

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

**Dr. James P. 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 one of the Executive Editors 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 an author of an original research article and the author of an accompanying editorial that appear in the April 2021 issue. With us today is Dr. Helene Beloeil. Dr. Beloeil is Professor of Critical Care Medicine and Perioperative Medicine at Rennes University Hospital and School of Medicine in Rennes, France. Dr. Beloeil is the first author on an article that appears in the April 2021 issue of the journal and it's titled, "Balanced Opioid-free Anesthesia with Dexmedetomidine versus Balanced Anesthesia with Remifentanyl for Major or Intermediate Non-cardiac Surgery, the POFA, P-O-F-A, Randomized Clinical Trial." Dr. Beloeil, thank you for joining us.

**Dr. Helene Beloeil:** Thank you for having me.

**Dr. James P. Rathmell:** We also have with us today Dr. Evan Kharasch. Dr. Kharasch is Professor of Anesthesiology at Duke University Medical Center in Durham, North Carolina and Editor-in-chief for the journal. Together with Dr. David Clark at Stanford University, Dr. Kharasch authored an editorial that accompanies Dr. Beloeil's original research article in the April 2020 issue and it's titled, "Opioid-free Anesthesia, Time to Regain our Balance." Dr. Kharasch, welcome and thank you for joining us.

**Dr. Evan D. Kharasch:** Thank you very much for inviting me to participate in this podcast and discuss issues that are of substantial importance to patients and practitioners.

**Dr. James P. Rathmell:** Dr. Beloeil, congratulations on the publication of your study. So let's start by setting the stage for listeners. It's been widely speculated that opioid-free anesthesia may provide adequate pain control while reducing postoperative opioid consumption. But there's currently no evidence to support that speculation. So your group hypothesized that opioid-free balanced anesthetic would reduce postoperative opioid related adverse effects compared with a balanced anesthetic that included an opioid. Can you tell us how you conducted your study?

**Dr. Helene Beloeil:** Yes, so it was an investor initiated prospective multi-center trial group, single blind, randomized and controlled trial conducted in ten centers in France. With an independent data and 50 monitoring boards to oversee the conduct and review safety data. So patients undergoing non-cardiac surgery received an intraoperative balanced anesthesia featuring remifentanyl plus morphine or a dexmedetomidine infusion.

All patients received intraoperative lidocaine and ketamine. Postoperatively all patients received paracetamol and nefopam, and they received morphine as needed.

**Dr. James P. Rathmell:** So why did you choose dexmedetomidine as part of the opioid-free limb of the study, and why did you choose remifentanyl as the opioid in the balanced anesthetic limb?

**Dr. Helene Beloeil:** We chose dexmedetomidine because previous studies have suggested that Alpha-2 agonist, especially dexmedetomidine, could provide hemodynamic stability traditionally provided by intraoperative opioids. However, I'd like to emphasize that our definition of opioid-free anesthesia, which was multi-modal anesthesia, including ketamine, lidocaine and dexmedetomidine, is not definitive. And other ways to administer opioid-free anesthesia have to be explored.

And for the control group we chose remifentanyl because it is by far the intraoperative opioid the most used in France. And we wanted to have a control group that reflected actual practices.

**Dr. James P. Rathmell:** So how did you define your primary and secondary outcomes for the study?

**Dr. Helene Beloeil:** The primary outcome was a composite of opioid related adverse events, including postoperative hypoxemia, (inaudible) and cognitive dysfunction in the first 48 hours postoperatively. The choice

of opioid related side effects as the primary outcome was guided by the need for clinically meaningful outcomes. Secondary outcomes were more classic. It was postoperative pain and opioid consumption during the first 48 hours following extubation, the time to extubation, the time to reach an (inaudible) score greater than nine after the discontinuation of remifentanyl or dexmedetomidine, postoperative nausea and vomiting and the duration of hospital stay.

**Dr. James P. Rathmell:** Now you ended up stopping the study early after enrolling a little over 300 patients. Why did you stop the study, and what did you find after analyzing the data from those who were enrolled?

**Dr. Helene Beloeil:** So the story went like this: because of an increased incidence of bradycardia, the independent data in 50 monitoring boards made the recommendation to lower the maximal dose of dexmedetomidine to 1 microgram per kilo per hour. And this was in December 2018. At the time 309 patients were already included. Then the independent data and safety monitoring board received warnings from the French Health Care Safety Agency. The independent data and safety monitoring board met again in January 2019 and decided to stop the trial. The decision was immediately accepted by the POFA, the trial joint committee.

Only seven patients were included between these two dates, between I mean, December 2018 when we lower the dosage, and January 2019. The reason for stopping the trial was severe bradycardia in five patients associated with asystole for three of them in the dexmedetomidine group. All these bradycardias happened before the reduction of dexmedetomidine dosages, decided December 2018. None of these bradycardias or asystole led to postoperative complications or sequelae. And out of the five cases of profound bradycardia in the dexmedetomidine group, three occurred during the gas insufflation before laparoscopy.

**Dr. James P. Rathmell:** So in the data that you analyzed, what were your findings?

**Dr. Helene Beloeil:** So the results of the analysis was that bradycardia requiring (inaudible) administration was more frequent in the dexmedetomidine group than in the remifentanyl group, with a relative risk of 2.14. And within the dexmedetomidine group, complications were analyzed according to the dosage of the dexmedetomidine, being lower or higher than the median value of the whole population and no differences were observed.

So in other words, opioid-free balanced anesthesia using dexmedetomidine was associated with severe bradycardia, and it was not strictly related to the dosage of dexmedetomidine. Meaning that reducing the dose may not be a strategy for mitigation.

**Dr. James P. Rathmell:** What did you conclude from the study?

**Dr. Helene Beloeil:** So from the study we concluded that opioid-free balanced anesthesia is not as outstanding when compared with (inaudible) opioids. And it's associated with severe bradycardia that led to the early termination of the trial. And our results also raised the question about the benefit of eliminating intraoperative opioids and using dexmedetomidine when lidocaine and ketamine are already used.

**Dr. James P. Rathmell:** So what do you think the limitations of your study were? In particular, how widely do you feel that your work can be generalized to other forms of opioid-free and balanced anesthetic drug combinations?

**Dr. Helene Beloeil:** Well, of course there are several limitations to our study. We already talked about the choice of dexmedetomidine that could be questioned, as there are other ways to administer opioid-free anesthesia. Secondly, because of the lack of validated (inaudible) and depth of anesthesia monitors during opioid-free anesthesia, the trial design based the dosage of dexmedetomidine on the patient's heart rate. And this might have led to higher dosage and side effects, such as sedation or bradycardia.

However, the optimal dosage of dexmedetomidine under general anesthesia has not yet been determined. Another limitation could be the high frequency of hypoxemia that occurred in our study, which was higher than expected. But one more time the definition of post-operative hypoxemia is not (inaudible). Which shows a (sounds like: SPA2 95) person as a definition of hypoxemia. And on top of that, our patient did not receive preventive

oxygen therapy. So maybe we saw more hypoxemia than in the (sounds like: research). So I think these were the main limitations of our research.

**Dr. James P. Rathmell:** Dr. Kharasch, I want to turn to your editorial, and it also appears in the April 2021 issue of the journal. I know you authored it together with Dr. David Clark at Stanford, and the editorial is entitled, “Opioid-free Anesthesia. Time to Regain our Balance.” You do a terrific job of putting Dr. Beloeil’s article into perspective in explaining the evolution of opioid-free anesthesia. I want to start by reading a few lines from your editorial.

You tell reads, “Fashions come and fashions go. Changes in clothing, automobiles and restaurants follow popular trends and are often periodic and cyclical. Ideally medical change is driven not by fashion, but instead by concepts of effectiveness and safety. And that these improve and refine as better data become available. Trends hold true also in anesthesia practice. Recent years have witnessed a new fashion in anesthesiology, opioid-free anesthesia. For some the opioid pendulum has swung clear past rational opioid use in balanced anesthesia, to eliminating opioids intraoperatively and sometimes also postoperatively. What has now come to be known as opioid-free analgesia.” You called this a movement. Talk us through how you think this movement began and gained so much momentum.

**Dr. Evan D. Kharasch:** It’s not perfectly clear how this movement began. In some ways this is a study of the sociology of medical practice and physician behavior. One thing which we think is clear is that it was grounded in the enthusiasm of physicians for trying to do the right thing. But we think that there are several possible factors which may have contributed. The first is the opioid crisis. No one could escape hearing about the opioid crisis through either medical literature or lay literature. And this include physicians and healthcare providers.

But it’s important to understand that the opioid crisis started in the inappropriate over prescribing of oral, outpatient opioids in patients in which they were not indicated or not effective. And ended up in addiction, misuse and unfortunately overdose and deaths. But nothing about this entire unfortunate history of the opioid crisis is associated with, caused or was caused by the appropriate use of opioids in the operating room and the recovery room to treat surgical pain.

It was a leap to say that there’s an opioid crisis, and therefore we should stop using opioids to treat surgical pain. But the steady drumbeat of the opioid crisis can influence physician behavior, either consciously or subconsciously. But if stopping treating surgical pain with opioids was a response to the opioid crisis, this was not an appropriate response.

Another possibility is the concept of opioid sparing, which we talk a lot about in anesthesia and perioperative care, that the excessive use of opioids, such that they cause unwanted side effects, is not in the best interest of patients. And we should spare the overuse of opioids. But again, perhaps this was taken too far, to the point of opioid eradication rather than the appropriate use of opioids.

And then lastly we hear a lot about the use of protocols in perioperative care. And there’s great enthusiasm for protocols, and people may have misinterpreted protocols which called for appropriate opioid use or opioid sparing to think that perhaps they called for the abolition or the eradication of opioids. But this was really a lot of misinterpretation or over interpretation, where we really swung from overuse all the way over to abolition. And abolition was not the right answer.

**Dr. James P. Rathmell:** Can you recap the major findings of Dr. Beloeil’s study and tell us why you think the study is important?

**Dr. Evan D. Kharasch:** This is a very well designed study, and it was well designed because it evaluated both the benefits and the risks of an opioid-free regimen. Very often studies will either only evaluate benefits of some intervention, or they may simply evaluate postoperative opioid use. But it’s important to understand that decreasing opioid use per se is not really patient centric. And it’s only a meaningful outcome if decreased opioid use is a surrogate for decreased postoperative pain. Or it’s accompanied by decrease opioid related side effects.

The strength of Dr. Beloeil’s study was that it evaluated not just opioid dosaging, but most importantly opioid related adverse events. And it also evaluated outcomes like postop pain, opioid consumption, nausea and

vomiting. And the major take home was that rather than the expected outcome of an opioid-free regimen decreasing opioid related side effects, it actually resulted in a great incidence of side effects. And that incidence was clinically important. It resulted in what we call serious adverse events, five episodes of bradycardia, three of them were frank asystole.

So the results were important. They were important to patients, and they showed that the incidence of side effects or adverse effects was greater than expected and greater than in the opioid group. It also showed that in the patients in the opioid-free or dexmedetomidine group, the times to extubation were longer. The times to discharge from the recovery room were significantly longer. And postop opioid consumption was not clinically meaningfully less.

**Dr. James P. Rathmell:** Now the April 2021 issue also includes a comprehensive narrative review by (sounds like: Jervis) Joshi, Karim Ladha and their colleagues titled “Perioperative Opioid Administration, a Critical Review of Opioid-free versus Opioid-sparing approaches.” Can you briefly summarize the findings of that review?

**Dr. Evan D. Kharasch:** This was a very well written review. The essential messages were that while opioid-sparing is possible in some context and in some procedures, there is no evidence that opioid-free strategies have any benefits above and beyond opioid-sparing strategies. That opioid-free strategies influence the risk or prevent persistent postoperative opioid use, or they prevent postoperative opioid over prescription.

They also show that opioid-free strategies are not evidence-based. They don’t allow the titration of analgesics to meet patient needs. They can be expensive and require more equipment. And they’re very unrealistic and difficult to implement in routine clinical practice. And perhaps their most important conclusion is that the undo focus on opioid-free anesthesia may actually be distracting practitioners from optimizing pain relief and minimizing any long-term consequences of surgery and surgical pain.

**Dr. James P. Rathmell:** All right, so how do we regain some balance in the way we approach the perioperative use of opioids?

**Dr. Evan D. Kharasch:** It’s very important to understand two essential messages. One is that surgery hurts and that more than 80% of patients say that their postoperative pain is not adequately treated. The second is to understand that the drugs we use are effective, but can also have unwanted side effects. Our goal is to use our drugs to treat surgical pain. To use them in combinations that ideally increase benefit and decrease the risk of side effects and to try and prevent the unwanted and significant side effects of the drugs we use.

But to remember that opioids are our most powerful medications to treat pain. That other drugs that we may use in combination with opioids when used alone, are not sufficient to treat moderate to severe pain. But we have to be patient-centric in our thinking and not simply focus on the eradication of one or other drug. But rather to focus on the goal, which is relieving patient pain, minimizing the potential for adverse effects. Minimizing the potential for the development of chronic post-surgical pain. And really to understand that we should avoid making patients pay with unnecessary suffering for the opioid mis-prescribing or over prescribing in outpatient non-surgical care.

**Dr. James P. Rathmell:** Well, I think that is a pretty good take home message for practicing anesthesiologists. Get some balance back. Opioids are an important part of our everyday practice. Dr. Beloeil, again, terrific work. What comes next for you and your research group?

**Dr. Helene Beloeil:** We, show that balance opioid-free anesthesia with dexmedetomidine resulted in a greater incidence of serious adverse events, as was just said. Of course more research on opioid-free anesthesia is necessary. As Dr. Kharasch said, we need a more rational approach. The solution is probably in a more personalized approach. So to my opinion we have to define which patients would benefit the most from an opioid-free anesthesia. For example, could it be chronic opioid users? And which specific opioid-free anesthesia protocol they would benefit from. So we should also probably work on the potential benefits of low opioid anesthesia protocols, including opioid bearing strategies. And low opioid anesthesia could be the strategy with the most benefits in between the two extremes. The extremes being on one hand high doses of intraoperative opioids, and on the other hand no intraoperative opioids.

**Dr. James P. Rathmell:** Terrific. I hope today's discussion will lead many of you that are listening to read this new article. It appears in the April 2021 issue of *ANESTHESIOLOGY*. And you can learn more about the limitations of opioid-free anesthesia. Dr. Jon Wanderer from Vanderbilt and I also created an infographic that appears in the same issue titled, "Bringing Back the Balance. Opioid Reduction in Anesthesia." Where we highlight the primary findings of these articles. Dr. Beloeil and Kharasch, thank you for joining me today and for the terrific explanations.

**Dr. Helene Beloeil:** Thank you very much.

**Dr. Evan D. Kharasch:** Thank you very much for allowing me to participate.

**Host:** You've been listening to the *ANESTHESIOLOGY* journal podcast, the official peer reviewed journal of the American Society of Anesthesiologists. Check [anesthesiology.org](http://anesthesiology.org) for an archive of this podcast and other related content.

**{Music}**

**THE END**