Intravenous Anesthesia With Bispectral Index Monitoring vs Inhalational Anesthesia for Rhytidoplasty
A Randomized Clinical Trial

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IMPORTANCE Minor adverse effects related to anesthesia are common and worrisome to patients, including perioperative vomiting, gagging on the endotracheal tube, incisional pain, and nausea. A previously published intravenous anesthesia protocol reports extremely low rates of postoperative nausea and vomiting (<1%) and decreases in postoperative pain perception compared with rates reported following administration of inhalational anesthetics.

OBJECTIVE To evaluate and compare postoperative outcomes in patients after administration of combined propofol and ketamine hydrochloride anesthesia with bispectral index monitoring (PKA-BIS protocol) vs inhalational anesthesia (IA) during lower rhytidoplasty.

DESIGN, SETTING, AND PARTICIPANTS We performed a prospective, double-blind, randomized comparison trial of the PKA-BIS protocol and IA in 30 consecutive female patients undergoing rhytidoplasty by a single surgeon at a single outpatient surgery center from October 2013 to June 2014.

MAIN OUTCOMES AND MEASURES Outcome measures included nausea, vomiting, pain, overall feeling of well-being, time to awaken, time to discharge, and cost. Patient measures were recorded using a combination of a 40-item validated postoperative quality of recovery questionnaire (QOR-40) and visual analog scales (VASs). Results were recorded immediately after surgery and on postoperative days 1 and 7.

RESULTS A statistically significant reduction in emergence time (mean [SD], 29.8 [10.6] vs 46.0 [10.2] minutes; \( P < .001 \)) and time to meet discharge criteria (51.4 [19.3] vs 66.1 [12.9] minutes; \( P = .02 \)) was seen in patients in the PKA-BIS group. Patient-reported (subjective) postoperative nausea (3 of 15 [20%] vs 7 of 15 patients [47%]; \( P = .12; \chi^2 = 2.40 \)), vomiting (0 vs 2 of 15 patients [13%]; \( P = .14; \chi^2 = 2.14 \)), and confusion on the day of surgery (3 of 15 [20%] vs 6 of 14 patients [43%]; \( P = .38; \chi^2 = 1.77 \)) were also decreased in the PKA-BIS group, but these differences did not reach significance. Differences in global recovery scores (QOR-40 scores in the postanesthesia care unit, 158.13 [22.68] vs 155.33 [18.09]; \( P = .71 \); at day 1, 166.47 [26.39] vs 166.00 [16.00]; \( P = .96 \)), postoperative overall feeling of well-being (VAS scores at day 1, 6.10 vs 6.26; at day 7, 7.49 vs 8.00), and postoperative pain perception (VAS scores at day 1, 3.40 vs 3.65; at day 7, 2.26 vs 1.81) between the PKA-BIS and IA groups, respectively, did not reach significance. The costs of anesthesia administration were similar between the PKA-BIS ($10.37/h) and IA ($8.47/h to $9.87/h) groups.

CONCLUSIONS AND RELEVANCE The PKA-BIS protocol for anesthesia appears to be a comparable alternative to traditional IA in patients undergoing elective rhytidoplasty. A larger patient sample size is needed to determine whether trends toward decreased nausea, vomiting, and postoperative confusion and differences in postoperative pain perception are significant.

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Fewer complications related to anesthesia are extremely rare; however, more adverse effects related to anesthesia are common and worrisome to patients. A survey by Macario et al revealed that patients undergoing surgery are most concerned, in order of importance, about perioperative vomiting, gagging on the endotracheal tube, incisional pain, and nausea. These concerns are important to remember, especially in the setting of elective cosmetic surgery. To address these patient concerns, we evaluated a previously published anesthetic protocol that reports extremely low rates of postoperative nausea and vomiting (<1%) and decreases in postoperative pain perception. This anesthetic protocol uses 5 simple medications (propofol, ketamine hydrochloride, clonidine hydrochloride, glycopyrrolate, and local anesthetic) with bispectral index monitoring (PKA-BIS protocol) as an alternative to traditional inhalational anesthesia (IA) in patients undergoing outpatient cosmetic surgery. The PKA-BIS protocol reportedly carries less than a 1% risk of postoperative nausea and vomiting, which is substantially less than reported rates of up to 30% postoperative nausea and vomiting with the use of IA. Because opioids have been reported to increase rates of postoperative nausea and vomiting, a protocol minimizing baseline postoperative nausea and vomiting and postoperative opioid requirements is enticing.

The 2 sedatives used in the PKA-BIS protocol are ketamine and propofol. Ketamine possesses sedative and amnestic properties and is also a powerful analgesic. Although ketamine has been touted for its minimal negative effect on the cardiovascular and respiratory systems, it can cause hypertension, tachycardia, increased respiratory secretions, and emesis and—in as many as 20% of patients—can lead to painful and unpleasant dreams or hallucinations. Conversely, propofol has powerful sedative properties but none of the amnestic or analgesic properties offered by ketamine. Propofol also possesses antiemetic properties and can minimize the hypertension and tachycardia caused by ketamine. In addition, pretreatment with propofol to place the patient into a hypnotic state before the administration of ketamine has been shown to prevent hallucinations with subsequent ketamine administration. These complementary properties make for a great marriage between propofol and ketamine. Other medications used in the PKA-BIS protocol include clonidine, glycopyrrolate, and local anesthetic. Clonidine was added to the protocol to decrease the amount of propofol used intraoperatively and to aid in preoperative anxiolysis. Increased oral secretions are counteracted by glycopyrrolate, and the intraoperative use of local anesthetic helps to decrease sedative requirements.

The PKA-BIS protocol includes 2 additional monitoring techniques—the bispectral index (BIS) monitor and electromyographic tracings. The BIS monitor is used to assess the depth of hypnosis. Studies have shown that a BIS level of 60 to 90 predicts impaired patient recall, and levels of less than 60 are associated with complete loss of consciousness. Its use has also been shown to reduce the overall amount of propofol administered and the times to awaken and to meet discharge criteria in numerous clinical studies. When used in combination with electromyographic tracings, which are reported by most modern-day BIS monitors, the likelihood of imminent patient movement can also be assessed. This monitoring allows for preemptive injection of local anesthetic as needed throughout the surgical case, which curtails the need for additional systemic anesthetic administration. Another benefit of the BIS monitor is verification that patients are not oversedated. This factor is especially important given the fact that deep hypnosis, as determined by a BIS level of less than 45, has been associated with an increase in mortality as late as 1 year postoperatively in noncardiac surgical patients.

Although the PKA-BIS protocol has been used successfully with reported decreases in postoperative pain perception, nausea, and vomiting, this technique has not been compared directly with traditional IA. We aimed to compare the PKA-BIS protocol with routine IA use (standard of care) in patients undergoing lower face-lift surgery (rhytidoplasty) in a prospective, randomized, double-blind manner at a single-surgeon outpatient surgery center.

**Methods**

### Selection Criteria

Thirty consecutive female patients undergoing primary or secondary rhytidoplasty performed at a single outpatient surgery center from October 2013 to June 2014 were included in this study. Many patients also underwent additional simultaneous surgical procedures for treatment of the aging face. Patients undergoing a forehead- and/or brow-lift at the time of rhytidoplasty were excluded from the study owing to inability to perform BIS monitoring properly during this portion of the procedure. Male patients were excluded to avoid possible sex-dependent variations in postoperative nausea, vomiting, and pain tolerance. Approval for our study was granted by the Mercy Institutional Review Board at Mercy Hospital Springfield, Missouri. The full study protocol can be found in the trial protocol in the Supplement. All study participants provided written informed consent at the time of study enrollment. All patient data were deidentified for data analysis.

Study participants were randomized into the PKA-BIS group or the IA group (Figure 1). Patient randomization occurred prior to study enrollment, and patients were blinded as to which anesthetic protocol they received. Patients in the PKA-BIS group were not given narcotics, benzodiazepines, or prophylactic antiemetics per the previously described protocol (Box). They were given 0.1 to 0.2 mg of clonidine hydrochloride for anxiety before surgery. Patients in the IA group received routine prophylactic antiemetics, including preoperative placement of a 1.5-mg scopolamine patch, 8 mg of ondansetron hydrochloride as an orally disintegrating tablet, and 10 mg of metoclopramide hydrochloride, as well as intraoperative ondansetron hydrochloride and dexamethasone sodium phosphate (Decadron). This group also received 2 mg of intravenous midazolam hydrochloride before surgery to aid in anxiety and amnesia.

All patients were provided postoperative prescriptions for antiemetics and narcotic pain medications to be taken as needed. The amount of medication taken outside of the office setting was not recorded.
Operative Procedure and Intraoperative Data Collection
All patients underwent rhytidoplasty by the senior author (K.A.L.). Lower face lifts were performed using limited or extended sub-superficial musculoaponeurotic system protocols, as previously described.14 Simultaneous procedures, such as upper and lower blepharoplasty, chin augmentation, fat transplantation, glabellar furrowplasty, perioral and periconical laser resurfacing, otoplasty, lateral canthoplasty, and ptosis repair, were also performed at the time of rhytidoplasty. Time from induction of anesthesia to the beginning of the case (as defined by injection of local anesthetic), operative time, and time from the end of surgery to arrival in the postanesthesia care unit (PACU) were recorded. The amount of local anesthetic used and routine anesthesia records, including medication type and quantity administered, were also recorded.

Multiple anesthesiologists participated in anesthesia administration. All anesthesiologists participated in administration of the IA and PKA-BIS protocols. Patients who were randomized to the IA group were placed under general anesthesia, and each anesthesiologist used his or her preferred method of general anesthesia induction and maintenance. None of the anesthesiologists chose to use the BIS monitor during administration of IA. Patients randomized to the PKA-BIS group received a propofol drip, and their level of sedation was measured using a BIS monitor with electromyelographic tracings per the protocol delineated (Box).3

Postoperative Data Collection
Once the patient was deemed coherent by the recovery room staff, a validated postoperative recovery survey (QOR-40) was administered to assess patient recovery before discharge from the PACU.15-17 Time from PACU arrival to awakening and being coherent and time to meet discharge criteria were also recorded. At the patient’s visit on postoperative day 1, the QOR-40 survey was again administered. Visual analog scales (VASs) measuring pain and the overall sense of well-being were administered on postoperative days 1 and 7. All surveys and VAS measures were administered by a staff member who was blinded to the type of anesthesia received. We then compared the data between the PKA-BIS and IA groups. A cost analysis was performed using records of preoperative and intraoperative medication administration, and the results were compared between study groups.

Statistical Analysis
Data analysis was performed during data collection (October 2013 to June 2014). The demographic characteristics of the 2 groups are presented as mean (SD). Differences between the 2
groups in nausea, vomiting, degree of pain perception, and confusion were calculated using independent t tests and reported with P values, with calculation of Pearson χ² values. Differences in symptom VAS scores measuring pain and overall well-being between the 2 groups are expressed as means (SDs). We also used independent t tests to compare differences in the duration of surgery, QOR-40 scores, occurrence of bad dreams, emergence time, and time to meet discharge criteria (reported as mean [SD]). Paired-sample t tests were also performed.

Results

A total of 30 patients were included in the trial. Fifteen patients were randomized to each study arm. The mean age of patients included in the study was 63.5 (6.8) years (range, 49-78 years). The mean ages of patients were not significantly different between treatment groups. The mean length of surgery was 388 (range, 283-552) minutes. The duration of surgery in the PKA-BIS group was significantly longer than that in the IA group (mean [SD], 410.3 [60.5] vs 366.5 [48.2] minutes; P = .04), likely related to an increased number of simultaneously performed procedures included in the PKA-BIS group. One patient in the PKA-BIS group required a laryngeal mask airway for airway maintenance, whereas the remaining 14 of 15 patients breathed spontaneously with the use of a nasal trumpet and transnasal oxygen supplementation. All patients in the IA group had a laryngeal mask airway or an endotracheal tube placed for airway management.

Time to awakening was significantly decreased in the PKA-BIS group (29.8 [10.6] vs 46.0 [10.2] minutes; P < .001), as was the time to meet discharge criteria (51.4 [19.3] vs 66.1 [12.9] minutes; P = .02). We also observed an improvement in the level of alertness in most of the patients in the PKA-BIS group on the day of surgery and at postoperative day 1. We found no significant difference in QOR-40 values (measuring quality of recovery) between the 2 groups on the day of surgery or on postoperative day 1 (QOR-40 scores in the postanesthesia care unit, 158.13 [22.68] vs 155.33 [18.09]; P = .71; at day 1, 166.47 [26.39] vs 166.00 [16.00]; P = .96).

Differences in patient-reported nausea, vomiting, and confusion between the 2 study groups were not statistically significant but did approach significance. Three of 15 patients in the PKA-BIS group (20%) reported experiencing some degree of nausea, whereas 7 of 15 patients in the IA group (47%) reported nausea directly after surgery based on their responses to the QOR-40 survey. Although the incidence of reported nausea in the IA group was more than double that in the PKA-BIS group, these differences were not statistically significant (P = .12; χ² = 2.40). Vomiting occurred in 2 of 15 patients of the IA group (13%) and in none of the patients in the PKA-BIS group, with the difference approaching significance (P = .14; χ² = 2.14). The levels of reported nausea and vomiting were higher than expected in both treatment groups; however, patients were more likely to report the presence of nausea during survey administration than to staff members routinely assessing postoperative nausea in the PACU.

Confusion was reported twice as often by patients in the IA group (6 of 14 [43%] vs 3 of 15 [20%]). When asked to qualify the degree of confusion, patients in the IA group also reported greater degrees of confusion than those in the PKA-BIS group. These differences also approached significance (P = .18; χ² = 1.77) (Table).

We found no significant difference in overall pain as recorded on the day of surgery or on postoperative days 1 or 7 based on the QOR-40 survey or the pain VAS score. The QOR-40 survey revealed that moderate pain was reported in the PACU with similar frequency by the IA and PKA-BIS groups (10 of 15 [67%] and 9 of 15 [60%], respectively; P = .71; χ² = 0.14), whereas 2 times the number of patients receiving IA reported severe pain in the PACU (6 of 15 [40%] and 3 of 15 [20%], respectively; P = .23; χ² = 1.43). This difference was not statistically significant. On postoperative day 1, the QOR-40 survey revealed no difference between the IA and PKA-BIS groups in reports of moderate (13 of 15 [87%] and 14 of 15 [93%], respectively; P = .54; χ² = 0.37) and severe (5 of 15 [33%] in both groups; P > .99; χ² = 0) pain. When again comparing between patients in the IA and PKA-BIS groups, the mean VAS pain scores on a 10-point scale (with 10 indicating unbearable pain and 0, no pain) were 3.65 and 3.40, respectively, at day 1 and 1.81 and 2.26, respectively, at day 7. None of these differences approached statistical significance. Anecdotally, patients receiving PKA-BIS anesthesia reported less need for analgesic use...
on the night of surgery; however, this value was not recorded as a part of this study.

Bad dreams during surgery were reported by 1 patient in each study group. No patient reported hallucinations, and no emergence reactions were noted on awakening. No statistically significant difference was seen in the overall feeling of well-being based on a 10-point VAS score at postoperative day 1 or 7. Comparison of the overall feeling of well-being between the IA and PKA-BIS groups revealed mean VAS scores of 6.26 vs 6.10, respectively, at postoperative day 1 and 8.00 vs 7.49, respectively, at postoperative day 7 (with 0 being worst possible and 10 being best possible).

Overall cost of anesthesia administration was similar between the IA and PKA-BIS groups. Examination of intraoperative anesthesia records revealed that the mean cost of IA use ranged from $8.47/h to $9.87/h depending on the type and amount of inhalational agent used, whereas the mean cost of PKA-BIS anesthesia was $10.37/h. If the cost of the BIS monitor is subtracted, the cost of anesthesia in the PKA-BIS group is $9.64/h, which is in agreement with previous studies showing that the use of a BIS monitor does not save money but that the overall increase in anesthesia cost is attributable to the cost of the monitor alone.3

Discussion

In the setting of elective surgery, patient comfort is of utmost importance. Ideally, patients undergoing elective cosmetic surgery would experience no adverse effects as a result of tissue insult or anesthetic administration. In the postoperative period, patients would awaken quickly without nausea, pain, or the commonly seen postoperative hazy associated with traditional IA. The PKA-BIS protocol has been reported to offer these benefits.3-5 However, a head-to-head comparison study between the PKA-BIS and IA protocols has, to our knowledge, never been performed.

Repetitive trauma or tissue injury, such as occurs with surgery, results in allodynia (pain produced at subthreshold stimulation levels), hyperalgesia (exaggerated pain), and, ultimately, secondary hyperalgesia (the spread of hyperexaggerated pain to surrounding uninjured tissues).18 This trauma-induced hypersensitivity leads to central sensitization, which is caused by activation of N-methyl-D-aspartate (NMDA) receptors in the spinal cord.18

Perioperative analgesics can aid in pain management but do not prevent central sensitization.18,19 Studies have shown that once central sensitization (or hypersensitivity) has been triggered, pain control becomes much more difficult and pain medications are less effective (Figure 2).3,18 Preemptive analgesia, thought to aid in the prevention and treatment of central sensitization, has been shown repeatedly to decrease postoperative pain perception.18,20-22 Blockade of NMDA receptors functions similarly to preemptive analgesics in experimental models.18 Previously reported decreases in postoperative pain perception with the use of the PKA-BIS protocol credit pain reduction to NMDA receptor blockade and the dissociative effects of intraoperative ketamine administration.3 However, clinical results are mixed regarding the ability of ketamine (as a stand-alone agent) to prevent pain perception when it is administered before surgical incision.18-21

The present study demonstrated no significant improvement in postoperative pain perception with the use of the PKA-BIS protocol compared with IA. Pain perception was evaluated and compared immediately after surgery and at postoperative days 1 and 7. We found no significant difference in postoperative pain perception at any of these time points. This could be due, however, to the overall low level of postoperative pain experienced following rhytidoplasty. In this case, a larger sample size would be necessary to evaluate for any true statistically significant difference in postoperative pain outcomes. The lack of a significant difference in postoperative pain could also be affected by the routine administration of ketamine during IA by some anesthesiologists. Given our goal of comparing the PKA-BIS protocol with the routine standard of care (IA), which has inherent variations, this study did not seek to place limitations on standard IA protocols but, rather, to evaluate a specific PKA-BIS protocol’s performance compared with standard IA protocols.

When comparing PKA-BIS with standard IA protocols, we found a trend toward decreased postoperative nausea and vomiting immediately after surgery in the PKA-BIS group that did not quite reach significance (P = .12; χ² = 2.40). We observed a 27% decrease in patient-reported postoperative nausea after the use of the PKA-BIS protocol and no vomiting in the PKA-BIS group. The number of patients reporting confusion was increased in the IA group compared with the PKA-BIS group. The degree of confusion was also higher in the IA arm, suggesting that the PKA-BIS protocol improves the rate and degree of postoperative confusion. These findings trended toward, but did not reach, statistical significance (P = .18; χ² = 1.77). The present study revealed a statistically significant decrease in emergence time (29.8 [10.6] vs 46.0 [10.2] minutes; P < .001) and time to meet discharge criteria (51.4 [19.3] vs 66.1 [12.9] minutes; P = .02) in patients receiving anesthesia with the PKA-BIS protocol during rhytidoplasty.
One potential limitation to interpreting these results is that maintaining an intraoperative BIS level of 45 to 70 has been shown to affect patient outcomes independently, regardless of the anesthesia type administered. An overall statistically significant decrease in postoperative nausea and vomiting (−6%, with a number needed to treat of 17), earlier awakening, decreased intraoperative awareness, increase in global recovery scores, and faster time to meet discharge criteria (4- to 15-minute decrease) are reported.9–11 To elucidate a causal relationship, the BIS monitor would need to be used in both treatment arms. This process was not feasible with the present study design given that we did not seek to limit the inherent variations of routine IA but rather compare 2 separate protocols. The BIS monitor was available to all anesthesiologists but was not chosen for use by anesthesiologists administering IA at our office because BIS monitoring is not routine in their practice. Our outcomes may have also been affected by the fact that multiple anesthesiologists participated in the study. The PKA-BIS protocol is an art and, from our observations, has a learning curve. A larger patient sample size is needed to determine whether trends toward decreased nausea, vomiting, and postoperative confusional are significant.

Conclusions

This prospective, double-blind, randomized comparison of the PKA-BIS protocol with standard IA demonstrated significant improvements in time to emergence and time to meet discharge criteria with the use of the PKA-BIS protocol for anesthesia. Differences in postoperative pain perception, reported nausea and vomiting, and global recovery scores did not reach statistical significance, although trends in improved nausea and vomiting scores and decreased levels of confusion in the PKA-BIS group on the day of surgery approached significance. The present study includes a small sample size, and larger studies may demonstrate statistically significant differences in nausea, vomiting, pain perception, confusion, and overall recovery scores in the immediate postoperative period. Studies including a larger sample size are needed to determine whether the PKA-BIS protocol indeed offers a significant clinical benefit to patients undergoing face-lift surgery. Further evaluation of differences in postoperative confusion and cognitive function are also needed.

REFERENCES