Clonidine Premedication Decreases Propofol Consumption During Bispectral Index (BIS) Monitored Propofol-Ketamine Technique for Office-Based Surgery

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BACKGROUND. **Propofol-ketamine anesthesia is a room air, spontaneous ventilation (RASV) , dissociative intravenous (IV) sedation technique reported to have a near-zero postoperative nausea and vomiting (PONV) rate. Clonidine premedication has been reported to control blood pressure intra- and postoperatively, as well as to reduce the requirements for hypnotic agents. The bispectral index (BIS) monitor is a reproducible, objective, observer independent, quantitative measurement of the hypnotic state.**

OBJECTIVE. **This study was designed to compare the propofol consumption rate during BIS monitored propofol-ketamine anesthesia for office-based, elective female facial rhytidectomy in patients with and without clonidine premedication.**

METHODS. **Six patients receiving clonidine (200 μg oral premedication administered 30–60 minutes prior to induction of anesthesia were compared with a recent, historical control group of six patients who received no premedication. A BIS of 60–70 was chosen as the standard of comparison for light hypnotic state. A dilute propofol solution was used to gradually titrate anesthesia to a BIS of 60–70 prior to the administration of ketamine.**

RESULTS. **A statistically significant reduction in propofol consumption was observed in the clonidine premedicated female elective rhytidectomy patients compared with those not receiving the clonidine. Other than modestly increased requirements for IV fluids, there were no adverse effects observed with clonidine premedication.**

WHILE SIMULATING THE operating conditions of general anesthesia (a relaxed surgical field in a quiet, immobile patient), the propofol-ketamine technique[1] is a room air, spontaneous ventilation (RASV), dissociative intravenous (IV) sedation technique derived from the diazepam-ketamine technique of Vinnik.[2,3] Significant cost savings may be realized if propofol consumption can be reduced while maintaining an equivalent hypnotic state. Decreased hypnotic administration should also result in an improved quality of recovery. Preanesthetic oral clonidine has been reported to reduce the anesthetic requirement in the perioperative period.[4–6] Clonidine premedication has also been reported as a means of enhancing intra- and postoperative blood pressure control as well as reducing hypnotic drug requirements during facial rhytidectomy.[7,8] Despite two recent reports[9,10] on clonidine premedication reducing propofol requirements, in neither study was the patient's level of hypnosis measured. Both of these studies relied on heart rate and blood pressure as indexes of hypnosis. The bispectral index (BIS) monitor (Aspect Medical Systems, Inc., Newton, MA) has been validated as an accurate means of measuring the hypnotic state with propofol.[11,12] BIS provides a direct measure of the hypnotic state, while heart rate and blood pressure more commonly reflect autonomic responses to noxious stimuli. Although changes in hypnotic state often influence heart rate and blood pressure, in many cases the patient's hypnotic state changes without corresponding changes in vital signs.[13] Using propofol-ketamine anesthesia, the BIS monitor has been reported to reduce propofol consumption rates by an average 20% ($P < 0.02$) in a group of 129 patients that included 21 female elective facial rhytidectomies.[14]

It is imperative with any anesthetic technique to provide the patient with a high-quality recovery. Patients will accept a variety of other alternatives including decreased mental acuity and increased pain in order to prevent postoperative nausea and vomiting (PONV).[15] A recent report[16] confirmed the finding of this 1992 abstract. PONV can be a disastrous outcome in facial rhytidectomy patients, leading to hematoma formation, seromas, and delayed wound healing. A near-zero PONV rate (0.6% or 7 of 1264 patients) has been reported using the propofol-ketamine technique in a 5-year review of office-based elective plastic surgical patients including 159 facial rhytidectomies.[17]

B.L. Friedberg, MD and J.C. Sigl, PhD have indicated no significant financial interest with commercial supporters.

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© 2000 by the American Society for Dermatologic Surgery, Inc. • Published by Blackwell Science, Inc.
ISSN: 1076-0512/00/$15.00/0 • Dermatol Surg 2000;26:848–852

None of the 159 rhytidectomy patients were among the 7 PONV patients. In addition to providing baseline data on propofol consumption rates in female patients receiving propofol-ketamine anesthesia prior to routine BIS monitoring (see Table 1), the 5-year review confirmed other reports[1,18,19] that hypnotic doses of propofol reliably prevented ketamine-induced hallucinations.

This study was designed to compare propofol consumption rates in female elective facial rhytidectomy patients receiving a 200 μg oral dose of clonidine premedication 30–60 minutes prior to the induction of anesthesia with the propofol-ketamine technique at comparable BIS levels with those female elective rhytidectomy patients who did not receive oral clonidine premedication.

Materials and Methods

After human ethics committee approval and written consent, 12 ASA I or II adult female elective facial rhytidectomy patients from a single surgeon's office-based cosmetic surgery practice were entered into this study. Six were part of an earlier reported group of 129 BIS monitored patients without clonidine premedication.[14] The second group of six received a 200 μg oral dose of clonidine 30–60 minutes prior to induction. An intravenous (IV) catheter (20 or 22 gauge) was started in all patients. The IV catheter was connected to a 15 gtts/min IV set and a 1000 ml bag of normal saline (NSS) was spiked with this set. A 50 ml bag of NSS was injected with two 200-mg ampules of propofol (10 mg/ml), resulting in an approximately 5 mg/ml propofol solution. The 50 ml bag was spiked with a 60 gtts/min IV set and piggybacked into the most distal port of the main IV set. The total dead space from the propofol piggyback port to the patient measured 1 ml. When the initial propofol preparation had been administered, the 50 ml bag was refilled with one 200-mg ampule of propofol diluted with an equal amount of NSS. That which remained in the 50 ml bag at the end of the case was subtracted from the total amount added to the bag as a means of determining the total propofol administered.

Baseline vital signs were obtained before any medications were administered. The awake BIS was observed to be the same in both groups, at 98–100. Both groups were induced over a 2–10 minute time frame in order to preserve spontaneous ventilation and a patent airway. Often a #28 French red rubber nasal airway was employed to maintain airway patency. Oxygen, Ambu bag, and suction apparatus were readily available for all patients. The office surgical facility was AAAHC certified. An electrocardiogram (EKG), noninvasive automated blood pressure (NIABP), and pulse oximeter (SpO_2) were monitored in addition to the BIS.

Propofol was titrated using the BIS, which is a dimensionless number from 0 to 100 that quantifies the patient's hypnotic state (Aspect Medical Systems, Inc., Newton, MA). Both groups of patients had 0.2 mg glycopyrrolate initially, followed by propofol titrated until the BIS was 60–70. Once this level of light hypnosis was achieved, a 50 mg bolus of IV ketamine was administered. The surgeon was then informed that within 2 minutes the patients should be "dissociated" or ready to remain motionless for the local anesthetic injection. Patients who moved purposefully in response to the injection halted the injection until a second 50 mg bolus of ketamine was administered, followed by another 1-minute interval before resuming the injection. After the local anesthetic was injected, no further ketamine was administered. Patients were maintained on the propofol infusion until the conclusion of surgery. No benzodiazepines, H_2 antagonists, metoclopramide, antacids, opioids, or antiemetics were used.

All anesthetics were administered by the anesthesiologist. The patients' age, weight, total propofol and ketamine doses, propofol infusion rate, and anesthesia times were tabulated by the anesthesiologist. Total lidocaine administered and lidocaine injected by the surgeon was tabulated by the scrub nurse and reported to the anesthesiologist. Admission

Table 1. Propofol Consumption Rates

	Dosage					
Characteristic	*0 midazolam 0 BIS 0 clonidine*	*2 mg midazolam 0 BIS 0 clonidine*	*4 mg midazolam 0 BIS 0 clonidine*	*0 midazolam + BIS 0 clonidine*	*0 midazolam +BIS 0 clonidine*	*0 midazolam + BIS + 0.2 clonidine*
N (all female)	293	9 rhytides	26 rhytides	201	6 rhytides	6 rhytides
Age (years)	42	63	57	44	53	52
Weight	58	59	58	63	58	66
Ketamine	70	86	131	76	80	83
T	96	317	293	141	190	199
Propofol (mg/min)	10.8[a]	8.3[b]	8.1[b]	8.1	8.1	5.6[c]
Propofol (μg/kg/min)	190[a]	151[b]	142[b]	176	139	90[d]

[a] From reference 17.
[b] Parsed from reference 17 database.
[c] $P = 0.019$
[d] $P = 0.008$

and postclonidine administration blood pressures and the time interval until anesthetic induction were noted by the nurse or medical assistant. Postoperative recumbent and sitting blood pressures were similarly noted before patient discharge.

Results

As seen in Table 2, the propofol rate decreased from 8.1 to 5.6 mg/min ($P = .019$) and the propofol dose rate decreased from 139 to 90 μg/kg/min ($P = .008$) in the clonidine premedicated group compared with the unpremedicated group, respectively. Modest reductions in blood pressure were noted from admission to 30–60 minutes after oral clonidine. No postural hypotension was noted either during ambulation from admitting to the operating room or upon standing from the operating table/recovery bed to sit in the wheelchair prior to discharge from the office to home. No PONV or hallucinations were reported in either group.

Statistical Analysis

Statistical analysis was performed using the Student's *t*-test. Factorial analysis was used to compare propofol consumption between premedication groups while controlling for lidocaine dose as a covariate. There were no significant differences in the age, weight, or anesthetic duration of the women in either group ($P < .05$). Propofol consumption was significantly lower in the clonidine premedicated group at similar levels of hypnosis defined as a BIS of 60–70. Although there was a statistically significantly greater total lidocaine dose used in the clonidine premedicated group, factorial analysis showed that the lidocaine dose was not a statistically significant predictor of propofol consumption after controlling for the presence of clonidine.

Table 2. Summary of Patient Data

Premedication	No clonidine	Clonidine
Age (years)	52.5 ± 7.8	51.5 ± 6.8
Weight (kg)	58.3 ± 2.8	65.7 ± 10.6
Propofol rate (mg/min)	8.1 ± 1.9	5.6 ± 0.8[a]
Propofol dose rate (μg/kg/min)	138.8 ± 34.0	89.8 ± 13.3[a]
Total ketamine (mg)	83.3 ± 40.8	83.3 ± 25.8
Total lidocaine (mg)	633.3 ± 121.1	868.3 ± 74.7[a]
Total lidocaine dose (mg/kg)	10.7 ± 2.2	14.4 ± 2.1[a]
Anesthetic duration (minutes)	190.0 ± 42.5	199.2 ± 21.8
Clonidine (μg/kg)	—	3.1 ± 0.5

All data are mean ± standard deviation.
[a]$P < 0.02$.

Discussion

> *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 unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science.*
>
> WILLIAM THOMPSON, LORD KELVIN
> POPULAR LECTURES AND ADDRESSES (1891–1894)

The end point for sedation is "soft" in comparison to the standard for general inhalation anesthesia. Subjective attempts to quantify sedation have included the Frizzelle sedation score,[20] the observer's assessment of alertness/sedation (OAA/S),[21] and the visual analogue scale (VAS).[22] These are qualitative attempts to translate the subjective "feel" of sedation into a number. The BIS is an algorithm derived from the EEG, which is neither subjective nor observer dependent. The BIS is an objective, reproducible, quantitative measure of the level of patient hypnosis.[23] The advent of BIS technology permits comparisons of sedation techniques (and variations thereof) with a degree of precision heretofore not possible using a BIS of 60–70 as the standard of comparison for light hypnosis. The minimal number of medications in the propofol-ketamine technique permits ready comparison of permutations.

There were significant differences in the total lidocaine doses between the treatment groups. Ideally in such a study the lidocaine doses should be equivalent, since it is possible that some of the effect attributed to the clonidine premedication may, in fact, arise from the differing lidocaine doses. To address this issue we conducted a factorial analysis, using both lidocaine dose and the presence or absence of clonidine premedication in a general linear model to predict propofol consumption. In this analysis the lidocaine dose was not a significant predictor, while the presence or absence of clonidine premedication was strongly predictive. This implies that the effect observed was indeed a clonidine effect, though a study in which lidocaine dose is randomized would be needed for confirmation.

Clonidine is supplied as 100 μg tablets. The 200 μg dose was chosen to most consistently administer more than 2.5 μg/kg but less than 5.0 μg/kg. There was no noticeable difference in the emergence between the two rhytidectomy groups compared to the findings of delayed emergence with isoflurane anesthesia reported by Goyagi et al.[24] using similar doses of clonidine. The difference in findings may be related to the level of hypnosis being defined by end tidal anesthetic concentrations in the Goyagi study as compared with this study using target organ (brain) measurement, that is, a BIS of 60–70.

No patients experienced PONV in this series, confirming earlier work.[17–19] No patients in this study reported hallucinations either upon emergence, discharge to home, or on postoperative visits to the surgeon's office, again confirming previously published experience.[1,17–19] No hypertension or tachycardia resulted from the injection of a 50 mg dissociative of ketamine during propofol hypnosis at a BIS of 60–70, confirming another recent publication.[25] Clonidine premedication did not consistently blunt the hypertensive and tachycardia response to the injection of the epinephrine containing tumescent solution at the beginning of the case. Labetolol 10 mg intravenously was used to manage this brief event. One the initial transient heart rate and blood pressure increases passed, the effect of the clonidine premedication produced blood pressures low enough to require increasing fluid administration to maintain the systolic pressure between 90 and 100 mmHg. Typically this resulted in fluid consumption between 1000 and 2000 ml. This level of volume administration is compatible with the mainstream anesthesia practice recently described by Joas.[26] Although the 1000–2000 ml range of IV volume administered was substantially greater than the 100–200 ml previously reported,[17] no change in clinical care was required. Both rhytidectomy groups had their bladders straight catheterized at the end of the case.

For normal healthy adults, the individual maximum recommended dose of lidocaine hydrochloride with epinephrine is 7 mg/kg (3.5 mg/lb) of body weight, and in general it is recommended that the maximum total dose not exceed 500 mg.[27] This has been demonstrated to be overly conservative when injecting the ultradilute (0.05% or 0.5 mg/ml) solutions proposed for tumescent anesthesia for liposuction by Klein[28] and Ostad et al.[29] Some surgeons have been using ultradilute lidocaine solutions for anesthetizing the face. The face has a substantially richer vascular bed than the peripheral fat stores. Unfortunately there are no published reports to date on the plasma lidocaine levels that result from ultradilute tumescent solution injected into the face. Initial sampling of hourly plasma lidocaine levels from the facial tumescent approach suggest a 1-hour peak level in the low end of the therapeutic range after injection of tumescent solutions (Sikorski LM, personal communication). There has been no clinical suggestion of lidocaine toxicity, even when the total tumescent injection dose was as high as 17 mg/kg, more than twice the level suggested by the *Physician's Desk Reference* recommendation. It should also be noted that in none of the cases was more than a total of 1000 mg lidocaine injected. Intraoperatively, no seizures, severe hypotension, or EKG A-V dissociation were noted. Postoperatively, no patient complaints of tinnitus or metal taste on the tongue were made. Although the total dose relative to the body weight was scrupulously documented, the lack of any of the stigmata of lidocaine toxicity either intra- or postoperatively suggests the absence of toxic levels of lidocaine from the use of tumescent anesthesia in the face.

At comparable BIS levels, premedicating female elective rhytidectomy patients with 200 μg oral clonidine 30–60 minutes prior to anesthetic induction resulted in a statistically significant savings of an average of 425 mg of propofol per patient (at $13.00 per 200 mg ampule, National Specialty Services, 1999 prices) compared with the unpremedicated group. This savings was obtained without either increased patient morbidity (ie, end of the case hypertension from distended patient bladder secondary to increased fluid requirements) or postural hypotension at the time of discharge from the office facility. The number of patients in this study is small. A larger study with more subjects would be desirable to confirm our findings. Oral clonidine premedication appears to reduce propofol requirements in a safe and effective manner for BIS monitored propofol-ketamine dissociative sedation anesthesia in female elective rhytidectomy patients in office-based surgery.

Acknowledgments We would like to thank Lenore M. Sikorski, MD, The Natural Image, Laguna Niguel, CA, the surgeon for all patients in this study; Judy Akin, RN, and Jennifer Torgersen, MA, for their enthusiastic cooperation and compassionate patient care which made performing this study feasible; and Marta Hammond, Aspect Medical Systems, Newton, MA, for the Lord Kelvin quote.

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