Dr. Anahi Perlas: Thank you very much, Dr. Rathmell, and it’s certainly a pleasure to speak with you today.

Dr. James Rathmell: Congratulations on the publication of your work. Can you start by framing this issue for listeners? I mean, the idea that risks associated with regional and general anesthesia might differ in some meaningful way has been around a long time, and it’s been examined more than once before. How did your approach to this study differ in a way that would bring new insights to the longstanding question of general versus regional?

Dr. Anahi Perlas: You’re absolutely right. As you point out, this has been a longstanding question in the minds of many anesthesiologists. And on the one hand, there have been many studies looking at outcome differences between spinal and general anesthesia, and most of the things we do know are mostly in the realm of physiologic advantages of one anesthetic versus the other. So, several of these differences have been fairly well-documented in the past.

In fact, many of these previous studies suggest that there are things like greater hemodynamic stability with a spinal anesthetic throughout the perioperative period. Certainly, spinal anesthesia tends to have a much more negligible effect on the respiratory system, and preserve respiratory dynamics, usually accompanied with less or lower incidence of postoperative delirium and other things like decreased blood loss, for example. And these have been shown time and time again. So, some of these sort of physiologic advantages, if you wish, already make spinal regional anesthesia quite an attractive anesthetic option, especially if you have an elderly patient or those with significant comorbidities.

But on the other hand, the specific question of whether these physiologic advantages translate into a survival benefit or a lower mortality—it actually has been a fairly elusive question to answer. Most of the reports just look at it as a secondary outcome, and most are smaller studies. And the reason is, because of the great progress that has been made in the last few decades in terms of the safety of surgery and anesthesia, has made the perioperative period a fairly safe one, especially for elective surgery like this one. So, the baseline incidence of mortality is quite low—anywhere from 0.1 to 0.4%, in different reports.

So, to appropriately answer this question of, does the anesthetic technique impact mortality, you really need a very large sample size; and not only that, but also enough information and granularity on all other aspects of the clinical presentation, and the patient, and the surgery—factors that may by themselves impact mortality. So, in order to isolate the anesthetic technique as a single factor, this has actually been quite difficult to accomplish with traditional prospective studies.

So, in fact, very little data, I would say, is in fact available on this important question of mortality. This is really what inspired us to pursue this project. At the same time, the fact that we have an increasingly more prevalent type of surgical procedures in the total joint population; and an ageing population as well.

Dr. James Rathmell: Perfect. So, enormous sample size was what you bring to this. You compared patients who had either total knee or hip arthroplasty using spinal anesthesia or general anesthesia, and the primary outcome was 30-day mortality. You looked at a number of secondary outcomes. Can you tell us what those were?

Dr. Anahi Perlas: Yes. Secondary outcomes we looked at were the incidence of perioperative myocardial infarction, composite outcome of major adverse cardiac events, often known as MACE, that includes cardiac arrest, myocardial infarction, or a newly-diagnosed arrhythmia; the incidence of pulmonary embolism; and the incidence of major blood loss, defined as requiring more than two units of packed red blood cell transfusion in the perioperative period; and also the hospital length of stay.

Dr. James Rathmell: So, we’ll come back to that in a minute, but first I want to get to the structure of your study. It was a retrospective study. There were 10,868 patients, of whom 8,553 had spinal anesthesia and 2,315 had general anesthesia. You compared the two groups using a propensity score-matched pair analysis. Can you explain in simple terms how that type of analysis is meant to work?

Dr. Anahi Perlas: So, as you point out, the entire cohort that we looked at consisted of over 10,000 patients; but actually, when you look at the baseline demographic characteristics, the preexisting comorbidities, and the baseline laboratory data of those patients that had received spinal anesthesia versus those patients that have received general anesthesia in this entire cohort, they were in fact very different. Those that received general anesthesia had a tendency to being sicker, if you wish. And you can see this very well in the study, in the first table—table one. So, obviously, it would be erroneous or even misleading to study these entire cohorts and to compare retrospective cohorts “as is,” let’s say.

So, the interesting thing—you know, there’s usually two frameworks, or two ways, that you can look at retrospective data in a manner that’s meaningful. The first way, perhaps more traditionally common, and there’s lots of studies that use it—it would be something like a multivariate logistic regression analysis that tries to isolate each factor, and accounting for all the possible known confounders.

On the other hand, we have this type of analysis, which is a propensity score-matching. And what this allows you to do is, it allows you to select two groups of patients that are very, very similar before the decision was made to undergo surgery, and the type of anesthetic.

So, how you do that is, you look at the entire cohort. And to build a propensity score model, you ask a series of questions. And the questions are as follows. For example, you pick a factor that could be related to the decision of, should this patient have a spinal or a general anesthetic at the bedside? So, for example, you can pick COPD. And then you look at the entire cohort and you say, okay, how likely—how much more likely, or less likely, was someone who had COPD to receive a spinal anesthetic?
And what you find—you assign a specific score to that "more likely" or "less likely." Sort of like a risk ratio, if you wish. And you do the same thing with a number of factors that you identify as potentially influencing that decision of spinal versus general anesthesia. So, you can do that with coronary artery disease; you can do that with the patient gender; with the patient age, and so on and so forth. You can run essentially an unlimited number of similar questions, based on all the patients’ baseline characteristics, based on the comorbidities, based on baseline laboratory data. We did that in our study with 17 different factors, all of which are previously known to influence mortality on their own and could therefore, you know, affect the results of this study.

So, at the end of this iterative process, you combine all these unique factors and scores into a mathematical model that accounts for all of them—that takes all of them account. And each individual subject in the entire cohort is given or is assigned a unique score, with five decimals, that tells you how much more likely or less likely was that particular individual patient to receive either a general anesthetic or a spinal anesthetic, based on who he or she was; how sick he or she was before the surgery.

So, obviously, the propensity score model—it's an artificial way of looking at the data, and it's only going to be as strong as those baseline data that you have and that you include in your model. The more baseline data you have, the stronger your model is going to be.

And then the next step is to identify pairs of individuals: one who received GA, and one who received spinal anesthesia, with the closest propensity score in the entire cohort. And you start with the five digits or five decimals, and work your way up. So, the advantage of doing this is that, now, at the end of this process, you are not going to be analyzing the entire cohort any longer. You analyze two new subgroups, one with general, one with spinal, that are in all other respects very, very similar in all their baseline characteristics, in all their baseline comorbidities, and even some of the laboratory work that we had available: things like hemoglobin, for example, and creatinine preop, both of which are very important and very well-known to impact mortality on their own.

So, all these patients, once they are matched, they are deemed to be very, very similar, and they only differ in one aspect, as far as we know, which is the type of anesthetic. At the end of this process, we were able to match 92% of all patients receiving general anesthesia. So, the final cohort was roughly just over 2,100 patients in each of the two groups, and that is what we compared. We compared, then, the outcomes of interest, in this case mortality and the major morbidity outcomes, in these two much more similar cohorts than at the beginning.

Dr. James Rathmell: That was an excellent explanation of something that really is very, very difficult to explain. Well done. So, what did you find? Was spinal or general safer? Or could you really even draw definite conclusions about which technique was safer?

Dr. Anahi Perlas: Well, that's, I guess, the core of the issue, really. So, when we compared these two quite similar cohorts—as I said, about 2,100 patients in each—we found there was a strong association between having had a spinal anesthetic with a lower 30-day mortality. So, those patients who received spinal anesthesia were only about half as likely to die within 30 days of the surgery than those who had general anesthesia. The incidence of death in the spinal anesthesia group was about 0.2%, while in the GA group was about 0.8%, with a risk ratio of 0.45.

Now, the important question here is, are our findings a proof of causality? Was this really related to the anesthetic? And that question is somewhat controversial and is not as cut-clear as a yes or no, as one—we might think. Now, certainly, within our current framework of research, we would say first of all that the cause and effect between a health intervention and a health outcome is very rarely established, or should not really be established, based on a single study, no matter how strong the study.

And within our current paradigm, of course, the ultimate gold-standard experiment to infer causality should be a randomized controlled trial. The problem here is that RCTs are often not feasible to study a relatively rare outcome, like mortality in the selected population, given the large sample size required and the lengthy and costly process involved.

And in fact, if you think how important this question is, and the fact that in the last 30, 40 years, as a specialty we have not been able to produce a good, large, randomized, controlled trial that answers these questions—because of these difficulties. Not that we've been lazy or we have not been interested in this question; but it's just something, many times, not feasible. And if you look specifically at the orthopedic population, the largest study I found, prospective randomized, was only in the range of about 200-something patients—obviously, not nearly enough to answer this question.

Dr. James Rathmell: This gets at some of the limitations of retrospective studies like this, even when the sample size is large, and in this case over 10,000 patients. You can find associations, but it's impossible to determine cause and effect.

Were there other limitations of the study? For instance, there were only four deaths in the spinal group of more than 8,500 patients, and only 17 deaths in the general anesthesia group of about 2,100 patients. Are those numbers big enough to draw these sorts of conclusions?

Dr. Anahi Perlas: So, let me start with the limitations of the study. First of all, the actual causes of mortality were not available to us. So, that is definitely a limitation of this study. So, we cannot really tell you why these patients die, exactly. We cannot report on that. We can only really speculate a little bit. For example, since the incidence of postoperative MI and major cardiac complications and PE were actually similar between the two groups, it's unlikely that the reason were mostly cardiac causes; but we can only really speculate.

The second issue is the fact that this is a single-center study, and that may limit its generalizability to other centers that perhaps have differing practices or patients. You know, you raise a good point: is it four deaths in one and 17 deaths in another—is this proof enough? That is an important question. But the key of the matter is, mortality in general is very rare. So, even though we can do a very large study, the numbers of events are going to be relatively small.

And I think this brings us back, a little bit, to the fact that this is indeed a retrospective study done on observational data. So, I think this issue takes us back a little bit to the issue of causality. And although I certainly agree that, you know, multiple RCTs would be the best way to answer this question, the fact of the matter is, they are just not there. We have not been able to do them as a specialty.

So, what are we to do? Are we just to say, well, we don't know; we'll never know? Or, should we look at, what is our best second type of data that we can actually generate? And if you read the literature across healthcare, I think there's a growing realization among even experts in research methodology that, for certain important but rare outcomes, like mortality in this case in elective surgeries, where RCTs may not feasible or are just not available, sometimes our knowledge of cause and effect may in fact come from these second-best studies, if you wish, which are these large studies based on observational data.

What I think we need to make sure is, we need to be really demanding and obsessive about these studies that we do; and we need to, you know, stay humble and not overstate our findings. But I think we need to do more of these types of well-designed studies on observational data and see whether—is this just an isolated finding, or are there other similar studies that show the same thing from different centers or from larger databases?
And on that note, I’d like to say, you know, one of the— for example, this study is a single-center study. That’s definitely a limitation. But on the other hand, it gives us the ability to have a lot of information on clinical aspects of care and clinical factors related to the patient that are usually missing from some of the larger administrative databases, for example, which gives us, you know, some hundreds of thousands of patients; but very often, the clinical information sometimes is just not there. So, I think we need to keep working at it and keep looking for these good sources of strong, detailed clinical information.

**Dr. James Rathmell:** What about the secondary outcomes? Did you find anything meaningful from those analyses?

**Dr. Anahi Perlas:** Yes. We observed a lower incidence of major blood loss—as I mentioned, defined as requiring more than two units of packed red blood cells during the hospital admission; and a shorter hospital length of stay of about one day.

Now, I think this is interesting, and I would like to put it in perspective. You know, sometimes when I was reading this study with some of my colleagues, they were saying, well, you know, your study actually spans over 12 years of our own practice, and of course practice has changed a lot over 12 years. And that is rightly so.

So, one of the things that we incorporated in our propensity score model is the year in which the patient had the surgery. And that is very important. Because if you had the same procedure in this hospital—I’m sure it’s the same for other centers—12 years ago, your expectations and your care was probably different from this year or last year. So, by doing this propensity score in our final cohorts, we actually had almost exactly—almost identical, the same number of patients year by year in the two cohorts. So, I think these findings are—I do believe them. Particularly, for example, the shorter hospital length of stay on average by about one day. I do think there is something there.

**Dr. James Rathmell:** Did your study reveal anything about why spinal anesthesia might be associated with better outcomes?

**Dr. Anahi Perlas:** Well, as I mentioned, actually, we do not have information about the causes of death. So, I think it’s really difficult, from the data that we have, to say, why did this happen? The data was just not available to us. And again, the cardiac outcomes in particular, which was initially what almost drove us to this study. We were surprised to see that the cardiac outcomes themselves were not different. Specifically, MI and MACE were very, very similar; almost identical in the two groups. So, unfortunately, we do not have data on respiratory complications or septic complications. They were just not available to us. So, I’m really unable to comment on those.

The trends that I see in our results is the higher incidence of major blood loss; and I also see a non-significant trend—a difference, but not significant—towards more PEs in the GA group. I cannot say this was a difference in our study because it was not statistically significant.

It’s certainly very similar to findings of other studies. There are many other studies out there in the orthopedic population that show higher incidence of TEs—thromboembolic events—and higher incidence of major blood loss. So, this is not an isolated finding of this study. This replicates what other studies, even prospective studies, have shown. So, you know, I wonder whether some of these causes of death could have resulted from this greater incidence of— in these two areas. But I can really only speculate.

**Dr. James Rathmell:** What are some of the unanswered questions about the risks and benefits of regional anesthesia, and what’s the next step for your own research group?

**Dr. Anahi Perlas:** Certainly, there’s many questions that remain to be answered—new avenues that are open for exploration. Like for any other research finding, you want to see some reproducibility. So, I’m looking forward to seeing similar studies, both from our center and from other centers; maybe even multi-centers.

Specifically, I think we need to look at these similar questions in different patient populations. Because, as we know, the issue of mortality is very specific; is very different whether you’re looking at elective orthopedic population versus, for example, urgent fractures. There will be a very different patient population. So, what you find in one specific patient population does not necessarily automatically apply to different patients. So, I do think we need to look at different patients having different surgeries, and I’m looking forward to looking beyond the elective total joint replacement, for example.

**Dr. James Rathmell:** Dr. Perlas, thank you for discussing your work with me today. You gave us some extraordinary explanations of some really complex methodologic issues, and I think this study is extremely well-done. Thanks for all of your contributions to anesthesiology.

**Dr. Anahi Perlas:** Thank you so much, Dr. Rathmell. It’s been a pleasure, and thank you for the opportunity.

**Dr. James Rathmell:** I hope today’s discussion will lead many of you listening today to read this new article about the impact of anesthetic technique on patient outcomes, to learn more. Dr. Perlas, I wish you well as you continue your efforts to examine the impact of regional anesthesia on the meaningful long-term outcomes of our patients.

**Dr. Anahi Perlas:** Thanks again.

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