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’re listening to an *Anesthesiology* podcast, designed for physicians and scientists interested in the research that appears in our journal.

Today, we are going to talk with the authors of a publication that appears in the October 2016 issue of the journal. With us today is Dr. Jesse Ehrenfeld, who is an Associate Professor of Anesthesiology, Biomedical Informatics, Surgery, and Health Policy at Vanderbilt University Medical Center in Nashville, Tennessee. Dr. Ehrenfeld is the senior author of an article titled “Nondepolarizing Neuromuscular Blocking Agents, Reversal, and Risk of Postoperative Pneumonia.” Welcome, Dr. Ehrenfeld.

**Dr. Jesse Ehrenfeld:** Thank you so much. I’m excited to be here today.

**Dr. BobbieJean Sweitzer:** Joining Dr. Ehrenfeld is Dr. Glenn S. Murphy, who authored an accompanying editorial titled “To Reverse or Not To Reverse?: The Answer is Clear!” He is a Clinical Professor of Anesthesiology at NorthShore University Health Center in Evanston, Illinois, and the University of Chicago Pritzker School of Medicine in Chicago, Illinois. Welcome, Dr. Murphy.

**Dr. Glenn S. Murphy:** Thanks. I’m excited to be here today.

**Dr. BobbieJean Sweitzer:** So, let’s start with Dr. Ehrenfeld. So, first, congratulations on publication of this work. Can you tell us briefly why you undertook this study?

**Dr. Jesse Ehrenfeld:** Sure, BobbieJean. So, you know, in my practice at Vanderbilt, we’re very focused on how we can improve care in the operating room that leads to better outcomes downstream. And to be honest, that’s often a challenge for us as anesthesiologists, because oftentimes the last time we see a patient is in the PACU. However, it became really clear to us that the relationship between our airway management in the OR, use of neuromuscular blocking drugs, and postoperative residual weakness and subsequent complications, was a really important problem to study and understand as a part of our efforts to better provide care that’s safe for our patients.

So, you might ask, why focus on postoperative pneumonia? Well, postoperative pneumonia’s associated with increased mortality, morbidity, hospital length of stay, and costs. And we hypothesized that patients who get nondepolarizing neuromuscular blocking agents during surgery might have been more likely to develop postoperative pneumonia. And furthermore, the patients who received those drugs who weren’t given reversal, may have even further increased risks of postoperative pneumonia. So, having that as background, we decided to undertake this study.

**Dr. BobbieJean Sweitzer:** So, in this study you used a statistical methodology of propensity score matching. What is the importance of this technique for the conduct of this study and the results you found?

**Dr. Jesse Ehrenfeld:** This was not a prospective randomized controlled trial, so we know that some patients may have been more or less likely to get a neuromuscular blocking agent from the start, because of either the procedure they were having, the surgeon who was doing the case, their age, their BMI, or even when the surgery was performed—like, in the middle of the night or during the day. So, to account for that, we used a technique called propensity score matching. All it does is, it enables us to apply a statistical matching technique to account for covariates that predict receiving the treatment—in this case, receiving a neuromuscular blocking agent.

**Dr. BobbieJean Sweitzer:** And why did you decide to perform two separate propensity score matched analyses in this study?

**Dr. Jesse Ehrenfeld:** So, in this study, we had two hypotheses: that patients receiving a neuromuscular blocking agent had a higher risk of developing postoperative pneumonia; and that patients who were not given reversal may have also had an even further increased risk of postoperative pneumonia.

So, because of that, we needed to perform two propensity score analyses: the first, to account for covariates that predict why a patient might receive a neuromuscular blocking agent from the start; and, second, a propensity score analysis to account for covariates that predict why a patient might receive reversal. In that propensity score analysis, among other things, we included, importantly, the time between the last administration of the neuromuscular blocking agent and the end of surgery.

**Dr. BobbieJean Sweitzer:** Out of a pretty large database—I think it was 13,100 eligible surgical cases—you ended up matching 1,455 cases who received a depolarizing intermediate-acting neuromuscular blocker to 1,455 patients who did not receive these drugs. And from over 10,000 surgical cases who received one of these muscle relaxants, you then were able to match 1,320 who did not receive reversal, to the same number who were reversed. Why were you only able to select a little over 10% of the cohort for matching?

**Dr. Jesse Ehrenfeld:** As we show in the first figure of the paper, of all the eligible surgeries we evaluated, there were only 2,500 that didn’t get a neuromuscular blocking drug, whereas we had 10,000 patients who did. So, our propensity score matching tried to match patients from that group of 2,500 controls to the 10,000 cases, and we ended up with 1,455 controls and 1,455 cases after the statistical matching was completed. Then, of those 10,000 patients who received the neuromuscular blocking drug, there were only 1,600 patients who didn’t receive reversal, so we used propensity score matching to again find similar cases, and we ended up with 1,320 patients who did receive reversal and 1,320 patients who did not.

**Dr. BobbieJean Sweitzer:** Excellent. So, you and your coworkers used this large sample of surgical cases who received general anesthesia and who underwent surgery; and you used the National Surgical Quality Improvement Program database. Now, were all of the general anesthetic cases managed with endotracheal intubation? And specifically, did you exclude patients having supraglottic airways or simply masked ventilation, or nothing more than supplemental oxygen with their general anesthesia?

**Dr. Jesse Ehrenfeld:** All the patients in the study, BobbieJean, did receive general anesthesia with an endotracheal tube. We did not evaluate patients who had a supraglottic airway only, or were just masked, or just got supplemental oxygen.
Dr. BobbieJean Sweitzer: Thanks for explaining that. And did your cohort include patients who remained intubated postoperatively—for example, taken from the operating room still with endotracheal tube in place? And did it also exclude those who perhaps were reintubated before the diagnosis of pneumonia was made?

Dr. Jesse Ehrenfeld: We excluded patients who remained intubated postoperatively, but we did not exclude patients who may have had to be reintubated prior to a diagnosis of pneumonia being made. Importantly, though, we did exclude any patient who had pneumonia prior to the start of surgery, meaning that it was a preexisting condition. We also excluded patients who may have died in the operating room, or patients who were lost to followup.

Dr. BobbieJean Sweitzer: So, Dr. Murphy, I have a question for you. Anesthesia providers seem to be very comfortable in using paralytic agents. But I recall as a new trainee who came from a medicine background that I actually was very apprehensive about taking away a human's capacity to breathe. Do you think perhaps anesthesia providers may be a bit too comfortable with using nondepolarizing muscle relaxants, and think these drugs are safer than perhaps they are?

Dr. Glenn S. Murphy: Oh, I completely agree with that statement. As someone who trained in the era of pancuronium, I think we had to learn to be very careful with dosing, monitoring and reversal of neuromuscular blocking agents. And with the era of intermediate-acting agents, I think anesthesiologists have become much more comfortable with the use of the drugs, and I think there's a perception by many practitioners that, oh, if it's been three or four hours after we've given a dose of an intermediate-acting agent, it should just wear off, which we know isn't the case. Four hours after a single dose of an intermediate-acting agent, up to 20% of people can still have residual block.

I think another factor is, people believe that neostigmine is very effective in reversing neuromuscular blocking agents. I think people aren't aware of the fact that neostigmine can take a considerable period of time, oftentimes, to work. For example, if you have two twitches in a train-of-four count, it can take up to 20 to 30 minutes to achieve a train-of-four ratio of 0.9 or greater, which is the threshold for acceptable recovery. So, I agree, I think that clinicians do feel a little bit too comfortable using these agents.

Dr. BobbieJean Sweitzer: I know, Dr. Murphy, for some time you have been working to bring awareness to the problem of residual neuromuscular weakness related to the use of paralytic agents, and have published extensively on this topic. Why do you think it still remains a problem?

Dr. Glenn S. Murphy: That's a very interesting question. If you look over the last 30 years, there've been well over 100 studies showing that probably about 40% of people who arrive to the PACU have residual block. Everyone—they've done surveys of anesthesiologists. Only about 15% of anesthesiologists say they've ever seen residual block in their clinical practices. So, this is a huge disconnect from what the science says and what people actually perceive in their clinical practices.

And I think the reasons for this are somewhat unclear, I think probably because most of the patients who have residual block who get to the PACU really do okay. They may feel a little bit weak; they may stay a little bit longer in the recovery room, but it's not a huge problem. I think where it is a problem is those patients who have limited physiologic reserve. Those are the patients that tend to get in trouble: the patient who is morbidity obese with sleep apnea; the patient with severe COPD. You know, I think when we see those patients, and they get to the PACU and they're having trouble, we tend to blame the patient. Well, the reason they were having hypoxia or airway obstruction is really because of their underlying disease. I don't think we want to think it's something that we did, that we left these patients with residual block.

You know, I think the easiest way to convince clinicians that residual block is a big problem is to keep a quantitative monitor, like a TOF-Watch, in the recovery room. If you do that, you'll find that many of the patients who are actually getting into trouble in the recovery room, actually have residual block. In fact, in one study we did, we found that 90% of the patients who were having critical respiratory events in the PACU actually had residual block. So, I think the real reason it's remained such a big problem is that clinicians don't recognize it. They're not looking for it, so they don't see it as a problem.

Dr. BobbieJean Sweitzer: So, TOF is train of four.

Dr. Glenn S. Murphy: Yes, that is correct.

Dr. BobbieJean Sweitzer: So, Dr. Ehrenfeld, your findings suggest that there was a risk of pneumonia in patients when muscle relaxation was not reversed; but also in those who received reversal agents, even had an elevated risk. I can understand that residual muscle weakness can result in pulmonary complications, which has also been shown in other studies. But what is the likely or possible reasons that reversal of neuromuscular agents can be also associated with pneumonia?

Dr. Jesse Ehrenfeld: Well, I think your fundamental question is, why did that group of patients that got these agents and then got reversal still have challenges, and a non-zero rate of having postoperative complications? And I think it comes back to what Dr. Murphy was just talking about, is we don't often recognize what the true physiologic state of our patients is. You know, it may be obvious if you have a patient with, say, myasthenia gravis. Our awareness of the risk of postoperative weakness, pulmonary complications and other morbidities is fairly high. But we may not recognize that in a patient who maybe has a little bit of COPD, or who's morbidly obese, or has undiagnosed sleep apnea.

So, in my mind, I think it comes back to really understanding, kind of, where a patient is. And unfortunately, you know, the train of four monitoring technology that we have available today, even with the advent of quantitative monitoring which we're using at our hospital, is difficult to use and still remains problematic in terms of really helping the end user—i.e., me, sitting at the bed, in the operating room, or in the PACU—make a good decision about where my patient is.

Dr. BobbieJean Sweitzer: So, that leads into my next question: is there an unequivocal circumstance in which reversal of neostigmine should not be used? Or is it fair to suggest that one should always administer reversal agent after the use of intermediate-acting nondepolarizing neuromuscular blocking drugs?

Dr. Jesse Ehrenfeld: That's a great, very practical question. I think the only blanket exclusion for why you shouldn't give neostigmine is if someone has an allergic reaction to it, and there are certainly patients where that's the case, although it's very rare. As with every drug that we give, we have to consider the risks and benefits. And while there are certainly some side effects associated with neostigmine and reversal of neuromuscular blockade, my take on our analysis, the results and the literature, is that there probably are very few circumstances where it would be inappropriate to give neostigmine after a neuromuscular blocking agent.

Dr. Glenn S. Murphy: Yes. I would also add, probably the only time I don't reverse is if I have a documented full recovery using quantitative monitoring. If I have a device like the TOF-Watch that shows me that the train-of-four ratio has recovered to 1, or back to
our baseline, that’s about the only circumstance that I would not use a reversal agent.

Dr. BobbieJean Sweitzer: Now, Dr. Murphy, you’ve mentioned the TOF-Watch a couple of times. Do you want to expand on a description of that?

Dr. Glenn S. Murphy: Sure. There’s two types of monitors we tend to use in the operating room. Now, we have the basic, simple, qualitative neuromuscular monitor, which is basically our peripheral nerve stimulator, where basically we stimulate a peripheral nerve, and we basically often do a – for example, a train-of-four count, or look for fade when we do a train-of-four count or tetanic stimulation. That’s a device that most anesthesiologists have in their armamentarium.

However, there’s another class of monitors, which are the quantitative monitors. And these are devices that allow us to actually very accurately measure and quantify the degree of muscle weakness. And these are devices that will actually give us a reading from zero to one, or zero to 100%, to tell us the degree of recovery we have. Now, the only device that’s available right now as a stand-alone monitor is the TOF-Watch, and they’ve actually discontinued making that just recently. But there are some other quantitative monitors that are available with some of the anesthesia machines that are sold right now.

You know, one of the limitations, as we’ve heard earlier, is, really, we don’t have any really good, simple, easy-to-use quantitative monitoring. That’s the reason it’s not used. Only about 10% of anesthesiologists in the United States even have the availability of using one of these types of quantitative monitors.

Dr. BobbieJean Sweitzer: Dr. Murphy, as you noted in your editorial, perhaps another reason for reluctance to reverse neuromuscular agents may be related to concerns about the potential of neostigmine to produce paradoxical muscle weakness, especially when administered at full neuromuscular recovery. This would not be a problem with sugammadex, correct.

Dr. Glenn S. Murphy: It shouldn’t, and we wouldn’t expect to find it, based on the mechanism of action of neostigmine. You know, the concept of this paradoxical muscle weakness is sort of an interesting one. It was first raised in 1995 by James Caldwell. He did a study where they gave 60 patients a single intubating dose of vecuronium, and they followed them one to four hours later, and then reversed at each of those intervals with a dose of neostigmine. And they found 80 of those patients actually had a drop in their train-of-four ratio, and all those patients – it occurred in patients who’d recovered a train-of-four ratio of 0.9 or greater. So, indicating that possibly it could produce some muscle weakness.

And most of this data actually come from Eikermann’s group out of Mass General. They’ve done some animal studies where they gave neostigmine at full neuromuscular recovery and found that it impaired upper airway dilator muscle function. And they followed that up by doing a study in human volunteers where they gave neostigmine at full neuromuscular recovery and also found that it increased upper airway collapsibility.

Now, they didn’t actually find that patients were obstructing, but when they did sensitive tests of airway function they found there was some weakness. And they have some theories for why this happens. It may be due to depolarizing neuromuscular block; it may be due to acetylcholine receptor desensitization open channel block, but it’s not entirely clear. But based on those mechanisms, it’s unlikely that sugammadex would cause this. In fact, one of the studies by Eikermann—they found when they gave these animal models neostigmine, they had upper airway dilator muscle dysfunction; but when they gave them sugammadex, it didn’t occur. So, we wouldn’t expect this paradoxical muscle weakness to occur with sugammadex.

Dr. BobbieJean Sweitzer: Dr. Ehrenfeld, do you think that your next study perhaps should be either a randomized trial of reversal using either an anticholinesterase agent such as neostigmine versus sugammadex; or, as sugammadex becomes more readily utilized in the – especially in the United States, of using a similar database, and doing a similar study to compare two different types of reversal?

Dr. Jesse Ehrenfeld: I find it hard to imagine a prospective randomized trial using the two techniques; but certainly, as the use of sugammadex becomes more common, that will open up the opportunities to do similar analyses to what we did, using existing datasets for retrospective trials.

Dr. BobbieJean Sweitzer: One more question for you, Dr. Murphy. In your editorial, you state, “in order to optimize patient outcomes, clinicians should only administer neuromuscular blocking agents when clinically necessary.” Can one make an argument to substitute succinylcholine, for example, for nondepolarizing blockers for intubation when muscle relaxation is not indicated for the procedure itself? Or, would that be trading perhaps one potential problem for others?

Dr. Glenn S. Murphy: I think I agree with your second proposition: we’re trading one set of problems for another. In our clinical practice, we’ve really been avoiding the use of succinylcholine. And I looked at our practice – how it’s changed over the last 10 years, and I think we’re using less and less. I think it’s a recognition – I think we all know the complications that are potentially associated with succinylcholine; particularly, I think, the biggest one being myalgias, which can occur in up to 89% of patients. And it’s more common actually in ambulatory patients, which more and more of our patients are. And again, there are the other more rare risks such as arrhythmias, hyperkalemia, increased intraocular pressure, and intracranial pressure.

Because this is a drug with significant side effects, I find we’ve actually moving away – we’re moving away from using succinylcholine. In fact, I think with the advent of sugammadex, we’ve sort of – are using it even less. For example, some of our surgeons are very quick and do skin-to-skin lap chole in 30 minutes. And that was always a problem for us, because your choices were, give a dose of succinylcholine, but you wouldn’t really have muscle relaxation during the procedure; or give a small dose of rocuronium, but oftentimes, even with a dose of 20 or 30 milligrams, you’d still have muscle weakness at the end of the procedure.

So, in those cases where we used to use sux, and I think we’re using more roc because we know we can effectively reverse it 20 or 30 minutes later with a dose of sugammadex. So, I find that we’re actually using less succinylcholine in our practice.

Dr. BobbieJean Sweitzer: So, Dr. Ehrenfeld, follow, sort of, on that same theme of your personal practice – have you – these findings of your study changed the way that you either personally administer or teach your residents and oversee CRNAs, for example, in using nondepolarizing muscle relaxants? Especially, you know, as part of an anesthetic technique, and how you monitor their effects, and in your decision specifically to reverse or not?

Dr. Jesse Ehrenfeld: Great question. I think it certainly has changed our practice, and has done a couple of things. One is, as a department, because we’ve shared these findings, we’ve had discussions about them, there’s much more recognition of the dangers of not reversing, and of the drawbacks of using these agents. And I’ve seen over time that there are practitioners who are using less neuromuscular blocking agents when they don’t have to.

And what I find the residents doing is saying, you know, unless there’s a really good reason for me not to reverse, they’re going to reverse.
And we have made the switch to quantitative neuromuscular monitoring, using a device that’s commercially available, and I think that’s also been a really important change in our practice.

**Dr. BobbieJean Sweitzer:** I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you, Drs. Ehrenfeld and Murphy, for discussing your work with us today and providing evidence of the hazards of postoperative residual neuromuscular block and the importance of reversing neuromuscular blocking agents. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

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