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EDITORIAL

Friedberg's triad, a pathway to opioid free anesthesia (ofa) and better outcomes

Tríada de Friedberg, un camino hacia la anestesia libre de opioides y mejores resultados

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Friedberg's Triad is 1) Measure the brain, 2) Preempt the pain, 3) Emetic drugs abstain (1) (Figure 1).

Why measure the brain? "If you cannot measure it, you cannot improve it": Lord Kelvin

Why preempt the pain? "An ounce of prevention is worth a pound of cure": Ben Franklin.

Why abstain from emetic drugs? "As long as emetogenic drugs are part of the anesthetic regimen, the use of anti-emetics is of *limited utility*": Christian Apfel.

No anesthesiologist would administer a blood pressure (BP) medication and fail to measure the BP response. Yet, in the 21st century, many continue to administer brain medications (i.e. anesthetics) and fail to *directly* measure the brain response. The 1996 Food and Drug Administration (FDA) approval of the first modern processed EEG monitor, the bispectral (BIS) index™, paved the way for practical *direct* measurement of cortical response to anesthetic agents like propofol and halogenated inhalational agents. There are other processed EEG monitors (i.e. SedLine™ and Entropy ™), but no publications assert superiority to BIS. My 20-year processed EEG monitoring experience was with the BIS.

Much literature has been devoted to BIS monitoring and awareness with recall. No deaths have been reported from awareness with recall. However, one American death occurs *every day*, independent of comorbidities, from anesthesia over medication, the natural consequence of failure to directly measure cortical response to anesthesia (2).

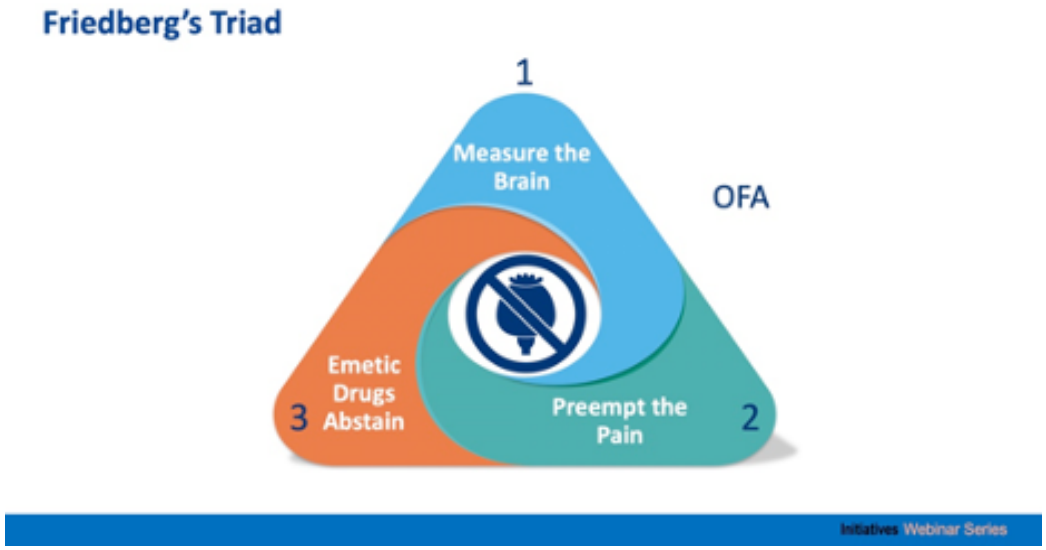

Figure 1. Friedberg's Triad.

The limitation of processed EEG monitoring is the time required to process the response. BIS values are delayed 15-30 seconds from real time and may appear like a short interval. However, the outcome of such a delay leaves the anesthesiologist 'catching up' to patient changes in hypnosis levels. This time delay deficiency can be remedied by selecting real time EMG as the secondary BIS trend in the free-standing model (Figure 2). EMG spikes signal *incipient arousal*, an indication of what is *about to happen* to the patients' hypnosis level. Arousal precedes nociception. Think hand touching a hot stove. Withdrawal precedes 'ouch,' not the other way around. Giving more propofol with alacrity to drive an EMG spike back to baseline prevents arousal. No arousal, no nociception!

Incremental, not bolus, propofol induction/maintenance with processed EEG monitoring allowed most patients to achieve moderate to deep sedation levels of 60 < BIS < 75 with baseline EMG at 25-50 mcg·kg^{-1}·min^{-1}. A few extremely sensitive, otherwise healthy patients required as little as 2 mcg·kg^{-1}·min^{-1} while a few extremely resistant patients required as much as 200 mcg·kg^{-1}·min^{-1} to achieve *identical* levels of sedation. *Directly* measuring effect allowed my patients to expose a 100-fold variation in propofol requirements to achieve numerically measured sedation levels. Providing a stable CNS propofol level is important to ketamine hallucination prevention as well as providing a statistically significant 30 % reduction in propofol (3).

Earlier attempts at pain preemption involved administering local analgesia after the induction of general anesthesia (GA) proved unsuccessful. GA does not block, much less *saturate*, critical subcortical NMDA receptors. In other words, despite GA, the brain is capable of receiving nociceptive stimulation. The so-called dissociative ketamine effect is immobility to noxious stimulation; i.e. multiple subcutaneous local anesthetic injections in cosmetic surgery or skin incision in medically indicated surgery.

Ketamine is our most unique pharmacologic agent. *After* achieving a stable CNS propofol level, the same 50 mg ketamine dose administered 2-5 minutes pre-stimulation, in more than 6,000 patients over 26 years, produced immobility in patients weighing between 30-146 kg and in ages between 7-94. I do not believe the effective NMDA saturating ketamine dose varies with body weight or age.

Violation of the barrier between the outside world of danger and the inner, protected world of self (i.e. the integument) is constant independent of cosmetic or medically indicated surgery (Figure 3). Once sedated, patients cannot differentiate between the therapeutic intent of a surgeon's scalpel and the malevolent intent of a mugger's knife. *Prima facie* evidence of NMDA receptor saturation is the *absence* of EMG spikes with noxious stimulation (4). The limitation of using EMG spikes is limited with neuromuscular blocking (NMB) agents. Increasing numbers of patients are receiving ultrasound guided regional anesthesia (UGRA) for major surgeries wherein NMB are not required. BIS/EMG trending will work as well for these surgeries as it has for mine.

In 1999, Macario et al published two scientifically validated surveys of anesthesiologists' and patients' attitudes regarding what anesthesia outcome to avoid was most desired (5,6). Unsurprisingly, anesthesiologists chose pain. Paradoxically,

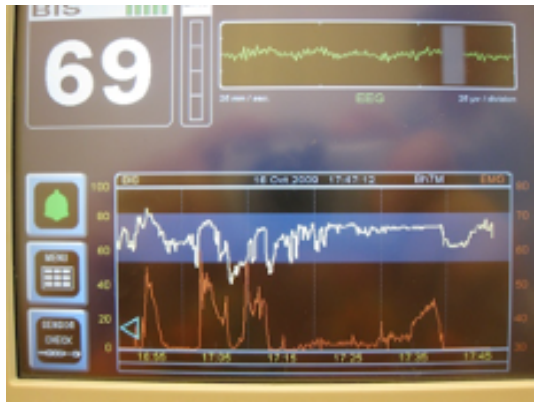

Figure 2. BIS/EMG trending. EMG is the lower, red trend.

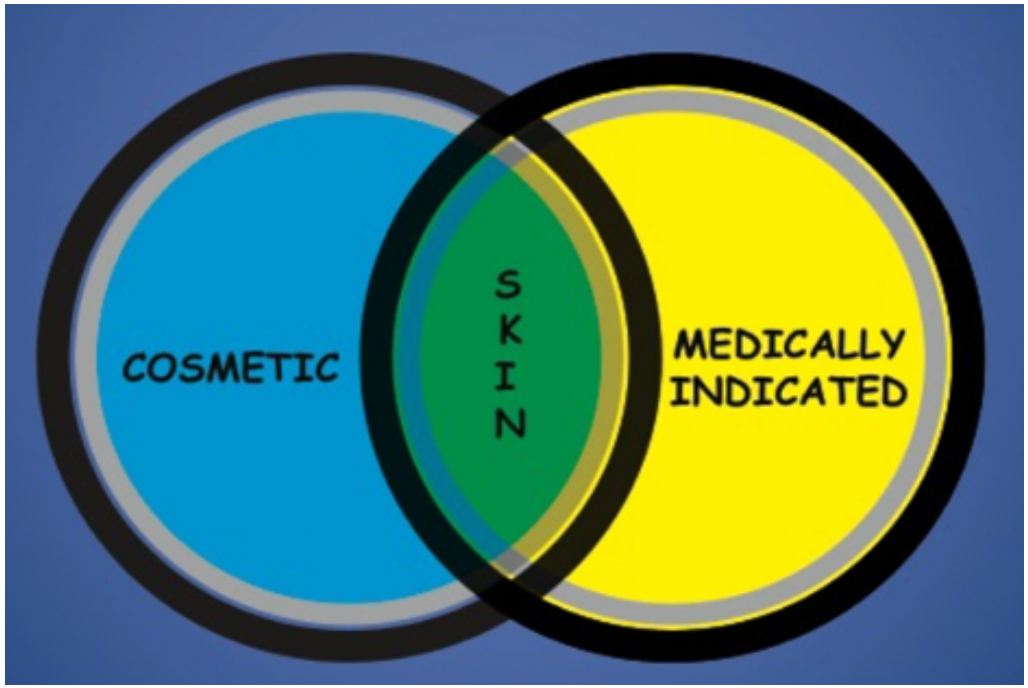

Figure 3. Common ground between Cosmetic & Medically indicated surgery.

patients chose postoperative nausea and vomiting (PONV). When patients sign a surgical consent, some degree of postoperative discomfort is an expectation. PONV, in particular, repeated emesis characteristic of opioid side effects, is most definitely *not* a patient expectation.

Why then do anesthesiologists pay so little attention to patients' number one outcome to avoid? Pain is a phenomenon we believe we are preventing in the OR whereas emesis is something that happens out of sight in recovery. Compounding the conundrum is our century-long belief opioids are effective in preventing pain during as well as after surgery. Lichtner et al published nociceptive activation persists even during deep general anesthesia (7). Frauenknecht et al meta-analysis of 23 studies in 1304 patients showed opioid-inclusive anesthesia not only failed to prevent postoperative pain but also increased PONV (8).

These two publications were compatible with my 20-year paradigm of processed EEG monitored propofol *then* pre-stimulation 50 mg ketamine *then* local anesthesia (9). What outcomes support my paradigm? Twenty-years in more than 4,000 opioid free outpatients produced not a single hospital admission for either pain or PONV. There were no opioid addicts and no opioid overdose deaths.

There may be many reasons for anesthesiologists not electing to pursue OFA, not the least of which is fear of ketamine hallucinations, postop pain or colleagues' criticism. My prayers are for this editorial to overcome the first two reasons. In places around the world, OFA patients have rejoiced, especially those who've previously experienced PONV or pain. I can understand the reluctance to change but not the reluctance to do better for patients. *Carpe diem, patiens aegroti sumus!*

Most of my papers can be found on open access Researchgate. My YouTube channel contains many of my opioid free lectures including my most recent webinar, shorturl.at/rEIJ8.

Disclaimer

Neither I nor my self-funded nonprofit Goldilocks Anesthesia Foundation have any financial interests to disclose.

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