidocaine would particularly be beneficial? Were there some previous data to draw upon?

Dr. Rebecca Y. Klinger: There’s actually a fair amount of animal and some human data that indicated that lidocaine might have a neuroprotective effect. So, the earlier studies showed neuroprotection with lidocaine in animals who were exposed to cerebral air embolism and then also in animals who were models of cerebral ischemia from carotid occlusion.

And how lidocaine potentially achieved neuroprotection was thought to be related to its sodium channel blocking properties and ability to block depolarization and secondary neurotoxic events in response to ischemia and then also potentially its anti-inflammatory properties.

Outside of the animal studies, there have been a few human studies suggesting that lidocaine could decrease POCD after cardiac surgery and that it enhances neurologic recovery in divers suffering from decompression sickness.

Our group previously published a large randomized trial looking at lidocaine versus placebo in cardiac surgical patients. In that study we were unable to demonstrate a protective effect of lidocaine on cognition in the global study cohort.

But what we learned, importantly, was that diabetes and a high lidocaine dose were detrimental to cognition and in a secondary analysis it pointed to a protective effect of pharmacokinetically-driven dosing of lidocaine in nondiabetic cardiac surgical patients.

Dr. BobbieJean Sweitzer: That’s interesting. So, did you exclude diabetics from your study?

Dr. Rebecca Y. Klinger: Yes, diabetes was one of the exclusion criteria for this study.

Dr. BobbieJean Sweitzer: So, maybe you can tell us what you found. Did it work?

Dr. Rebecca Y. Klinger: So, the short answer is that we found that there was no difference in either the incidence of POCD or in that change in global cognitive score between those patients that received lidocaine and those that received placebo, and that was the case at both the six-week and one-year time point postoperatively.

Dr. BobbieJean Sweitzer: Disappointing. So, did you find any adverse effects like you had found previously with that diabetic group?

Dr. Rebecca Y. Klinger: Yes. So, that’s an important question and we had that previous indication that there was a potential for adverse effects with lidocaine and we all obviously know that lidocaine administered at toxic levels can give you local anesthetic toxicity.

So, all of the patients in this study had their plasma lidocaine levels measured at multiple timepoints and anyone with a plasma lidocaine level of more than 5 mg per ml had their study drug stopped.

A lidocaine level that high was only seen in one patient and there were no adverse effects in this or any other patient from the lidocaine. And we, of course, monitored all of the patients for a host of other adverse events and the rates of adverse effects did not differ between patients who received lidocaine and those who got placebo.

Dr. BobbieJean Sweitzer: So, were you surprised by their results, and why or why not?

Dr. Rebecca Y. Klinger: Yes. I mean, I think we were surprised because there was a decent amount of both animal and human data to suggest that lidocaine could potentially be neuroprotective and, of course, we were also disappointed.

As of yet, nobody has figured out a way to prevent or treat POCD and that’s probably because we don’t fully understand yet what it is exactly about surgery, anesthetics, preoperative patient factors and the combination that leads some patients to develop POCD.

Dr. BobbieJean Sweitzer: So, I think as you’ve pointed out and as probably a lot of our listeners know, we’ve felt that inflammation is most certainly implicated in some of the development of cognitive decline and one of those benefits, as you’ve pointed out, was lidocaine seems to have some anti-inflammatory – does have anti-inflammatory properties.

And I recall you did try to measure some inflammatory markers. Can you tell us about what you measured and what you found in those specific domains?

Dr. Rebecca Y. Klinger: Yes. So, based on the data indicating that lidocaine has anti-inflammatory properties, we underwent a substudy to try and look at this more rigorously. So, in the first 202 patients that were enrolled...
in this study, we measured transcerebral gradience of activated platelets and conjugates comprised of activated platelets adhering to leukocytes.

We did this by looking at how many of the activated platelets or conjugates were found in radial arterial blood samples compared to blood samples taken from jugular venous blood, or blood that has just left the brain, with the assumption being that an increase in the number of activated platelets or conjugates in the jugular venous samples compared to the arterial samples would imply that these activated platelets or conjugates were created in the cerebral circulation presumably in response to inflammation in the cerebral environment.

So, lidocaine, as we’ve discussed, has known anti-inflammatory properties such as reducing inflammatory cell adherence to the vascular endothelium. We found that in the patients who received lidocaine, the transcerebral formation of platelet and monocyte conjugates was decreased beginning after aortic cross-clamp release and peaking at the end of the cardiopulmonary bypass.

When we went back and looked at the cognitive scores in this group of patients, there was still no difference between those who had received lidocaine versus placebo, suggesting that the changes that we observed in these transcerebral platelet monocyte conjugants didn’t necessarily affect cognitive outcomes.

But it’s important to keep in mind that this subgroup of patients wasn’t powered to detect cognitive outcomes.

Dr. BobbieJean Sweitzer: But could maybe still be helping them.

Dr. Rebecca Y. Klinger: Yes.

Dr. BobbieJean Sweitzer: So, are there or do you have some presumptive reasons or rationale for the differences in the results of the previous studies looking at lidocaine and to preventing the conjugative decline even in your own work and then this study?

Dr. Rebecca Y. Klinger: So, unfortunately despite what the animal studies has suggested, the data for neuroprotection from lidocaine in humans has been conflicting. Some of the early animal data was in the cerebral air embolism models, but this might not be an accurate translational model for POCD.

And then as I also mentioned, one of the early positive human studies for lidocaine neuroprotection was in patients undergoing open valve procedures where there’s a much higher risk of gas embolism to the brain compared to closed-chamber procedures like coronary artery bypass grafting.

Our patients underwent a mix of open- and closed-chamber procedures, but when we looked at the effect of procedure type, we still didn’t see a treatment effect.

Interestingly, in one of our sensitivity analyses, we did note that cognition was worse in patients who underwent valve surgery versus CABG. So, we don’t really have a good explanation of why we’re not seeing a similar benefit to lidocaine that has been seen in other animal or human studies.

Dr. BobbieJean Sweitzer: I know you mentioned how you measured lidocaine levels and I think there was only one patient who had exceeded the accepted doses and I think you mentioned in your previous study that those patients with diabetes who had high lidocaine levels actually did worse.

So, is there reason to think that there’s a dose effect that for some patients they need more or you’re maybe giving them too much and you didn’t reach the level to cause adverse effect, but you balanced out, I guess, the good effects of the lidocaine?

Dr. Rebecca Y. Klinger: Right. So, as we were talking about in our previous study, we found that higher lidocaine doses were detrimental to cognitive function and in that study lidocaine had been dosed as a fixed rate, so mg per minute. So, patients who were lower in weight were exposed to higher levels of lidocaine than patients who had a greater weight.

And then because of this result, we preformed the pharmacokinetic modeling prior to initiating the current study to determine how to dose lidocaine based on weight and over the duration of this 48-hour infusion to maintain plasma lidocaine levels that were therapeutic, but not harmful. So, certainly your lidocaine levels have to be contained within a safe range.

However, outside of our previous result of higher doses of lidocaine being associated with worse cognitive performance, we don’t really have any evidence of a dose-related effect of lidocaine.

Dr. BobbieJean Sweitzer: That seems like a really high proportion of patients; almost half of them having cardiac surgery with a serious adverse event in the postoperative period of cognitive dysfunction. It seems like there’s a lot of opportunity to look for ways to help those patients.

Has there been any studies rather than preventing, I guess, cognitive function in treating the cognitive dysfunction in patients?

Dr. Rebecca Y. Klinger: To address the first part, as you’ve mentioned, there was a rather large proportion of patients who had serious adverse events, but we did monitor a whole range of adverse events, most of which were actually relatively uncommon.

By far, the most common adverse event that we recorded was atrial fibrillation which we are all already aware is a problem after cardiac surgery and that many people are trying to solve.

Interestingly, the incidence of atrial fibrillation was identical between patients who received lidocaine and those who did not in our study. But in terms of the future, I think that all of this means that we still need to work on figuring out what it is about surgery and anesthesia and cardiac surgery in particular that causes some patients to develop POCD.

A number of different therapeutic measures have been tried in the past—lidocaine being one of them, magnesium, other drugs including ketamine—and none of those has really borne out a protective or therapeutic effect in POCD.

POCD likely has as much to do with latent unmeasured patient characteristics—for example, clinically silent neurodegenerative disease—as it does with surgery and anesthesia. So, ultimately, we hope that one day when we better understand what causes POCD, we will be better able to prevent or treat it.

Dr. BobbieJean Sweitzer: So, did your involvement with this study and others influence your discussions with patients about the risks associated with anesthesia in cardiac surgery?

Dr. Rebecca Y. Klinger: Yes. Certainly I discussed the potential for POCD with my patients who are about to undergo cardiac surgery. Based on what we currently know about POCD and cardiac surgery, it’s very difficult to tell an individual patient what their risk of developing POCD is. We can reassure patients that certain factors are protective, including younger age and more years of education.

Unfortunately, we still cannot predict the severity of POCD if it occurs in a patient or to what extent it may affect their daily lives. But we, and many others in the field, are going to continue our work to better understand POCD so that hopefully one day we can prevent it from happening or at least have effective tools to help our patients recover from POCD.

Dr. BobbieJean Sweitzer: Do you have any other projects in the pipeline already?

Dr. Rebecca Y. Klinger: We have some early work looking at resting state functional connectivity as it relates to POCD after cardiac surgery and showing some actual changes in the brain that are occurring in postsurgical patients. So, that will be an area of investigation in the future.

Dr. BobbieJean Sweitzer: Interesting. We look forward to that. So, 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. Klinger, 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.

Dr. Rebecca Y. Klinger: Thank you so much for having me. It’s been a pleasure.

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