The Use of Propofol/Ketamine Anesthesia with Bispectral Monitoring (PKA-BIS) versus Inhalational Anesthetics in Rhytidoplasty (Facelift Surgery) - A Prospective, Double-blinded, Randomized Comparison Study

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Objective: To determine whether post-operative side-effect profiles in patients undergoing elective cosmetic facelift surgery can be decreased through the use of propofol/ketamine anesthesia with bispectral monitoring (PKA-BIS) rather than general anesthesia, without increasing intra-operative time, side-effect profiles, or patient recall.

Background: Although the risk of a severe complication related to anesthesia administration is extremely low, minor side-effects are common. Of these side-effects, patients are most concerned about post-operative nausea and vomiting and pain. Anesthesiologists have, in turn, attempted multiple regimens of medication administration in order to minimize post-operative nausea, vomiting, and pain. This study aims to look at one of these proposed intravenous anesthetic cocktails (propofol/ketamine) in comparison to routine inhalational anesthetic use in patients undergoing facelift surgery at a single-surgeon outpatient facial plastic surgery center.

In order to understand the proposed PKA-BIS method and its proposed mechanism of pain suppression, we must first have a better understanding of the mechanism of pain perception. Pain perception occurs in two regions: a peripheral component due to acute stimulus and a central sensitization which occurs with repetitive peripheral pain stimulus. Pain can further be divided into physiologic pain (well localized and short-lived), which acts as our everyday warning system, and clinical pain (pathologic hypersensitivity) incited by tissue trauma such as surgery. It is this clinical (or pathologic) pain that we wish to suppress following surgery. Both the peripheral and central pain perception pathways undergo changes during tissue injury resulting in decreased pain thresholds. These changes result in allodynia (pain produced at sub-threshold stimulation levels), hyperalgesia (exaggerated pain), and ultimately, secondary hyperalgesia (the spread of hyper-exaggerated pain to surrounding uninjured tissues). One method of preventing clinical pain is to prevent inflammation, and this has been shown to be effective in some studies, i.e. through the use of peri-operative NSAID administration. Another proposed mechanism of pain prevention is pre-emptive treatment to prevent central sensitization from occurring in the first place. Studies have shown that once central sensitization has been triggered, pain control becomes much more difficult and pain medications become less effective (Figure 1).

![Figure 1](borrowed from Woolf and Chong, Anesth Analg. 1993;77:362-79)
The activation of NMDA receptors by glutamate is the main mechanism of central sensitization. It stands to reason then, that pre- and intra-operative administration of an NMDA receptor antagonist, such as ketamine, may prevent central sensitization and therefore lead to decreased post-operative pain levels (see Figure 1).\textsuperscript{3,4,5} Ketamine is known to have powerful analgesic properties.\textsuperscript{6} It also acts as a sedative as well as demonstrating some amnestic properties.\textsuperscript{6} Ketamine is also unique in its ability to cause complete dissociation between the thalamic and limbic regions of the brain with minimal effect on the cardiovascular or respiratory systems.\textsuperscript{5,7} As a matter of fact, respiratory depression is not seen with ketamine administration, and patients maintain their protective airway reflexes. However, these desired benefits do not come without undesired side-effects. Ketamine is also known to cause hypertension, tachycardia, increased respiratory secretions, emesis, and in 20\% of patients, can lead to powerful and unpleasant dreams or hallucinations.\textsuperscript{5,6,7} These side-effects are bothersome enough to patients that ketamine is rarely used as a sole sedation therapy. The addition of propofol is useful in preventing the undesired effects of ketamine administration, while benefiting from its dissociative effects.\textsuperscript{5,6} This propofol-ketamine combination has been used with great success. Propofol alone has powerful sedative properties but has none of the amnestic or analgesic properties offered by ketamine. Propofol also acts as an anti-emetic, counteracts the hypertension and tachycardia related to ketamine administration, and, when titrated to an adequate level of hypnosis, patients also do not experience hallucinations with the subsequent administration of ketamine.\textsuperscript{5} These complimentary properties make for a great marriage between propofol and ketamine. There have also been reported decreases in post-operative pain perception, nausea, and vomiting with the use of certain propofol-ketamine regimens.\textsuperscript{5}

The success of PKA-BIS using propofol in combination with ketamine lies in the explicit pretreatment with propofol in order to place the patient into a hypnotic state PRIOR to the administration of ketamine.\textsuperscript{5,8} A Bispectral index (BIS) monitor is employed in order to make certain that an adequate level of hypnosis has been obtained. The BIS monitor is placed along the patient’s forehead and is based on the Bispectral index - a parameter which is derived from the patient’s electroencephalogram (EEG) reading.\textsuperscript{9} The BIS level is measured on a scale of 0-100, with 0 indicating complete lack of brain activity and 100 indicating an awake state. The BIS level can be reliably used to assess depth of hypnosis in patients undergoing a variety of anesthetic techniques.\textsuperscript{5,9} Studies have shown that a BIS level of 60-90 impairs patient recall and levels <60 are associated with complete loss of consciousness, measured by a lack of response to verbal command.\textsuperscript{9} The BIS monitoring system was approved for clinical use by the Food and Drug Administration in 1996. Its use has been shown to reduce the overall amount of propofol administered, as well as decrease time to wake-up and time to meet discharge criteria in numerous clinical studies.\textsuperscript{5,7} When used in combination with electromyography (EMG) tracings, the likelihood of patient movement can also be assessed. This allows for pre-emptive injection of local anesthetic as needed throughout the surgical case, curtailing the need for additional systemic anesthetic administration.\textsuperscript{5} Another benefit of the BIS monitor is its ability to verify that patients are not “over” sedated. This is important given the fact that deep hypnosis, as determined by BIS levels <45, has been significantly associated with an increase in mortality up to 1 year post-operatively.\textsuperscript{10} Therefore, the BIS monitor is an important component of the proposed sedation method.
The proposed PKA-BIS protocol has reportedly led to very low levels of post-operative pain and
nausea, suggesting that patients would benefit from the use of this technique.\(^5\) However, to our
knowledge, there have been no direct comparison studies performed using the PKA-BIS
technique versus general anesthesia.

Study Design: This study is a prospective, double-blind, randomized comparison study of
different anesthesia methods in rhytidoplasty surgery. Approximately 40 subjects undergoing
facelift surgery performed by the principal investigator will participate.

**Procedure:** Eligible patients who choose to participate in the study will be randomized to
undergo one of 2 anesthesia protocols.

<table>
<thead>
<tr>
<th>Group 1: general anesthesia via a combination of inhalational, intravenous, and local measures. Patients will receive standard anesthesia based on the anesthesiologists’ preference. No protocol will be set as this is the standard for all patients receiving general anesthesia in our practice. (BIS monitor placement prior to induction.)</th>
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<tr>
<td>Group 2: a previously published PKA-BIS protocol will be administered as follows: (^5)</td>
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<tr>
<td>1. Pre-medication with 0.1-0.2mg po clonidine(^{11})</td>
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<tr>
<td>2. Pre-medication with 0.2mg IV glycopyrolate</td>
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<tr>
<td>3. BIS monitor placement and baseline, awake reading recorded</td>
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<td>4. Propofol gtt titrated to BIS of 60-75 (indicative of moderate hypnosis)</td>
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<td>5. 50mg Ketamine IV bolus (once a central state of moderate hypnosis has been reached)</td>
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<td>6. Local anesthetic injection (combination of lidocaine, bupivacaine, and epinephrine)</td>
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<td>7. Additional administration of Ketamine IV bolus as needed (not to exceed a total of 200mg)</td>
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<td>8. Additional administration of local anesthetic as needed</td>
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Both groups will undergo placement of a BIS monitor pre-operatively so that participants remain
blinded as to which anesthesia protocol they receive. Group 1 will receive standard anti-emetics per the ASA PONV guidelines.\(^{12}\) In previously published studies using the proposed propofol-ketamine regimen, the risk of PONV is so low that patients did not require any anti-emetics. This was also aided by the fact that these patients did not require opioids following surgery.\(^5\) Based on these studies, anti-emetics and opioids will not routinely be administered to patients in Group 2. The surgical protocol will remain constant for both groups. All patients will have a 1-day as well as a 1-week post-operative clinic appointment.

Emergence time and time to discharge will be recorded as will the administration of all
medications (including opioids and anti-emetics). All study participants will be asked to
complete the QoR-40 questionnaire (see attached), a validated questionnaire used to assess post-
anesthesia recovery.\(^{13,14}\) This subjective questionnaire will be administered by blinded
interviewers both in the post-anesthesia care unit, prior to discharge, and at the patient’s first
post-operative appointment, within 24 hours of surgery.\(^{15}\) Visual analog scales will be
administered 1 day and 1 week post-operatively to evaluate pain and subjective perception of
overall quality of life. Along with all of the patient variables already mentioned, overall cost of
each type of anesthetic and total cost of surgery will be assessed and compared between patient groups.

Hypotheses: We hypothesize that compared to the controls, patients undergoing PKA-BIS will have decreased pain, decreased nausea and vomiting, and decreased time to discharge following surgery. We also anticipate a decrease in the cost of anesthesia and decreased need for peri-operative narcotics in patients undergoing PKA-BIS.

Data analysis: Standard demographic information including age and relevant medical history will be compiled and analyzed descriptively. Assuming normality of the data and an appropriate sample size, statistical analyses will be performed comparing the control and PKA-BIS patients on time in surgery, type and amount of all medications, QoR-40 scores, visual analog pain scales (before patient discharge, and at 1-day and 1-week post-op), cost of anesthetics administered, and total cost of surgery. For all continuous variables, independent t-tests will be conducted to compare the groups. Chi-square tests will be used as necessary to compare groups on categorical variables.

Study drugs/devices: No study drugs or devices will be used.

Cooperation and Costs: No additional costs will be incurred by patients who choose to participate in this research.

Human subjects:

Study population: Patients undergoing rhytidoplasty surgery.

Inclusion/Exclusion criteria:

Inclusion criteria:
- Female
- 18 years of age or older
- Undergoing elective rhytidoplasty

Exclusion criteria:
- Male
- Under 18 years old
- Pregnant or breastfeeding
- Medically unfit to undergo surgery
- Undergoing brow-lift in conjunction with rhytidoplasty (due to the inability to properly secure the BIS monitor as it would lie within the surgical field)

Research material to be retrieved: Demographic information, type and amount of anesthetic medication, post-operative nausea and vomiting, post-operative pain, QoR-40 scores, costs associated with surgery and administered medications.

Confidentiality: Standard confidentiality measures will be taken in this study such that participants’ identifying information will be kept separate from data used for analyses. Results may be written up and presented at local or national conferences, and may be
published in journals. No specific identifying patient information will be reported with any form of presentation that results from this study.

*Tissue banking*: No existing specimens will be used, and there will be no tissue banking.

*Risks, benefits, and alternative treatments*: Risks of the surgery are minimal and participating in this research does not cause any additional risk.

There are no additional benefits for participating in this research. Results of this study may add to the body of knowledge about PKA and its efficacy.

Patients may choose not to participate in this research.

*Arrangement to minimize harm/risks*: Risks are minimal, and there will be no additional arrangements to minimize risks.

*Reasonableness of risks re: potential for subject’s benefit*: Risks are minimal.

*Costs to subjects and extra costs to third party payors*: No extra costs will be incurred by subjects or third party payors.

*Consent procedure*: Participants will be consented for the research at the same time consent is obtained for their rhytidoplasty procedure. Personnel will be present to answer any questions the patient might have.

*Consent document*: Please see attached ICF dated 08-28-13.

*Attachments*: Please see attached QoR-40 questionnaire.


