

## Can Friedberg’s Triad Solve Persistent Anesthesia Problems? Over-Medication, Pain Management, Postoperative Nausea and Vomiting

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**Summary:** Friedberg’s Triad is (1) measure the brain; (2) preempt the pain; (3) emetic drugs abstain. Persistent anesthesia problems include over- and under- medication, postoperative pain management, and postoperative nausea and vom- iting. Inspired by Vinnik’s diazepam-ketamine paradigm, Friedberg’s propofol ketamine paradigm was first published in 1993. The 1997 addition of the bispec- tral (BIS) index brain monitor made the propofol ketamine paradigm numeri- cally reproducible. The 1998 addition of the *frontalis* electromyogram (EMG) as a secondary trend to the BIS transformed the time-delayed BIS monitor into a real-time, extremely useful device. Before BIS monitoring, anesthesiologists only had heart rate (HR) and blood pressure (BP) changes to guide depth of anes- thesia. Not surprisingly, the American Society of Anesthesiologists’ Awareness study showed no HR or BP changes in half of the patients experiencing awareness with recall. HR and BP changes may only reflect brain stem signs while conscious- ness and pain are processed at higher, cortical brain levels. BIS/electromyogram measurement can accurately reflect propofol effect on the cerebral cortex in real time. Although propofol requirements can vary as much as a hundred-fold, ti- trating propofol to  $60 < \text{BIS} < 75$  with baseline electromyogram assures every pa- tient will be anesthetized to the same degree and allows more scientific analysis of outcomes. Numerous publications are cited to support the author’s 25-year clinical experience. Over that period, no office-based, cosmetic surgery patients were admitted to the hospital for unmanageable pain or postoperative nausea and vomiting. Friedberg’s Triad appears to solve persistent anesthesia problems. (*Plast Reconstr Surg Glob Open* 2017;5:e1527; doi: 10.1097/GOX.0000000000001527; Published online 20 October 2017.)

“**M**easure the brain; preempt the pain; emetic drugs abstain” is Friedberg’s Triad. Persistent anesthesia problems may be summarized as (1) over- and under-medication; (2) pain management; and (3) postoperative nausea and vomiting (PONV).

### OVER- AND UNDER-MEDICATION

When you can **measure** what you are speaking about, and express it in **numbers**, you know something about it; but when you cannot measure it, when you cannot express

it in numbers, your knowledge is of a meager and unsat- isfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of **science**.

William Thompson, knighted Lord Kelvin.

Popular lectures and addresses 1891–1894

Before the 1996 Food and Drug Administration ap- proval of the direct cortical response monitor, that is, bispectral (BIS) index monitor, the determination of an- esthetic dose relied on body weight, medical and physical assessment [i.e., American Society of Anesthesiologists’ (ASA) status], and heart rate (HR) and blood pressure (BP) changes, especially these vital signs changes occur- ring with initial incision.

The cerebral cortex is the target of anesthetics. The adult brain weighs approximately 1.4–1.8 kg and does not vary substantially with body weight; i.e., the brain weight

*From the Goldilocks Anesthesia Foundation, Newport Beach, Calif. Received for publication June 28, 2017; accepted August 23, 2017.*

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DOI: 10.1097/GOX.0000000000001527

**Disclosure:** The authors have no financial interest to de- clare in relation to the content of this article. The Article Processing Charge was paid for by the Goldilocks Anesthesia Foundation, a non-profit, 501c3 corporation.

of a 114 kg male patient is not twice that of a 45 kg female patient. Average body weight doses based on the “70 kg” patient will likely over- or under-medicate many patients. ASA status is also an unlikely guide to individual cortical responses to body weight-based drug doses.

Vital signs (i.e., HR and BP) are brain stem functions. The ASA awareness with recall study showed that half of the patients who experienced awareness had no change in either HR or BP during the case with which to alert their anesthesiologist.<sup>1</sup> This finding was not especially surprising because consciousness, memory, and pain perception are cortical, not brain stem, functions (Fig. 1).

Under-medication is estimated to occur in only 0.1% of patients and may result in posttraumatic stress disorder in them. Unpleasant an experience as awareness with recall can be, there are no documented cases of death from anesthesia awareness. Many of the remaining 99.9% of patients may be subjected to routine over-medication.

Not only does 1 American patient every day perish (mortality) from anesthesia over-medication but also 16M of the 40M patients (40%) every year emerge with “brain fog” (morbidity).<sup>2</sup> Brain fog may be defined as delayed anesthetic emergence, but also can include postoperative cognitive dysfunction or even delirium.<sup>3-5</sup>

Postoperative brain fog creates additional morbidity while adding substantial additional costs to the health care system caring for patients who cannot be quickly processed and discharged from the system. Additionally, patients must endure the long-term consequences of their anesthesiologists’ short-term care.

The BIS monitor has been validated in over 3,500 published studies and can be found in 75% of the U.S. hospi-

tals. The question remains “why is *directly* measuring the organ being medicated with a BIS monitor infrequently used?”

On a unit-less scale of 0–100, the lower the number, the more sedated the patient. This number is a derived, not directly measured, value. The 15-30-second delay from real time places the anesthesiologist in the unfavorable position of catching up to patient needs instead of being able to anticipate them and react preemptively. Part of the answer to “why” may lie in the manner in this monitor was originally configured or the factory default setting displaying only the BIS trend horizontally. The electromyogram (EMG) is displayed, but only as a vertical column and described as a “contaminant.” (True, but only if one does not recognize the significance of an EMG spike and respond appropriately with additional hypnosis sufficient to return the EMG to baseline.) Anesthesiologists tend to process information better with the horizontal sweep. The absence of a real-time EMG signal with the BIS trend creates a situation akin to trying to drive one’s car with only the rearview mirror’s information, not safe or useful.

For the last quarter century, this clinician has practiced exclusively in office-based anesthesia for elective cosmetic surgery using propofol hypnosis followed by ketamine dissociation.<sup>6</sup> BIS monitoring experience began for this author on December 26, 1997, and, after a year of frustration, the company salesman suggested trending EMG as a secondary trend. Beginning December 26, 1998, the propofol ketamine (PK) paradigm was enabled to be numerically reproducible across the interpatient variability.

The propofol and ketamine are not mixed in the same syringe (aka “ketofol”) but rather are given separately to

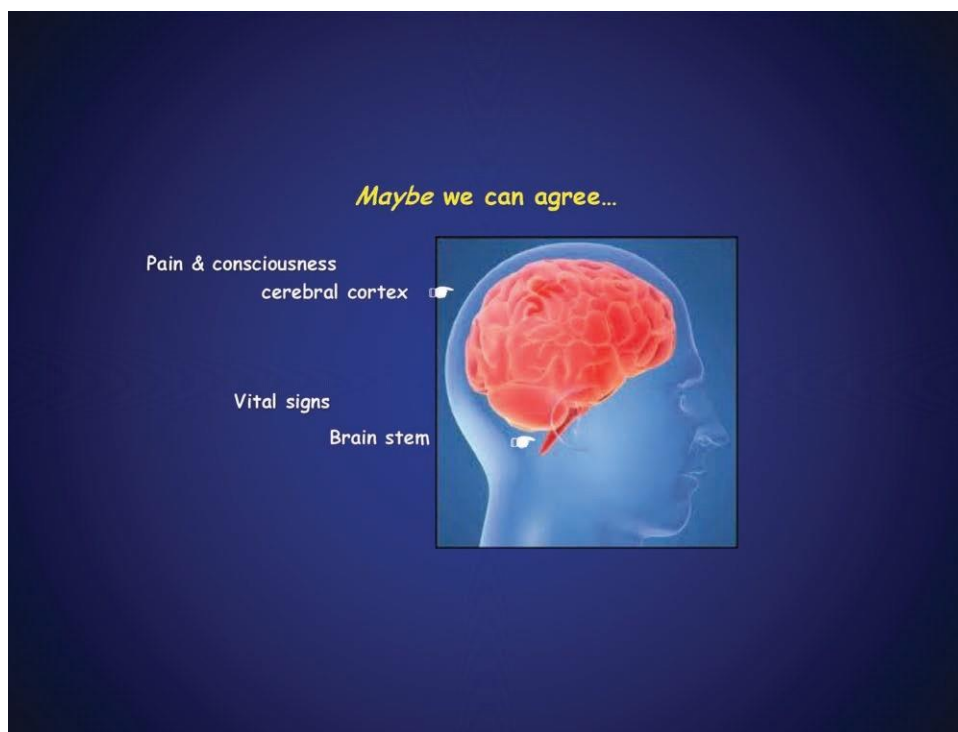


Fig. 1. cortex vs. brain stem functions.

specific endpoints, that is, propofol to loss of lid reflex/loss of verbal response sans BIS/EMG, or  $60 < BIS < 75$  with baseline EMG. All patients had propofol hypnosis incrementally (not by bolus) titrated to maintain spontaneous ventilation.

Only after BIS was incrementally titrated to  $< 75$  with baseline EMG (NB baseline is either “0” on the left-hand BIS scale 0–100 or “30” on the right-hand EMG scale 30–100), 50mg intravenous ketamine is given, sufficiently blocking the midbrain EMG receptors for patients to remain motionless for local anesthetic injection preceding surgical incision. Even without preincision local analgesia, ketamine still blocks EMG spikes. However, the benefit of preincisional local analgesia followed by preclosure, subcutaneous bupivacaine (not to exceed a total 125 mg or 50 cc 0.25%) is to prolong the time for the cortex to “discover” the violation of the skin barrier, minimizing postoperative pain while healing takes place in that time interval. Deceiving the cortex might be considered like landing the paratroopers without setting off the enemy alarms.

This numerically reproducible PK paradigm avoids opioids, leaving propofol as the sole respiratory depressant to facilitate spontaneous ventilation (Table 1). In lieu of opioids, local analgesia with dilute lidocaine and epinephrine solutions were used for analgesia.<sup>8</sup> The PK paradigm has also been adopted by the U.S. military for advance units treating peripheral, nonpenetrating soldiers’ injuries without need of an anesthesia machine or large quantities of oxygen<sup>9</sup> (Fig. 2).

The original factory default setting of the BIS only included the BIS trend on the screen. Since the BIS value displayed is delayed by 15–30 seconds resulting in the need to “catch up” to patient need for increased hypnosis and/or analgesia. Without a BIS/EMG monitor, differentiating cortically generated movement (suggesting awareness or recall) from spinal cord generated movement (devoid of either awareness or recall issues) was very frustrating, and because of its perceived lack of utility, most anesthesiologists abandoned the device.

The frontalis muscle EMG is a directly measured, not algorithm derived, physiologic parameter that is a real-time signal akin that of the EKG of cardiac muscle. Trending EMG transforms the BIS device into a real-time, very useful monitor for 2 specific reasons (Fig. 3).

**Table 1. Clinical Pathway for BIS/EMG PK**

1. Glycopyrrolate 0.2 mg IV with 1.5 ccs 2% lidocaine plain  
\*\*\*Trend EMG 2<sup>o</sup> BIS; set BIS range 60–75
2. Propofol pump set to 50–100 microgram/kg bolus  
Titrate to BIS  $< 75$  with multiple, 50–100 microgram/kg miniboluses
3. Propofol initial basal infusion rate 25–50 microgram/kg/min  
\*\*\*Respond to EMG spikes  $\approx$  HR or BP  $\Delta$ s, i.e., bolus propofol c  
↑ EMG spike until spike returns to baseline
4. Cease bolus, observe BIS trend ... avoid overshoot (BIS  $< 55$ )
5. Ketamine 50 mg IVP ... wait 2–3 min, then
6. Optional Lidocaine 1 mg/lb (preempt laryngospasm)
7. Lidocaine c epinephrine local analgesia injection or skin incision  
Skip c nonincisional procedures, that is, lithotripsy, closed reduction
8. Propofol boluses guided by EMG titrate to BIS 60–75, EMG  $>$  baseline  
Using EMG to fine tune BIS value range
9. Lidocaine 1 mg per POUND IVP c cough or sneeze  
Critically important: recognize laryngospasm prodrome and rx stat!

First, by responding to EMG spikes (as if they were HR or BP changes), the anesthesiologist stays ahead of patient need and avoids the need to catch up. (One tends to observe far fewer HR or BP changes when conducting anesthesia this way, perhaps giving greater credence to the notion that vital signs are indeed a brain stem effect but consciousness, memory, and pain processing occur at higher, cortical levels).

Second, EMG spikes persist, even with Botox or neuromuscular block (NMB). EMG spikes signal incipient arousal and the need to proactively increase sedation to return the EMG to baseline with additional propofol while avoiding the loss of spontaneous ventilation.<sup>10</sup> To display the EMG, use the existing software to select and save it as the secondary trend.

Most patients achieve propofol sedation enough to prevent awareness and recall at  $60 < BIS < 75$  (with baseline EMG) level of with 25–50 micrograms/kg/min. Over 18 years’ experience titrating propofol with BIS/EMG, variation of as little as 2.5 micrograms/kg/min and as much as 200 micrograms/kg/min has been observed to achieve the same  $60 < BIS < 75$  (with baseline EMG) with amnesia and sedation. “Apples” to “apples” comparisons between patients, despite the nearly hundred-fold observed variation in propofol requirements to achieve, become more meaningful when using numerically based definitions of similar levels of consciousness achieved.<sup>10</sup> When propofol is measured with BIS/EMG, amnesia was observed, avoiding midazolam premedication.

Postoperative brain fog likely is a multi-factorial problem. Until universal BIS/EMG monitoring becomes a standard of care, it may not be possible to clarify the degree routine over-medication plays.<sup>11</sup> It may be beneficial for elderly patients to receive a statistically significant 30% less propofol than what is needed to achieve  $60 < BIS < 75$  with baseline EMG.<sup>12</sup>

## PAIN MANAGEMENT

Most people know it does no good to close the barn door after the horses have escaped. However, too many anesthesiologists still need to be convinced that it’s futile to try to prevent postoperative pain by allowing surgeons to cut without first blocking the midbrain N-methyl, D-aspartate (NMDA) receptors<sup>13,14</sup> (Fig. 4).

Local anesthetic skin injection or incision is an extremely potent signal to the brain that the “world of danger” has invaded the “protected world of self.” The sedated brain cannot differentiate between the mugger’s knife and the surgeon’s scalpel (or trocar). Although there are certainly other internal pain receptors, no signal is more determinant of postoperative pain than of skin incision (or skin injection). An unprotected incision sets off the major cortical alarms that initiate the wind-up phenomenon.

Surgery is a painful experience. Most anesthesiologists believe a cardinal function is the prevention of pain during surgery. From 1975 through 1993, this author had never once considered why there was a need for postoperative opioid rescue for many, if not most, patients.

## Congressional Award



Feb 16, 2007

Congressional award is given to Dr. Barry Friedberg for his contribution to military anesthesia in Iraq and Afghanistan, sparing the need for anesthesia machines in the field hospitals as well as the logistical difficulties involved in supplying large quantities of oxygen to run the machines,

### **John Campbell**

US House of Representatives  
48th District

Fig. 2. U.S. congressional recognition award.

In 1992, a clinical trial began using 50mg IV ketamine, 2–3 minutes before stimulation AFTER propofol hypnosis to dissociate patients for preincisional local anesthesia injection.<sup>15</sup>

When propofol is incrementally titrated, ketamine hallucinations are eliminated.<sup>16</sup> For elective surgery, customary propofol increments are 50–100 micrograms/kg repeated either to loss of lid reflex/loss of verbal response or to  $60 < \text{BIS} < 75$  with baseline EMG. This BIS level is usually attained within 2–3 minutes. Starting with such an apparently homeopathic propofol dose quickly allows the anesthesiologist to quickly identify an extremely sensitive

patient, avoid prolonged emergence, and, likely, less brain fog.

The benefit of incremental induction is creating a stable CNS level of propofol to protect from ketamine side effects, preservation of spontaneous ventilation, maintenance of  $\text{SpO}_2$ , and not creating the difficult airway.<sup>17</sup> Incremental propofol induction most commonly preserves the tone in the masseter, genioglossus, and orbicularis oris muscles, commonly maintaining a patent airway. Absent a propofol bolus induction, baseline BP is also maintained. After observing the first 50 cases emerge without opioid rescue, it was reasonable to conclude the principle reason

## Work smarter not harder

Real-time BIS looks like this

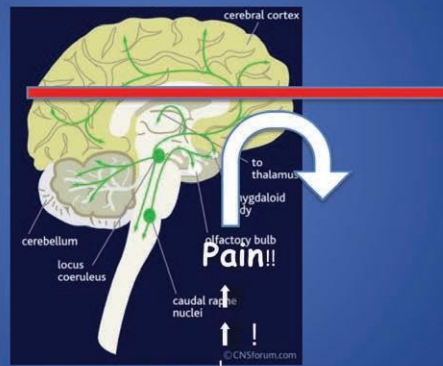


\*\*\* EMG 2° Red Trace \*\*\*  
Rx EMG spikes as if HR or BP changes

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Fig. 3. BiS is not used more often for lack of real time information.

## Preemptive analgesia principle



Brain X respond to information X received

Fig. 4. cortex cannot respond to information not received ... preemptive analgesia principle.

patients have pain after surgery is that they have had pain during surgery. The lack of opioid rescue continued over the next 1,214 patients<sup>18</sup> and through to the present day of > 6,000 cosmetic surgery patients including very painful classical abdominoplasty and subpectoral breast augmentation. Skeptics may elect to discount a consistent, 25-year record of consistent clinical success without a level I randomized controlled trial to support this large, yet numerically reproduc-

ible anecdote. All this author respectfully asks is to try it.<sup>19</sup> Dissociation, or immobility to noxious stimulation, appears to result from mid-brain NMDA blockade. Immobility (i.e., dissociation) to the stimulus of local anesthetic injection or incision has been consistently observed in 45kg female patients and 114kg male patients with the same 50mg ketamine dose.

Why does the effective dissociative dose of ketamine not appear to be related to body weight? The adult brain

weighs approximately 1.4–1.8 kg and does not vary with body weight. The midbrain is a very small part of the adult brain, and the NMDA receptors are a very small part of the midbrain. Prestimulation NMDA block denies the cortex the knowledge of the intrusion of the outside world of danger, avoiding the windup phenomenon.

What ortho-, neuro-, gynecologic surgery and cosmetic surgery have in common is the violation of the skin barrier. Violating the skin without an EMG spike response is empiric evidence of NMDA receptor saturation and preemptive analgesia. Once the brain protection is measured with BIS/EMG, there is very little downside and, considerable upside, to the nifty fifty.

Cognitive dissonance generated by the lack of or dramatically reduced opioid rescue with prestimulation ketamine dose is so great that many, if not most, anesthesiologists will need to observe 10–20 cases to believe them. However, the post anesthesia care unit nurses will notice more quickly and ask what is being done differently. Surgeons and patients' family members will be as impressed as the recovery personnel. Once the patient is protected as described above, the nonopioid, 50 mg ketamine "miracle" is reproducible with propofol sedation, regional analgesia/propofol sedation, and general inhalational anesthesia.

## POSTOPERATIVE NAUSEA AND VOMITING (PONV)

Much has been written about PONV. In 1996, Apfel et al.<sup>20</sup> identified the 4 most predictive PONV factors, namely, nonsmoking, females, history of PONV, planned use of postoperative opioids. Apfel<sup>21,22</sup> subsequently referenced Friedberg's 1999 study<sup>18</sup> in his PONV chapters.

PONV chapter by Apfel<sup>21</sup> is 86 of 89 chapters in *Millers' Anesthesia*. PONV is not lethal to patients, but they, especially abdominoplasty patients, may wish for lethality. Greater importance to PONV needs to be heeded by our profession as patient satisfaction now plays a role in government and other third party reimbursement.

The data for this 5-year review documenting a 0.6% PONV rate (i.e., 7 of 1,264 patients) were collected by 1997 but not published until 1999.<sup>19</sup> These patients turned out to be an Apfel-defined high PONV risk patient population that received no antiemetics! No intraoperative opioids or inhalational ("stinky gases") agent were used.<sup>23</sup> Postoperative opioids were routinely prescribed but rarely used.

Analgesia was provided with adequate local analgesia.<sup>8</sup> Assuring good local analgesia is facilitated with BIS/EMG monitoring to assure the surgeon the patient only needs more local, and not more hypnosis, to eliminate movement without concomitant EMG spike. Spontaneous ventilation was preserved using only a single respiratory depressant, propofol, and scrupulously avoiding intraoperative opioids. No patients received neuromuscular blocking medications although the use of NMB does not eliminate useful EMG spikes. Spontaneous ventilation allows the possibility of patient movement.

Patient movement under sedation in cosmetic or other surgery is usually the cause for great stress on all involved in the operating room, especially the surgeon

who may have preoperatively injected the operative field with syringes of lidocaine and epinephrine. Observing vasoconstriction, the surgeon (but incorrectly) surmises adequate analgesia is present and clamors for more sedation (Table 2). The anesthesiologist usually responds with a request for additional analgesia. Tempers rise leading to the inappropriate addition of opioids, benzodiazepines, and so on, or worse the abandonment of sedation in favor of general anesthesia (GA) with NMBs. These added maneuvers may placate the surgeon but fail to treat the cause of the movement, inadequate analgesia.

The presence or absence of an EMG spike on the BIS monitor enables a dispassionate discussion of what the patient most accurately (and minimally) needs to return the patient to the desired motionless condition. In the pre-BIS era, all patient movement was treated lest it might signify be awareness and recall. As with the headless chicken, a brain is not necessary to generate movement.

No spinal reflex can stimulate the EMG of the forehead frontalis muscle. Patient movement without an EMG spike can only be generated by subcortical areas. The Surgeon's Golden Rules needs the anesthesiologist's time preoperatively with the surgeon to assure success without increasing the known risks of GA. This author believes it is very difficult to accept GA risks for patients having surgery without medical indication, that is, elective cosmetic surgery. A more enlightened approach is possible using the absence of the EMG spike with patient movement to refute the notion that the patient is "too light."

## CONCLUSIONS

Less is more. – Mies van Der Rohe

Without direct cortical measurement of anesthetic effect, neither reproducible science nor minimally trespassing on patients' physiology will occur. Predictably, problems like over and under-medication, postoperative pain management, and PONV will continue to plague anesthesiologists and their patients while incurring avoidable costs.

Propofol measurement to  $60 < BIS < 75$  with baseline EMG provides amnesia and the perceived need of the commonly used 2 mg midazolam premedication. Eliminating midazolam also may eliminate prolonged emergence in sensitive and/or elderly patients.

Direct cortical response measurement enables anesthesiologists to treat patient requirements as the individuals they are as opposed to the 80% of patients in the middle of the bell curve. Doing so eliminates outliers, transforms every patients' "mystery" into an "open book test," and creates the basis for more humane, cost-effective anesthesia care.

### Table 2. The Surgeon's Golden Rules

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1. Propofol titrated to  $60 < BIS < 75$  c baseline EMG = adequate amnesia and hypnosis
  2. Blanched surgical field = evidence of vasoconstriction but not adequate analgesia
  3. Reinject immediate area stimulated if pt. mvmt occurs at  $60 < BIS < 75$  without EMG spike
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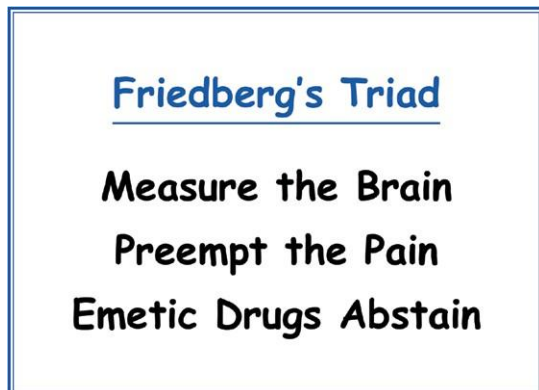


Fig. 5. Friedberg's Triad.

Over 25 years and in more than 6,000 patients, there has not been a single hospital admission for brain fog, postoperative pain management, or PONV. Friedberg's Triad appears to answer anesthesia's persistent problems (Fig. 5).

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