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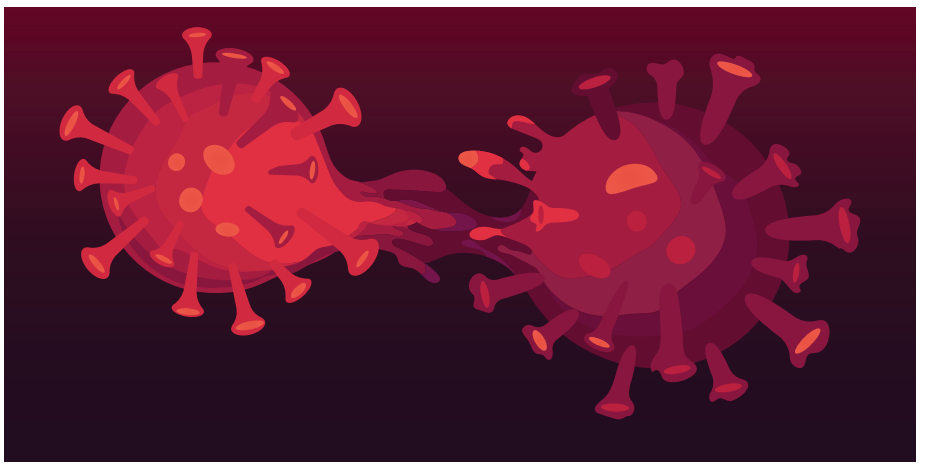
The Emerging Threat of SARS-CoV-2 Variants

Richard Simoneaux **Steven L. Shafer, MD**
Editor-in-Chief



The progress of SARS-CoV-2 has been marked by the emergence of several different genetic variants. In a recent Viewpoint article in JAMA, Lauring and Hodcroft discuss the history and background of SARS-CoV-2 variants (JAMA January 2021).

Many variants substitute one amino acid for another in the "spike protein" – the spike on the outside of the virus that makes it look like a WWII underwater mine. These variants are typically named by the substitution, using single letter names for the amino acids. For example, the SARS-CoV-2 variant D614G substitutes glycine (G) for aspartate (D) in position 614. The D614G variant emerged last spring, simultaneously appearing across several geographic regions. Rapid spread is strong evidence of a survival advantage, such as greater infectiousness, ability to evade antibodies, or reduced lethality. In the case of D614G, the primary benefit was a substantial increase in infectiousness (*Science* 2020;370:1464-8).

In early November 2020, outbreaks of COVID-19 associated with mink farms were observed in the Netherlands and Denmark. Among the mutations noted there were many instances of isolated sequences having a Y453F mutation (tyrosine replaced by phenylalanine at position 453) in the receptor-binding domain (RBD) of the spike protein. This variant helps the virus escape neutralizing antibodies (*bioRxiv* November 2020). It has since spread to patients in

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Exploring the Purdue Pharma Settlement and the Opioid Epidemic

Gordon Glantz

With lawsuits piling up against drug companies believed complicit in the opioid crisis, a major precedent was set in November 2020 when Purdue Pharma was ordered to pay an $8.3 billion settlement.

The order from Judge Robert Drain, who described the ruling as a "critical building block" to resolve mounting lawsuits against the company, capped off a federal investigation of programs that offered incentives to physicians and an electronic health records company for driving opioid prescriptions.

Purdue Pharma – owned by the Sackler family since 1952 (when it was known as Purdue-Frederick) – agreed to plead guilty to three felony criminal counts of wrongdoing.

According to The Washington Post, Purdue – with headquarters in Stamford,

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Reducing Postoperative Delirium with Intraoperative Processed EEG

Jacqueline M. Leung, MD, MPH **Daniel J. Cole, MD, FASA**

Postoperative delirium is a geriatric syndrome associated with prolonged hospital length of stay and worsened functional and cognitive status after hospital discharge. Despite its prevalence, its pathophysiology is incompletely understood. Delirium is a complex interplay between patient vulnerability and precipitating factors. Although surgery is not a prerequisite for the occurrence of delirium, the prevalence of postoperative delirium after major surgery in the older patients is high, ranging from 10%-60% (*Psychiatr Clin North Am* 1996;19:429-48). Understanding the pathophysiology of postoperative delirium may also lend insight into revealing the mechanism underlying neurodegeneration such as Alzheimer's Disease, as postoperative delirium typically occurs in patients with prior cognitive impairment.

Given the powerful effects of general anesthetics on the brain and the numerous medications surgical patients are exposed to during and after surgery, some have hypothesized that anesthetics may be toxic to the brain, manifested as adverse postoperative cognitive changes, including delirium. Specifically, are we often "overdosing" our patients and unnecessarily exposing them to the potential adverse effects of general anesthetics?

Recent advances in anesthesia research have focused on neurotoxicity and neu-

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PERIODICALS

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Your Patient's Brain

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roinflammation as potential mechanisms in postoperative cognitive changes, but a comparable animal model of postoperative delirium is not feasible, therefore the exact pathophysiology of postoperative delirium is still unknown. However, if the hypothesis that "excessive anesthetics" is harmful to the patient is proven true, then a device that would monitor such "overdose" would be immensely helpful during surgery.

Recently, it has been proposed that use of a processed electroencephalogram (EEG) monitor during surgery may be associated with a lower rate of postoperative delirium. Several studies speculated that patients who were monitored with processed EEG may have a lighter anesthetic depth as estimated by processed EEG, which may lead to lower rates of postoperative delirium. Subsequent studies reported that patients with more EEG burst suppression as monitored by processed EEG during surgery were more likely to experience delirium (*BMC Anesthesiol* 2015;15:61; *Anesth Analg* 2016;122:234-42; *Anesthesiology* 2020;133:280-92). A burst suppression pattern on EEG is typically associated with a severe reduction in the brain's neuronal activity and metabolic rate.

Given these reports, there was a lot of excitement as to whether processed EEG should be routinely used during surgery, particularly in older surgical patients. The hypothesis is that anesthetics particularly in excessive doses may be toxic to the brain, manifested as postoperative delirium. Therefore, a monitor that can detect "anesthetic overdose" as evidenced by burst suppression may be reduced through a down titration of the anesthetic, typically a volatile agent. In fact, some suggest that processed EEG should be incorporated in a delirium reduction clinical pathway. So, is this recommendation, in fact, evidence-based?

"...are we often 'overdosing' our patients and unnecessarily exposing them to the potential adverse effects of general anesthetics?"

Although several cohort studies showed that intraoperative burst suppression was associated with postoperative delirium, it is unclear whether the use of a processed EEG results in a reduction of postoperative delirium directly through a reduction in burst suppression. Further, it is unclear whether the occurrence of burst suppression can be reduced by modulating anesthetic doses.

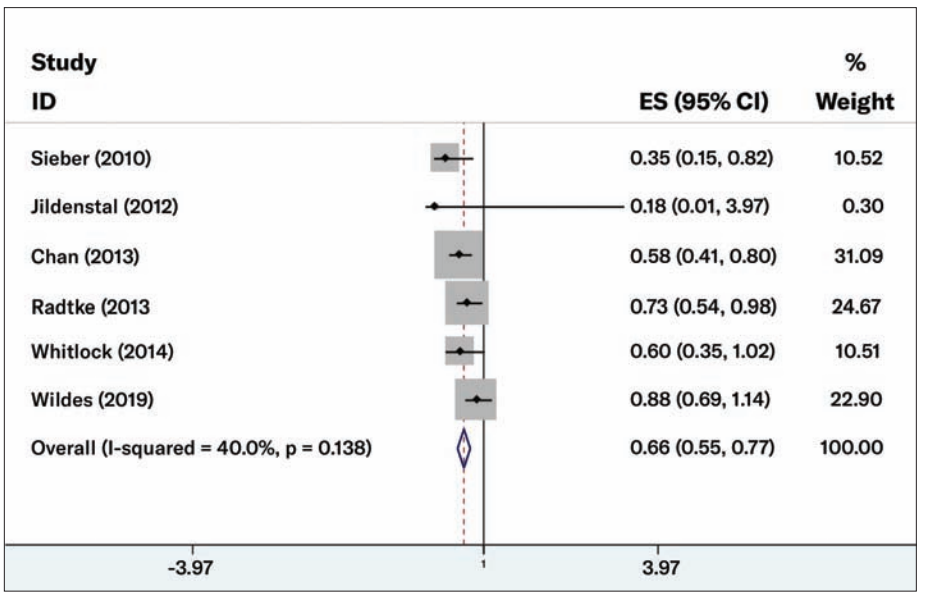

Figure: Forest plot of odds ratios (OR, solid dots) for postoperative delirium in the trials of processed electroencephalogram-guided (high target) vs. routine (low target) anesthesia. The gray squares are shown in size proportional to weight assigned in meta-analysis. The aggregated odds ratio is shown as the vertical dotted line. Associated 95% confidence intervals are indicated by the solid bars and lateral tips of the diamond.

Leung et al. (*Anesthesiology* 2018;129:417-27) conducted a meta-analysis that included five studies in a quantitative postoperative delirium analysis, with data pooled from 2,654 patients (*Mayo Clin Proc* 2010;85:18-26; *J Neurosurg Anesthesiol* 2013;25:33-42; *J Anesth Clin Res* 2012;3:6; *Br J Anaesth* 2013;110 Suppl 1:i98-105; *Anesth Analg* 2014;118:809-17). The use of processed EEG-guided anesthesia was associated with a 38% reduction in odds for developing postoperative delirium [Odds ratio (OR = 0.62; p<0.001; 95% confidence interval (CI) 0.51 to 0.76]. Including the data published more recently by the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes trial (*JAMA* 2019;321:473-83) resulted in the accompanying forest plot. The aggregated OR computed between processed EEG monitoring and postoperative delirium for all six studies using the fixed-effects model was 0.66 (p<0.001; 95% CI, 0.55 to 0.77; I^2=40%) (Figure). However, if excluding the one study by Sieber et al. that had a slightly different study goal in which patients undergoing hip fracture surgery and spinal anesthesia were monitored with processed EEG with the bispectral index (BIS) and randomized to receive either deep (BIS, approximately 50) or light (BIS, ≥80) sedation, the relationship between the use of processed EEG and reduced incidence of postoperative delirium was no longer significant (*Anesth Analg* 2020;131:712-9).

Assuming that the use of a processed EEG does result in a reduction of postoperative delirium, a major unanswered question is whether the effect is directly via a reduction in EEG activity or some other associated mechanism linked to a reduction in anesthetic dose. Further, it is unclear to what extent the clinician can simply modulate the anesthetic dose to minimize time spent in burst suppression, thereby reducing postoperative delirium. Provoking a postoperative state of delirium is a complex, multifactorial process that is unlikely to be dependent on a linear relationship to a single variable. Prior studies also did not consider whether preoperative cognitive status influences the effects of anesthetic on the brain. Accordingly, we conducted an exploratory randomized controlled trial to determine whether the use of a processed EEG monitor to guide anesthesiologists to keep a dimensionless processed EEG value above a specified value reduced intraoperative burst suppression when compared to standard anesthetic care (*Anesth Analg* 2020;131:1228-36). What we found was that targeting a dimensionless processed EEG value reduced the percent of surgical time spent in burst suppression, particularly in those with preoperative cognitive impairment. However, we did not find that the anesthetic doses differed between study group. Our results suggested a potential mechanistic insight into the relationship between EEG suppression and postoperative delirium. Specifically, preoperative cognitive impairment moderated the association between the intervention and burst suppression. This result explains in part why the prior studies in the meta-analysis did not result in a more beneficial effect, favoring the use of processed EEG in reducing postoperative delirium as these investigations studied unselected group of patients. It is likely that the use of processed EEG to guide anesthetic depth would yield a more beneficial effect in patients who are cognitively vulnerable. Further, the relationship between anesthetic doses and postoperative delirium is not linear.

Therefore, whether the use of processed EEG will reduce the occurrence of postoperative delirium through a reduction in burst suppression remains unknown as it is likely that this hypothesis will be proven true only in patients who are cognitively vulnerable, a much-needed future investigation. ■

Jacqueline M. Leung, MD, MPH
Professor and Vice Chair of Academic Affairs, Department of Anesthesia and Perioperative Care, University of California, San Francisco.

Daniel J. Cole, MD, FASA
Vice President, Anesthesia Patient Safety Foundation, and Professor of Clinical Anesthesiology, Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, University of California, Los Angeles.

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