Welcome to the SEE Podcast, presented by the American Society of Anesthesiologists. SEE, translating emerging anesthesia knowledge for your daily practice.

Robert L. Hsiung, M.D.: Welcome to this SEE Podcast. I’m your host, Robert Hsiung, one of the SEE editors from Seattle. Today I have Dr. Regina Fragneto, our Editor-in-Chief and Dr. Claas Siegmueller from UCSF Department of Anesthesia joining us. First, I’m going to have Dr. Fragneto highlight this newest issue. Regina.

Regina Fragneto, M.D.: Thanks, Rob. I have to say I’m really excited about this newest issue of SEE. As I’ve mentioned on previous podcasts, after each of our editorial board meetings I ask all our editors to send me what they found to be the most interesting and clinically relevant topics covered in the issue of SEE we had just edited.

And I think with the current issue, we generated the longest list of especially interesting topics we ever have. So, let me mention just some of what you will find in the 34B issue of SEE.

We’re all affected by the opioid epidemic and many of us are seeing an increasing number of patients presenting for surgery and anesthesia who are also receiving chronic buprenorphine therapy. In this issue, we summarize an important review article that provides us all with practical advice about how to
manage these patients’ pain during the perioperative period, which certainly can be a challenge.

And what about those patients that give you a long list of food allergies during your preop evaluation? We also summarize a review article that addressed how food allergies could impact your anesthetic practice.

Many of us often wonder what should we do about ACE inhibitors in the preoperative period: hold them or give them? We discuss an article that investigated the effects of holding versus administering these medications preoperatively.

A couple other important topics in this issue I hadn’t previously been aware of include the possibility of safely doing MRIs in some patients with pacemakers and ICDs. And another study that found that intraabdominal fluid extravasation during hip arthroscopy can lead to increased postoperative pain.

And then what about the patient presenting with a drug-eluting stent? Part of our preoperative planning always includes what to do about their antiplatelet therapy. We discuss a study that specifically addresses the newest generation drug-eluting stents and the effect of the duration of dual antiplatelet therapy on outcomes in the patients that have these stents.

Now, as you know, the ASA has taken a leadership role in addressing the drug shortages that confront all of us every day as we take care of patients. In this issue, we report on a study that looked at hospitals that were most affected by a national norepinephrine shortage a couple of years ago. And without giving away too much about this SEE item, I will tell you that these shortages adversely affected patients with sepsis.
However, we also report on a new innovative way to manage sepsis with one study showing improved outcomes with the administration of Vitamin C. Now, hopefully that won’t be the next drug shortage.

I know many of us get frustrated with mandates in our operating rooms, like telling us what we can wear on our heads that aren’t necessary based on evidence. In this issue we summarize a single-center study that looked at surgical site infections when we’re wearing those ugly-looking bouffant caps compared to those nice-looking traditional surgical caps.

Finally, as an obstetric anesthesiologist, I can’t highlight what’s especially clinically relevant in this issue without mentioning some obstetric studies. In this issue we summarize results of the WOMAN Trial which was a very large, multi-national study that investigated the use of tranexamic acid for the management of postpartum hemorrhage.

While there have been some criticisms of the study, I do believe, based on the results of the study, that we should now consider including this drug as part of our armamentarium when managing this complication that continues to be a leading cause of maternal mortality throughout the world, including in the United States.

And now I’m going to turn things over to Dr. Hsiung and one of our SEE question writers, Dr. Siegmueller, to discuss in detail one of the items in this newest issue of SEE that will certainly be of interest to those of you who care for obstetric patients undergoing caesarean section.

And now to you, Rob.
Robert L. Hsiung, M.D.: Thank you, Regina. I’m moving back to Dr. Siegmueller. Would you tell us how you found out about SEE and then became a writer?

Claas Siegmueller, M.D.: Yes. Thanks, Rob. First of all, let me thank you for the opportunity to take part in this podcast today. I started writing for the SEE program about a couple of years ago after my colleague Adrian Gelb at UCSF made me aware of it and mentioned that there was an opportunity to contribute.

Robert L. Hsiung, M.D.: So, today’s SEE item starts with this: a recent meta-analysis investigated the effects of prophylactic administration of 5-hydroxytryptamine3, so that’s 5-HT3 receptor antagonists, on spinal anesthesia-induced hypotension.

Based on the results of this study, which of the following outcomes was most likely when a 5-HT3 receptor antagonist was administered prophylactically before spinal anesthesia?

A. The need for vasopressors to treat hypotension was reduced;
B. Ondansetron at any dose reduced the risk of hypotension in non-OB patients;
C. 5-HT3 receptor antagonists significantly reduced the risk of hypotension in OB patients; or,
D. The risk of bradycardia was not affected in OB patients.

So, the correct answer is C, that 5-HT3 receptor antagonists significantly reduced the risk of hypotension in OB patients.

Dr. Siegmueller, can you tell us about the study design and how this study came to be? And can you also remind us what a meta-analysis is?
Claas Siegmueller, M.D.: Of course. The idea behind a meta-analysis is really to pool the results of different trials, published on the same subject or addressing the same question, in order to achieve higher statistical power over individual studies.

The increased sample size can then enable us to draw conclusions with more certainty. And in some cases, meta-analysis is also useful to resolve uncertainty when published studies disagree on a question.

The results are typically reported as an odds or risk ratio and meta-analysis usually show findings in a graphic format too, almost always as a forest plot. I think a forest plot is really helpful in interpreting results. It will show you the outcomes of all the individual studies in the meta-analysis, including their confidence intervals and their weighted contributions to the overall aggregate outcome.

A challenge of doing meta-analyses is that studies to be included are almost always somewhat different from each other. There can be differences in subject recruitment, randomization, inclusion and exclusion criteria, statistical analysis, significance level and even definition of outcome measures. So, if you perform a meta-analysis, you have to be really careful what studies to include and how to account for heterogeneity among them.

You can’t really use meta-analysis to create one large good study out of many small poorly designed ones; therefore, you should only include studies in your meta-analysis that meet certain quality standards.

Now, back to the effects of 5-HT₃ antagonists on spinal anesthesia-induced hypotension. Since we’re dealing with a meta-analysis here, some work on the
subject has obviously already been published. We know that up to a third of patients receiving spinal anesthesia develop hypotension, with an even higher proportion of 50% in the OB population.

Responsible for this are vasodilation due to sympathetic blockade and the Bezold-Jarisch reflex which causes vasodilation, bradycardia and hypotension in response to decreased venous return to the right heart. This triggers receptors in the cardiac wall. 5-HT₃ receptors are involved in this reflex arc and 5-HT₃ antagonists have been found to block the Bezold-Jarisch reflex.

At the start of their investigation, the authors performed a literature search; they found 369 publications which mentioned 5-HT₃ antagonists in combination with spinal anesthesia. They then narrowed this down significantly by applying a number of criteria. Excluded were all studies which did not specifically explore the effect of intravenous 5-HT₃ antagonists compared with placebo for prophylaxis of hypotension in patients undergoing spinal anesthesia for any type of surgery including cesarean delivery.

They also only included studies which were randomized, observer-blinded and had a placebo group. And then studies had to use 5-HT₃ antagonists prophylactically and not as a treatment for hypotension that had already occurred.

So, in the end, 17 studies including 1,604 patient were selected for the meta-analysis.

Robert L. Hsiung, M.D.: So, what were the main findings and was there a number-needed-to-treat?
Claas Siegmueller, M.D.: Well, the primary outcome measure was hypotension. In addition, the authors looked at a couple of other secondary outcome variables as well, such as incidence of bradycardia, vasopressor use, as well as some maternal and fetal outcomes.

They also performed several subgroup analyses. For example, they looked at obstetric and non-obstetric patients in isolation and grouped studies which used ondansetron versus ones using other 5-HT3 antagonists.

Other subgroups were created based on the dosing of ondansetron. The investigators looked at a group of trials of a low-dose regimen of ondansetron with doses up to 4 mg versus studies which used doses up to 12 mg.

In all trials combined, prophylactic administration of 5-HT3 antagonists significantly reduced the risk for hypotension with a risk ratio of 0.54. The numbers-needed-to-treat for all studies was 6.3.

And just as a reminder, a risk ratio of 1 means there’s no advantage of treatment over placebo, whereas a risk ratio below 1 indicates that the treatment is favored over the placebo. So, with regards to risk ratio, lower is better.

Robert L. Hsiung, M.D.: Thank you. So, do you believe in the effect size? And you told me about the number-needed-to-treat. What’s considered a good number needed to treat?

Claas Siegmueller, M.D.: Well, there’s always the question whether a statistically significant effect is also clinically relevant. A number-needed-to-treat has to be interpreted in its context. Questions you need to ask, for example, are how
robust and significant the treatment outcome is, whether there are side effects from the treatment or if there are alternative therapeutic options.

So, it’s difficult to say what a good number-needed-to-treat is. For example, triple therapy for H. pylori eradication has a number-needed-to-treat of 1.1. So, that’s pretty low and close to the ideal.

Antihypertensive management of type 2 diabetic patients to prevent one death over ten years has a number-needed-to-treat of 15, which seems high. But both are accepted treatments and considered worthwhile with a good number-needed-to-treat.

This meta-analysis here tells me that I would have to treat 6.3 patients with a 5-HT3 antagonist to prevent one more case of hypotension. And, sure, hypotension is important, but once I consider that there are treatment alternatives which work reliably and fast—such as vasopressors—and the fact that 5-HT3 antagonists have side effects in themselves, this number-needed-to-treat does not seem all that low anymore.

Also, 5-HT3 antagonist use did not lower the number of patients who required a vasopressor for the treatment of hypotension, although the dose of vasopressor use was significantly lower in 5-HT3 antagonist-treated patients. So, patients were still given ephedrine or phenylephrine.

Robert L. Hsiung, M.D.: So, does this apply to both OB and non-OB groups?

Claas Siegmueller, M.D.: No. And this is really important: there was definitely a difference between the obstetric and non-obstetric groups. In the obstetric studies alone, the risk ratio was 0.52 and the number-needed-to-treat 4, which was statistically significant.
Looking at non-obstetric studies in isolation, the risk ratio was 0.56 and this did not reach significance level. But the confidence intervals for the non-OB studies was really wide, which suggested to the authors that the data was inadequate to draw any definitive conclusions.

So, the really interesting data comes from the OB-side group.

Robert L. Hsiung, M.D.: Knowing what you know, did this change your personal practice or perhaps your group’s practice? And since I don’t do OB, is this now mainstream practice and I don’t know about it?

Claas Siegmueller, M.D.: Well, it has not really changed my practice and I’m not aware that prophylactic administration of the 5-HT3 antagonist is practiced widely, certainly not by colleagues in my department.

I think we have to interpret the results of this meta-analysis with a degree of caution: there’s some limitations, as the authors point out. There was a high degree of heterogeneity among the included studies. This was due to differences in the spinal anesthesia technique, fluid management, vasopressor use—and maybe most important—differing definitions of hypotension.

Some studies looked at mean arterial pressures, others at systolic blood pressure and some defined a 20% change from the baseline pressure, others used a 15% change. Some studies also defined hypotension as blood pressure falling below an absolute value.

I do most of my spinals for emergency cesarean sections and to a lesser degree for hip and knee arthroplasty. Hypotension is certainly a common side effect. But while up to 50% of OB patients can develop hypotension, as the authors
state in their paper, the other 50% do not. So, I’m a bit reluctant to give ondansetron, for example, to every patient prophylactically when the effect is only moderate, especially when we consider that we can treat hypotension quite easily and rapidly with, for example, phenylephrine or norepinephrine.

Maybe this is why the authors conclude their paper with the suggestion to investigate 5-HT3 antagonists for the treatment of hypotension which is an intriguing concept for future research.

Robert L. Hsiung, M.D.: Thank you, Claas, for your insight and interpretation on this topic. I found it very interesting.

Thank you, listeners, for joining us today for the SEE Podcast. I want to also add that the medical literature is constantly expanding and if you wish to write for SEE, please contact us at see@asahq.org. Tune in next time.

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Host: Thank you for listening to the SEE Podcast, presented by the American Society of Anesthesiologists. For more information on SEE and other educational products, please visit shop-asa.

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