Title: Opioid-Induced Respiratory Depression: Who Should We Monitor?

Additional Titles:
Predicting Patients at Risk of Opioid-Induced Respiratory Depression on the Medical/Surgical Floor

Benefits and Learnings from the PRODIGY Study

Results: Prediction of Opioid-Induced Respiratory Depression in Patients Monitored by Capnography

Meta: In these snippets from the Society of Critical Care Medicine's iCritical Care podcast, Ludwig H. Lin, MD, talks to Ashish K. Khanna, MD, FCCP, FCCM, about his abstract deviation and validation of an opioid-induced respiratory depression risk prediction tool.

Social Media Options:
Option 1: This blog post offers a look into the Society of Critical Care Medicine's iCritical Care podcast, where Ludwig H. Lin, MD, talks to Ashish K. Khanna, MD, FCCP, FCCM, about his abstract deviation and validation of an opioid-induced respiratory depression risk prediction tool, a Medtronic-sponsored clinical study.

Option 2: Want to learn more about the PRODIGY study? Ashish K. Khanna, MD, FCCP, FCCM, talks to the Society of Critical Care Medicine about his abstract deviation and validation of an opioid-induced respiratory depression risk prediction tool.

Author: Greg Spratt, BS, RRT, CPFT, Director of Clinical Science, PACE, Medtronic

Nearly half of all in-hospital cardiorespiratory arrests occur on general care floors[1] and opioid-induced respiratory depression (OIRD) is one potential cause of these events.[2] Ashish K. Khanna, MD, FCCP, FCCM, an intensivist, associate professor of anesthesiology, and associate chief for research at Wake Forest University School of Medicine in Winston-Salem, North Carolina, USA, investigated incidents of OIRD as part of the PRODIGY trial, a Medtronic-sponsored clinical study.

The following blog article contains snippets from the Society of Critical Care Medicine's (SCCM) iCritical Care podcast, in which Ludwig H. Lin, MD, an intensivist and anesthesiologist at Summit Alta Bates Medical Center in San Francisco, California, USA, talks to Dr. Khanna about his abstract deviation and validation of an OIRD risk prediction tool.

* Disclaimer: This blog article is a summary in question and answer format and is not a full and complete recitation of the podcast. This summary has been prepared to highlight the key elements from the podcast and every effort has been made to avoid any mischaracterizations. Any failure to do so is unintentional. Furthermore, Statements of fact and opinions expressed in this podcast are those of authors and participants and do not imply an opinion on the part of the Society of Critical Care Medicine or its officers or members. This podcast is supported by an unrestricted educational grant provided by Medtronic.

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Dr. Lin: How did you come to want to do a study about this topic?

Dr. Khanna: The general perception is that our general care floors are a safe haven for our patients. We send our patients there from the intensive care unit (ICU) or from the postanesthesia care unit (PACU) and hope they're going to recover there and ultimately go home.

The issue though is that what we have seen from recent literature is that there are increasing incidents of sudden acute cardiorespiratory events on the general care floor. And when these incidents happen, the mortality associated with it is significant.

For example, the Get With the Guidelines Database looked at all index events across the United States over the last decade or so. The database found that these index events are common to the tune of many thousands of events across the hospitals that participated. When these events happen, these patients had a mortality rate of almost 40%, so nearly half of these patients will die. And this outcome is much worse than patients who have a sudden cardiorespiratory event in a monitored scenario like the ICU or the PACU. I felt that, because we were sending our patients to the general care floor, it was our responsibility to make sure that they were safe.

Now the other side of the coin is how we monitor our patients on the general care floor. Our traditional monitoring systems are based on snapshots in time. A nurse or a nursing assistant will check a patient's vital signs and do a quick neurological assessment and then there will be about a three- or four-hour gap in time where the patient is in the room with no real-time monitoring going on.

It's these gaps in time where respiratory events tend to happen. Because we know that cardiorespiratory events are common on the general care floor, current monitoring standards

might not meet criteria to pick up on these cardiorespiratory events. And finally, it's almost impossible to predict which patients are going to have these cardiorespiratory events.

We've done work before where we looked at various predictors and tried to see if there is an easily validated tool that can be used to predict the happening of these events, and unfortunately we had found nothing so far. The PRODIGY trial essentially aimed to monitor patients continuously, then derive a tool based on real-time monitoring outcomes to see if this tool can be plugged into clinical practice.

Dr. Lin: Tell us more about the PRODIGY trial. What does PRODIGY stand for?

Dr. Khanna: PRODIGY stands for the prediction of opioid-induced respiratory depression in patients monitored by capnography.

The thought behind the trial was to monitor patients continuously and develop a risk prediction tool. We ended up calling this the PRODIGY score. The way we did this trial was we had 16 sites across three continents (United States, Europe, and Asia) where we recruited and enrolled patients on the general care floor—whether it was a medical service or a surgical service—who would be receiving parenteral opioids and were hooked up to continuous capnography and pulse oximetry monitoring.

What was unique about the way we did the monitoring part was that we put all our patients on continuous monitoring using a portable monitoring system. We monitored heart rate, respiratory rate, oxygen saturation, and end-tidal CO_2.

However, we blinded and silenced our monitor so neither the patient nor the bedside providers had access to what the monitor was doing or showing. The bedside providers still did their traditional monitoring every four to six hours. What we uncovered was real-time data of patient deterioration events that we would not have picked up had we unblinded these monitors and allowed intervention.

One novelty was the way we did our monitoring. The second novelty was that even though we had tons of monitoring data, we had to be sure that this was not artificial and was a real signal to harm. We sent our monitoring data to a four-member clinical event committee. These were four experts on perioperative respiratory depression. They were not investigators on the trial, so they were as unbiased as possible.

They looked at all the waveform data and were able to separate what was an artifact and what was a real respiratory depression episode. We use predefined criteria to define a respiratory depression episode. Our criteria was a respiratory rate of five or less, oxygen saturation of 85 or less, and end-tidal CO_2 of 15 or less or 60 or greater. All of these must have lasted for at least three minutes, any apnea episode for 30 seconds or more, or any predefined respiratory opioid-related adverse event.

If a patient had any of these, he or she would be marked off as having a respiratory depression episode. The clinical event committee would see the real-time data showing end-tidal CO_2, oxygen saturation, respiration rate, and heart rate. They would then determine if it's a real episode or perhaps an artifact because the nasal cannula picking up the end-tidal CO_2 is not properly

connected on the patient's forehead, or it has fallen off, or the saturation probe is not properly connected.

What we had in the end was high-fidelity data that we then used to associate with 46 potential predictors and build our risk prediction model.

CTA: Discover the clinical and economic benefits of capnography monitoring. View the clinical summary.

Dr. Lin: How did the number you picked in terms of defined respiratory depression events compare to the clinically developed detected clinical events in the hospital by the regular team?

Dr. Khanna: The results themselves showed that, out of 1,335 patients that we enrolled and included in our final analysis, only 615 of them had a respiratory depression episode as we defined and picked up on the monitor. Forty-six percent of our patients had respiratory depression episodes, according to the monitor.

However, I could count on my fingertips the clinical episodes that were picked up by a bedside provider. This showcased a huge divergence between what we're picking up and what is happening. And this, by the way, is not the first time this has happened.

At the Cleveland Clinic, we worked on data where we had put our non-cardiac surgical patients on continuous pulse oximetry monitoring that was blinded, and in a cohort of about a thousand patients we are seeing that to the tune of 90% of all episodes of desaturation lasting for an hour or more were not picked up by traditional vital sign monitoring.

That is how divergent continuous monitoring data is from traditional monitoring; clearly there is a miss somewhere.

Dr. Lin: How many patients did you enroll? How many wound up in the study? And what were the inclusion and exclusion criteria?

Dr. Khanna: We looked at initial eligibility for nearly 2,000 patients across three continents. Our big exclusion criteria were patients with do-not-resuscitate (DNR) orders who were receiving opioids secondary to palliative care and things of that nature. Patients who did not qualify were under 18 years of age or were older patients who had cancer chemotherapy and were receiving opioids.

Our inclusion criteria included adult inpatients on the general care floor who would have a minimum of one hour and a maximum of 48 hours of monitoring and who would receive parenteral opioids.

The demographic patterns are interesting because we did this across three continents. One of the ideas was to see opioid behavior in terms of prescription practices in the United States, Europe, and Asia. Some of the interesting demographics that came out were that the American population was younger but much heavier compared to the European and Asian populations. Higher body mass index (BMI) and higher neck circumference translate into a higher STOP-Bang score and risk for obstructive sleep apnea (OSA) for the American population.

CTA: View more resources on respiratory compromise.

Dr. Lin: I know that you're still analyzing the data, but can you give us some examples of the high-risk populations that you found?

Dr. Khanna: Our primary outcome, in addition to the increased incidence of respiratory depression episodes, was to build the PRODIGY risk prediction score. The risk prediction score, as we've analyzed based on a multivariate risk prediction model, has essentially five variables to it.

We found that, beyond age 60, every decade adds to the risk and was the one that was most strongly associated with OIRD. Other factors on that score: male sex, opioid-naive patients, presence of sleep-disordered breathing—either diagnosed OSA or a high score on the STOP-Bang risk tool—and presence of chronic heart failure.

So these five variables are easy to use. Each of them would then get a weight based on their odds ratio being associated with a perioperative OIRD event and then the PRODIGY score would go from a minimum of zero to a maximum of 39. And what we also estimated further was that we saw a significant intergroup separation. So what I mean by that is we divided our patients. The 615 who had an OIRD episode we divided into low, intermediate, and high PRODIGY risk scores. A low risk score was a total score of less than 8, intermediate was 8 to 15, and a high PRODIGY risk score was greater than 15.

We found, for example, that someone at the highest risk (> 15) had a six times greater likelihood of having OIRD when compared to someone who scored at the lowest risk (< 8) on the PRODIGY risk score, at least within our cohort. And we found that not only the lowest and highest risks were different. Even the folks who were intermediate risk had a significantly different likelihood of having OIRD episodes.

Dr. Lin: How could this potentially change our management of these patients and our treatment of them?

Dr. Khanna: This is a very easy-to-use bedside calculator. In fact, I wouldn't even call it a calculator. Anyone could do this, and that's the one thing I wanted to achieve. Some of our risk prediction scores in anesthesia and preoperative medicine are complicated. I need you to go online, log into something, calculate something. Here is something where a bedside nurse could pick it up, see the patient's age and gender, look at three elements from the history, and you have a score.

When someone has a higher score, I would say that is the person who absolutely needs continuous multiple-parameter monitoring with a central monitoring platform that's going to separate noise from true events.

Then you need to be proactive with your interventions. So it's all about pattern detection, as I call it. If you see someone with OSA who is having repetitive depths of hypoxemia and hyperventilation events and the frequency of that sort of pattern is increasing, you know that this is going toward that spiral, and he or she is going to have a respiratory arrest soon.

So you need to go in and intervene as soon as you identify that pattern. It's almost like bedside EEG monitoring that we do for seizure detection. You've got to identify patterns and intervene when the pattern looks abnormal, before an event happens. We as a community of critical care providers and anesthesia providers have been guilty of running our rapid response teams as a response to a catastrophic event. I want to run my rapid response teams as proactive interveners to avoid those events. It's not good enough to have an event, someone codes, and then you run into the room and try and resuscitate that person. You must prevent that code from happening, because these are avoidable events.

Dr. Lin: How do we pay for this technology? How do we rationalize it? How do we justify it? How do we find the money?

Dr. Khanna: I can tell you that previous literature has shown that patients who have OIRD events stay longer in hospitals, which costs a hospital a lot of money.

It's about $2,000 a day to have someone as an inpatient. If that patient goes to the ICU, it's probably $5,000 a day, with the cost of mechanical ventilation, procedures, and everything else. So my argument would be: deploy continuous monitoring. You'll probably need some investment upfront, but you'll see returns over the next five to 10 years.

And not only that, I honestly feel it's a patient safety issue. We owe this to our patients. And I will sound dramatic when I say this, but if it was my mom or dad who was recovering on the general care floor and, at least based on what I know today, I would not be agreeable to leaving them on a two- to four-hour vital sign check.

Dr. Lin: I know that you are analyzing your data right now, and you don't have all of it, but I was wondering if there are any surprising outcomes that you saw when you started analyzing?

Dr. Khanna: The one surprising outcome was certainly the incidence of respiratory depression episodes that we uncovered. Literature that's available to us now found incidents about three to 21% of respiratory depression episodes on the general care floor, and we saw that 46% of patients were experiencing episodes confirmed by independent review of four physicians.

There is a reason for this discrepancy. First, that literature is based on mostly snapshots in time of monitoring vital signs. It's usually based on a singular monitoring system like only the pulse oximeter or the capnograph. However, we used continuous real-time monitoring, which explains why we picked up more respiratory depression episodes. That, for me, was the biggest eye-opener; I didn't expect that almost every other patient on the general care floor is having respiratory depression episodes frequently.

What I'm really interested in are the finer points that will come out once we take a deep dive into the data. I'm also interested in what people do with the score when it's out there. Are we going to change our culture or change our practices?

Dr. Lin: We've talked about some of the big goals you have going forward. What are some of the immediate steps you are planning on taking in terms of the next study and the next steps?

Dr. Khanna: Right now, the effort is to focus on the trial itself, and make certain that we present the trial to the world. And that everyone can know our results and hopefully bring it to their clinical practice.

The most immediate next step would be to look at opioid delivery patterns. To better understand our opioid administration, such as how frequently they're administered and what the timing of events was after PACU discharge. Because that's also something very interesting: how long should we keep these patients in the PACU?

I can tell you that across continents it's very different. In Europe, for example, they tend to board patients in the PACU for 24 hours if they feel a patient is at a higher risk. In the Americas, we have a general tendency to either send them to the general care floor or to the ICU. There's nothing quite in between. We don't like holding patients in our PACU. So there is that difference. Is the European model better because they're keeping all eyes on the patient for longer? Or can we do better?

We're also looking at when these events happen after discharge. We had a mix of hospitals in our PRODIGY trial, both academic and private practice community hospitals.

We'll also be going back and looking at where these events were happening. Does the presence of trainees in the hospital, which obviously occurs in academic centers, make a difference? And the economic analysis is also going to be extremely important.

Dr. Lin: I'm really looking forward to seeing what your results are. It's an impressive amount of work that you've already done, and I think all of us need to applaud you and be advocates for being more aware of the potential morbidity for these patients.

CTA: To Listen to the full podcast, click here.

References

1. Perman SM, Stanton E, Soar J, et al; American Heart Association's Get With the Guidelines®—Resuscitation (formerly the National Registry of Cardiopulmonary Resuscitation) Investigators. Location of in-hospital cardiac arrest in the United States—variability in event rate and outcomes. *J Am Heart Assoc.* 2016 Sep 29;5(10):e003638. doi: 10.1161/JAHA.116.003638.
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