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

Dr. James 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 the editor and chief 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're going to talk with one of the authors of an original research article and accompanying editorial that both appear in the March 2024 issue of the journal. With us today is Dr. Mark Neuman. Dr. Neuman is an Associate Professor in the Department of Anesthesiology and Critical Care at the University of Pennsylvania in Philadelphia, Pennsylvania. Dr. Neuman is the senior author on an article that appears in the March 2024 issue of the journal and it's titled, Long-term Outcomes With Spinal Versus General Anesthesia for Hip Fracture Surgery, a Randomized Trial. Dr. Neuman, thank you for joining us.

Dr. Mark D. Neuman: It's a pleasure to be here.

Dr. James Rathmell: Also with us today is Dr. Elizabeth Whitlock. Dr. Whitlock is an Assistant Professor in the Department of Anesthesia at the University of California in San Francisco, California. Along with Dr. Alexander Smith, Dr. Whitlock co-authored an editorial that accompanies Dr. Neuman's original research article. It's also in the March 2024 issue of the journal and it's titled, Regaining the Freedom to Choose Insensibility for Hip Fracture Surgery. Dr. Whitlock, welcome and thank you for joining us.

Dr. Elizabeth L. Whitlock: Happy to be here.

Dr. James Rathmell: Dr. Neuman, congratulations on the publication of your study. Let's start with a little background about the controversy surrounding spinal versus general anesthesia for hip fracture surgical repair.

Dr. Mark D. Neuman: It's been a bit of a journey to work on this project and really the controversy, as you phrased it, is something that's been around for a very long time in the specialty. Really since the 1800s when August Bier first developed spinal anesthesia as a potential alternative to general anesthesia. It was intended to decrease the risk associated with surgery. And really since that time there's been a fair bit of debate but not a lot of clear evidence about whether or not outcomes might be improved by avoiding general anesthesia and using spinal anesthesia.

The idea of the REGAIN randomized trial was to try and produce a better answer than what we had had before in terms of the trade-offs these two treatments might offer. We've published other papers that have shown no real differences in short-term outcomes up to about 60 days when you look at ability to recover function, survival and major medical complications after surgery, like delirium. But this new paper which we're thrilled to have coming out in *ANESTHESIOLOGY* looks over the long-term to see whether or not receipt of spinal versus general anesthesia might impact people's outcomes at up to a year.

Dr. James Rathmell: So you and your study group designed the REGAIN trial to test the hypothesis that spinal anesthesia is associated with better long-term outcomes than general anesthesia. Tell us more about the REGAIN trial, the initial results that were published earlier in the New England Journal of Medicine and what this longer-term analysis is all about.

Dr. Mark D. Neuman: Yeah, the initial paper which came out in October 2021 was an analysis that looked at a composite endpoint of death or new inability to walk at 60 days. Patients were randomized to what we called "standard care spinal or general anesthesia." Which was either a type of anesthesia as typically delivered in practice at 46 of our partner hospitals around the country and in Canada. We enrolled 1600 patients, and they were randomly assigned to the two treatments. We followed them up in the hospital and after they went home via telephone follow up.

And when we looked at the results from that study for the initial publication we found that about 19% of patients in each group, between 18 and 19% met our primary composite outcome. We also noticed that similar proportions of patients in each group got delirious. Similar proportions died at 60 days. So based on that we concluded that our study didn't support a clear difference or a clear benefit of spinal over general anesthesia. We continued to follow our patients over time, and about 90% of our patients had data available at one year on survival, and that's what the present analysis focuses on.

Dr. James Rathmell: Okay, so this was a pre-specified analysis of long-term outcomes of your completed randomized superiority trial. Tell us more about how you conducted the one year analysis that's coming out in *ANESTHESIOLOGY*.

Dr. Mark D. Neuman: We continued to follow our patients by telephone. We called them at the initial touch point, which was 60 days but then also at 180 and 365 days. We also conducted a search of the National Death Index, which is a Public Health Vital Status database that allowed us to detect deaths that we couldn't catch by telephone. And the telephone contacts for people who had died, those were follow ups we conduct with family members, friends, things like that to confirm people's vital status.

When we connected with people at these time points we asked if they were back walking at their usual state of function and where they were living. Whether they were in a nursing home or at home in the community. What we ended up finding at one year was that all of these outcomes were very similar for patients who'd received spinal and general anesthesia consistent with our earlier results that I'd mentioned before.

Dr. James Rathmell: Can you elaborate a little bit more on what you learned, and was there anything surprising to you in your findings at one year?

Dr. Mark D. Neuman: Absolutely. When we looked at the overall study samples rate of survival at 365 days, we ended up finding that the one year mortality for patients in the spinal anesthesia arm was about 15% compared to about 13% in the general anesthesia arm. This wasn't a statistically significant difference in the hazard ratio, which was from a statistical model that's designed for these kinds of outcomes, was about one. So we really didn't see much of a difference, and we looked at some subgroup analyses for people who were in the very elderly group, age over 85 or those who lived in Canada versus the US. And neither of those shook out as significant.

When we looked at functional and resident's outcomes we found very similar patterns. About 24% of patients in the spinal group had died or become newly unable to walk at 365 days versus 21% in general anesthesia. And again, not a significant difference there. We also saw that the number of patients who had died or transitioned to nursing home care was similar in each group.

So overall we saw very, very similar outcomes across groups. I found this surprising and insightful. One reason I found it surprising was that it was so similar across groups. Even in our initial REGAIN publication in New England Journal of Medicine, there were some very faint signals that may have suggested that there may have been some shorter-term complication differences across groups. None of these were statistically significant because the numbers were quite small. But it was quite reassuring to see how similar the groups were in the long run. Suggesting that whatever might be going on in the short-term generally seemed to resolve to the point that it didn't make a difference in how people were doing over time.

Dr. James Rathmell: What were the limitations of your study?

Dr. Mark D. Neuman: As a randomized trial there are certain generic types of limitations that we dealt with, and we did our best to address them. One basic limitation is that in a randomized trial with consent you can only study the patients who agree to enroll in the study and who meet the inclusion/exclusion criteria. We had very, very broad inclusion/exclusion criteria. But there were still a number of patients who did not meet them, and there were other patients who declined to participate.

Obviously our study results can only be directly applied to the types of patients who enrolled in this study. Although I think that there is insight they can still provide to other groups. We had some degree of loss to follow up, about 10% of patients in each group did not have outcome data available at the study end point, 365 days. But when we looked at the

characteristics of patients in those groups they looked generally similar, which was reassuring that this would not be a huge source of bias. And we did supplemental analyses to confirm that.

Lastly we did have some crossovers from one group to another in the study, and we did additional analyses to reassure ourselves that those were unlikely to be major problems. So we felt that the study provided a high degree of reassurance to people who might be interested in choosing general anesthesia. But certainly leaves the door open to other work to confirm or extend our findings.

Dr. James Rathmell: All right, so what's the take home message for practicing anesthesiologists?

Dr. Mark D. Neuman: I think the big message that I offer when I speak about this is that for most patients our study makes it clear that either spinal or general anesthesia can be a safe option for hip fracture surgery. This doesn't exclude that there might be certain patients where one choice might be better than another based on medical considerations. But from the results in the study that we have there's a high degree of reassurance I think we can provide to the typical hip fracture patient that either choice can be safe and that what their preference is, whether it's spinal or general anesthesia, can be safely used to guide that choice.

Dr. James Rathmell: Dr. Whitlock, I want to turn to your editorial that accompanies Dr. Neuman's original research article. It's also in the March 2024 issue of the journal and it's titled, Regaining the Freedom to Choose Insensibility for Hip Fracture Surgery. You do a terrific job of putting Dr. Neuman's article in it, the trial design into perspective. Can you talk a bit about why the REGAIN trial is important?

Dr. Elizabeth L. Whitlock: Yeah, well, you have to kind of think back to 15 years ago or sorry, 10 years ago when the REGAIN trial was being designed. There was a lot of enthusiasm around spinal anesthesia for pretty good reasons. There were pre-clinical studies that sort of initiated some concerns about the way that volatile anesthetic specifically behave on the brain. There were a lot of small studies looking at spinal versus general anesthesia, which generally tended to find benefit for spinal anesthesia.

And so the milieu at the time that REGAIN was designed was pretty pro spinal. REGAIN was designed as a multi-center trial using routine practice. And that's why I thought it was such a critical contribution to the literature. Not only was it very large and everybody loves a large trial. But the way that the spinal and general anesthetics were provided wasn't highly protocolized. It was up to local practice and reflected the way that we practice in the United States and Canada where the centers were located.

So kind of a priori based on the design of the REGAIN trial, I was really excited that the results were going to be revealed at the ASA meeting because I knew or I felt that I was going to be able to trust the results and their implications to practice simply based on the design characteristics of the trial. When those results came through and there were very minimal differences between the randomization groups, I was really surprised. And it brought forth further questions about how we can put this into context with what we already had known.

Dr. James Rathmell: All right, I want to delve a little bit further there. You tell readers in your editorial that REGAIN's pragmatic design yielded critical strengths for generalizability. Can you discuss the design and why you feel it's so strong in helping answer this question?

Dr. Elizabeth L. Whitlock: Yeah, one of the things that you worry about in a small single center trial is that maybe this local place is inherently different from other centers around the country. For example, that they are using some sort of miracle (sounds like: cane) spinal, or that they have a really detailed general anesthetic plan that everybody uses that's completely different from the way that other people in the country are practicing. So when REGAIN put its chips down and said, we're just going to take advantage of the variety of practices that happen in these countries and reflect current practice, which includes a fair amount of sedation for many patients. Fairly deep levels of sedation for some. Although REGAIN's study population was not general anesthesia on top of spinals generally.

We know that this variability means that we can probably apply these results to our own local practice in ways that we wouldn't be able to if care had been highly protocolized or care was inherently very different in the REGAIN trial compared to the way that I, for example, individually practice.

Dr. James Rathmell: I too really like the trial because of the pragmatic nature as it applies to the way we really practice. Can you compare and contrast REGAIN with previously published studies? I think you've done that a bit already, but what are the big differences with this trial?

Dr. Elizabeth L. Whitlock: Yeah, actually so we briefly talked about some of the previous studies that prompted maybe the design of the REGAIN trial. But I actually want to talk about a study that was published only one month after REGAIN came out, and this is the RAGA trial. It was another large randomized trial of hip fracture patients done in China where people were randomized to general anesthesia or to spinal with no sedation. Because REGAIN to some extent left open the door of whether the amount of sedation that was administered to the spinal anesthesia group was driving the lack of a difference between the two randomization groups.

RAGA's results, which showed no difference again between the two randomization groups, were really, really compelling because the folks who were randomized to spinal received no sedation whatsoever, no Versed, no propofol, nothing. That is not practicable in my practice in general. But it yielded a really scientifically critical answer of whether there was the issue of sedation being provided in this pragmatic REGAIN trial, was driving the fact that there was no difference between the randomization groups.

Dr. Mark D. Neuman: I think Liz brings up a really good point, and this comes up in my conversations with clinicians a lot. And there's questions, somebody might say, well REGAIN didn't test a quote, unquote, pure spinal, i.e. a spinal without sedation. And while we see that kind of care in the context of obstetrics frequently, it's extremely uncommon in the US to see spinal anesthesia delivered without any sedation for orthopedic surgery. The way we designed REGAIN was intended to reflect typical practice. But I'll also note that the type of care people got in REGAIN was very good care.

People got more nerve blocks than we commonly see in usual practice, peripheral nerve blocks for pain, at a rate of about 30% across groups. Which is more than seven times what we usually see in typical practice. So people were getting pretty good care. And the level of sedation, as Liz mentions, was something we asked clinicians to be careful about and they were. People got sedation at infusion rates that were in the range of 20 to 30 mics per kilo per minute. A very judicious level of sedation.

So I think Liz is right in characterizing REGAIN as being reflective of usual practice as we see it. But it was also reflective of clinicians who were taking really careful steps to make sure that the patients were getting in a sense recommended best care as we would define it in typical US and Canada practice.

Dr. James Rathmell: All right Dr. Whitlock, back to you. You tell us that REGAIN obliquely demonstrated that patients may have strong preferences about the care they receive. Can you elaborate?

Dr. Elizabeth L. Whitlock: So one of the cool secret nuggets about REGAIN is hidden in a figure caption, Mark no shame, but hidden in the figure caption in a paper published in the Annals of Internal Medicine, is that right? And it goes through reasons that people declined to participate in REGAIN. So when I say that patients may have strong preferences about the care they receive, I think people should be aware that almost 1000 people declined to participate in REGAIN because they didn't want spinal anesthesia. They had concerns about spinal anesthesia. And almost 500 folks said they had concerns about general anesthesia. They would not be willing to be randomized to general anesthesia.

Frankly that's pushing – it's almost 1500 patients, which is close to the whole trial size of REGAIN itself. So I think it's really important to recognize that patients are not necessarily themselves agnostic to what type of anesthetic strategy they receive. That there are feelings that folks have. That's why when we have a result like REGAIN's short and

long-term findings that suggests it would be safe to provide either of these, it's actually a really huge win for patients.

Dr. Mark D. Neuman: I think that's a great observation, and one of the things I tell people is, is I have some of the best conversations with patients that have ever had about their anesthesia choices when I was doing consent conversations for REGAIN. Because by the nature of trial informed consent, you need to have a real conversation about these things. And what I learned is that there are many, many patients who have a lot of good questions about anesthesia, that are able to think through this as a choice and want to be involved in the choices.

One of the things I hear in debates about our study and how it should be applied is that patients aren't interested in anesthesia choices, or they're not capable of engaging in these things. I think those are myths. I think people have a lot more ability and desire to be involved in these care choices than we often give them credit for. And one of the things I'm most proud of about REGAIN is rather than calling one or another type of anesthesia uniformly the best for everyone, it gives us some context to have better discussions.

Dr. James Rathmell: All right, Dr. Whitlock, I want to go back to that patient perspective and have you tell us what the take home message is for older patients with hip fracture who are contemplating the type of anesthetic they might desire.

Dr. Elizabeth L. Whitlock: Yeah, so that's – we put it in the title of our editorial here, Regaining the Freedom to Choose Insensibility. Based on these results it is a reasonable choice for an older patient who looks like this trial population to prefer to receive a general anesthetic during a hip fracture surgery. And that shouldn't sound like a super – it's not a revolutionary conclusion. But at the same time, a lot of centers put quite a strong push on the rates of neuraxial anesthesia in hip fracture surgery specifically.

And that push is not necessarily evidence based. That tracking rates of neuraxial anesthesia being provided in hip fracture, for example, probably is not a good quality metric because it's not reflective of quality of care. We're not seeing a signal that the quality of care is affected by the choice of general versus neuraxial. And as I say in the editorial, practicing anesthesiologists probably have all had this experience of trying to support a patient who is – maybe has dementia at baseline. Maybe has concurrent delirium because concurrent delirium is quite common prior to a hip fracture surgery. Trying to get them to sit up and their hip hurts and it's 10:00 at night and you don't have a whole bunch of buddies around to help support the patient.

It is acceptable to choose a general anesthetic. You shouldn't need to justify why a general anesthetic was selected in a situation where a spinal, for example, is very, very difficult, uncomfortable for the patient, problematic for an individual patient. That kind of freedom I think is really critical as we partner with our patients to try and come up with the best, safest strategy to get them through this major surgery.

Dr. James Rathmell: Dr. Neuman, again, congratulations. Can you tell us what comes next for you and your research group?

Dr. Mark D. Neuman: This is a very apropos conversation for us because we're thrilled that we've recently been funded for a new study from PCORI to do just the kinds of things that Dr. Whitlock is explaining. We have a new project that's been funded through PCORI's dissemination and implementation portfolio called My Anesthesia Choice. And what My Anesthesia Choice is all about is using evidence-based tools to put the information from REGAIN into practice to help make decisions better and make conversations better between clinicians and patients.

The project will be starting some time this summer, in summer of 2024. And we have six great partner organizations around the country that we're thrilled to work with on this. So we'll have more information coming soon. But our hope is that we can take REGAIN out into the clinic and use it as a model for how trial results can help make decisions better at the bedside.

Dr. James Rathmell: Terrific, can't wait to see some of your new findings. I hope today's discussion will leave many of you listening to read this new article and the accompanying editorial that appear in the March 2024 issue of *ANESTHESIOLOGY*, where you can learn more about the REGAIN trial and spinal versus general anesthesia for hip fracture repair surgery. Drs. Holly Ende and Jon Wanderer from Vanderbilt University create an infographic titled, A Trip Around The Sun, that summarizes both the 60 day and 1 year outcomes of the REGAIN study. Drs. Neuman and Whitlock, thank you for joining me today and for the terrific explanations.

Dr. Mark D. Neuman: Thank you so much.

Dr. Elizabeth L. Whitlock: Yeah, thanks for the invitation.

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