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Ketamine Associated Laryngospasm during Processed EEG Monitored Propofol Sedation

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Introduction

The rapid growth of minimally invasive outpatient surgery, especially elective cosmetic surgery, has increased the rationale for minimally invasive anesthesia (MIA). Minimally invasive, *progressive* airway management, another feature of MIA, exposes patients to atypical ketamine associated laryngospasm (KAL). Outcomes for cosmetic (or other) surgery breaching the integument barrier to the outside world of danger improve with *opioid-free* MIA. These outpatients experienced fewer undesirable side effects; i.e. postoperative nausea and vomiting (PONV), pain, delayed emergence and unanticipated hospital admission [1]. As opposed to *treating* high-risk patients with antiemetics, Apfel, et al. asserted *opioid-free* regional anesthesia technique is the most effective way to *prevent* PONV [2]. *Opioid-free*, MIA brain monitored propofol was the genesis of a lesser patient trespass or minimal pharmacologic/airway invasion.

Without antiemetics, the *opioid-free*, propofol *then* ketamine *then* subcutaneous local analgesia paradigm achieved a 0.6% PONV rate in an Apfel-defined high-risk population (i.e. non-smoking, female, PONV/motion sickness history, emetogenic surgery) [3]. The 1998 addition of *real-time* electromyogram (EMG) trending to bispectral (BIS™) index brain monitoring for propofol sedation made assigning *numbers* to the level of propofol sedation possible and more useful than BIS alone. Measuring the sedation level minimizes the pharmacologic trespass to the patient. Less is more.

BIS information is delayed from real time by 15-30 seconds. The EMG of BIS is a *real-time* facial *frontalis* muscle signal analogous to the electrocardiogram (ECG) signal. EMG activity is preserved even in the presence of Botox® Spikes in the EMG trend signal incipient arousal [4]. Arousal precedes nociception [5]. EMG spikes demand more propofol sufficient to decrease them to baseline [1]. Direct cortical propofol response measurement with *real-time* EMG/BIS achieved a statistically significant 30% propofol reduction [6]. The remunerative value of a 30% reduction has been diminished once proprietary propofol (Diprivan®) became generic. However, the ability to use less propofol for the same level of sedation remains a value whenever drug shortages occur.

Opioid-inclusive anesthesia not only fails to prevent postoperative pain but also increases PONV [7]. Postoperative emesis is patients' number one outcome to avoid [8]. Using MIA, all commonly performed cosmetic surgery cases (i.e. liposuction, breast augmentation, rhytidectomy, and abdominoplasty) have been safely performed with fewer drugs and less pharmacologic/airway trespass than general endotracheal anesthesia (GA/OET). Retching after surgery is a potential source of hematomas and wound dehiscence [9]. Retching can also rupture abdominoplasty *rectus* muscle imbrication stitches. Patient as well as surgeon complaints will follow such complications.

MIA eschews 2 mg midazolam, 100 mcg fentanyl premedication. Lesser anesthetic trespass begins with direct cortical response measurement with *real-time* EMG/BIS monitoring. By avoiding opioids, one eliminates adding to propofol respiratory depression. An *incremental*, not bolus, propofol induction initiates the paradigm. Supplemental oxygen is not routinely needed or given. A physiologic SpO_2 is preserved with incremental induction. Spontaneous ventilation and patent airway are also preserved. (see shorturl.at/gyzJK) *n.b.* During this induction style, no SpO_2 changes are evidenced. The airway remains patent secondary to preservation of the *genioglossus, orbicularis oris and temporalis masseter* muscle tone. Neither anterior mandibular displacement to increase *genioglossus* tension nor positive pressure bag mask ventilation is required to maintain an adequate SpO_2.

Real-time EMG/BIS numerical measurement of propofol levels makes moderate to deep propofol sedation levels (i.e. 60 < BIS < 75 with baseline EMG) *minimally invasive* compared to GA/OET at 40 < BIS 60. Over a 20-year experience *without* midazolam or fentanyl premedication, no hallucinations or awareness with recall were reported when *opioid-free*, propofol sedation was maintained at 60 < BIS < 75 *with* baseline EMG [1].

Ketamine has been used as an adjuvant to propofol sedation for *opioid-free* MIA [1,10]. Laryngeal reflexes are increased with ketamine [11]. Ketamine associated laryngospasm (KAL) is a recognized adverse effect. While laryngospasm rarely occurs, there are potentially serious outcomes like negative pressure pulmonary edema [12]. KAL during propofol sedation is usually caused by stimulation of the vocal cords by secretions that can be reduced with glycopyrrolate premedication [13].

After 0.2 mg IV glycopyrrolate premedication, propofol was incrementally induced with repeated 50 mcg·kg^{-1} doses (*with* initial base infusion rate of 25 mcg·kg^{-1}·min^{-1}) to achieve BIS < 75 *with* baseline EMG *prior* to ketamine administration. Stylistically, achieving minimally invasive propofol sedation levels with incremental induction is more akin to achieving therapeutic dopamine levels than achieving therapeutic lidocaine levels; i.e. no initial propofol bolus is administered. Induction typically takes < 3 min *after* which a 50 mg ketamine dose is administered 2-5 min prior to local anesthetic injections or skin incision. The 50 mg ketamine dose results in patient immobility (i.e. dissociative effect) for approximately 10-20 min in patients weighing between 35-145 kg [1,3]. During this MIA paradigm, KAL may occur. *Caveat emptor!*

Progressive, minimal airway instrumentation requirement to maintain SpO_2 is another feature of MIA or brain monitored, propofol *then* ketamine sedation. Approximately 60% of this author's cosmetic surgery patients' airways were maintained *without* instrumentation. Initially, the rhytidectomy position (i.e. chin up, head lateral-two *genioglossus* force vectors) was used to maintain the airway. If the rhytidectomy position was insufficient, an *unheated* IV bag under the patient's shoulders is added to the rhytidectomy position to maintain the airway and SpO_2 during the case. An additional 30% of patients required nasal airways. Less than 10% of patients required a laryngeal mask airway. None of more than 5,000 patients in this author's 26-year experience required endotracheal intubation [1]. Less instrumentation produces less sore throat outcomes. Sore throat after airway instrumentation is another potential postoperative complaint cause, especially in cosmetic surgery patients.

Laryngospasm is historically recognized by the 'crowing' noise generated from incomplete closure of the vocal cords. Traditional non-pharmacologic laryngospasm therapy consists of (painful) anterior jaw thrust along with supplemental oxygen & positive pressure ventilation [14,15]. These maneuvers fail to resolve the laryngospasm [3]. Unanticipated postoperative jaw discomfort secondary to jaw thrust can be another source of cosmetic surgery patient complaint.

Inasmuch as cosmetic surgery is often performed under GA/OET, KAL has received little attention. In a spontaneously breathing, non-intubated, *opioid-free*, propofol-*then*-ketamine patient, an abrupt loss of end-tidal, carbon dioxide ($EtCO_2$) signal may facilitate the KAL diagnosis. Absent $EtCO_2$ monitoring, rocking respiratory efforts and a drop in SpO_2 may aid in the KAL diagnosis, albeit in a less timely fashion than making the KAL diagnosis with $EtCO_2$ monitor information. In this author's 26-year experience with rare KAL, no 'crowing' sound occurs owing to the *complete* closure of the vocal cords. The KAL prodrome is only a cough or sneeze. Upon recognizing a patient's cough or sneeze, lidocaine IV 1 mg·lb^{-1} or 2 mg·kg^{-1} STAT has been uniformly effective in KAL treatment [1].

Why not succinylcholine to treat KAL? [16] Succinylcholine is a known malignant hyperthermia (MH) trigger. Neither propofol nor ketamine are MH triggers. Elective cosmetic surgery has very few medical indications like post-mastectomy reconstruction. No matter how low the MH risk, it may be hard to justify a*ny* MH risk in patients having cosmetic surgery without medical indication. (See https://www.cbsnews.com/news/fla-teen-dies-during-breast-surgery/) Post-succinylcholine myalgias would *very* likely result in postoperative patient complaints.

A non-paralyzing rocuronium dose is another possible treatment option for KAL. However, the potential need to support ventilation after rocuronium would be very disruptive during a rhytidectomy or other facial cosmetic surgery. A KAL preemptive suggestion was to maintain propofol at lower BIS values (i.e. 40-60). Propofol at those BIS levels are compatible with GA, thereby forfeiting the claim to minimally invasive sedation. Propofol at 40 < BIS < 60 may also expose the anesthesiologist to criticism of giving GA with an unprotected airway. A simpler, spontaneous ventilation-supporting, solution has reliably been IV lidocaine. Interested readers are referred to an excellent, very recent, academic paper [17].

Conclusion

There were no hospital admissions for either PONV or pain in the 26 years between March 26, 1992-November 28, 2018. Patients emerged quickly, clear headed and were successfully discharged to home without need of professional aftercare providers. Postoperative opioid rescue was rare. No opioid addicts or overdose deaths occurred. Direct cortical response measurement makes this paradigm reproducible. All rare KAL episodes were treated successfully with IV lidocaine 1 mg·lb^{-1} or 2 mg·kg^{-1} without endotracheal intubation. *Opioid free* MIA is a boon for patients. However, anesthesiologists must be prepared to recognize and promptly treat KAL.

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