Statistical Analysis Plan

**Effect of Perioperative Gabapentin Use on Postsurgical Pain in Patients Undergoing Head and Neck Mucosal Surgery**

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# 1. Introduction

## 1.1 Background

Otolaryngology patients often undergo painful and functionally debilitating operations of the head and neck because of the neuroanatomy of this region. As a result, they are at increased risk for developing persistent postsurgical pain, dysphagia, and other complications. Effective management of acute postoperative pain reduces postoperative morbidity, increases patient satisfaction, shortens hospitalizations, and reduces hospital costs. Narcotic medications used to treat postsurgical pain are associated with constipation, nausea, and long-term addiction. Optimizing pain control to improve recovery and avoid overuse of narcotics is an important postoperative goal.

Multimodal therapy, a widely accepted practice within pain management, uses nonnarcotic medications to improve pain and decrease narcotic requirements. Various surgical cohorts have demonstrated the benefits of multimodal therapy in acute postoperative pain. For instance, Gabapentin, a medication that targets neuropathic pain, has been investigated as a postoperative pain adjunct.

## 1.2 Study Objectives

The goal of this study is to investigate gabapentin use in patients undergoing larger head and neck mucosal operations associated with significant risk of postoperative pain and dysphagia.

## 1.3 Study Design

## In this double-blinded, placebo-controlled randomized clinical trial, 250 adults were screened for participation. Then we need to eliminated the patients with inappropriate surgery, prior gabapentin use, baseline chronic pain, or outpatient surgery status. The final participants are patients 18 years or older with a glomerular filtration rate of greater than 30 mL/min/1.73 m2, no history of dementia, no history of chronic pain (defined as ≥6 months of pain or current pain unrelated to their index case), no current gabapentin use, and at least 1 night of inpatient admission planned were included.

## Participants were randomly assigned to the gabapentin or the placebo group using a computer-generating scheme with blocks of varying sizes. Participants received liquid gabapentin, 300 mg, or an equivalent volume of placebo twice daily per tube or orally from July 25, 2016, through June 19, 2017. Days in the study were termed postoperative days (PODs) 0 (date of procedure) through 3 (last day of participation possible), and participants remained in the study up to POD 3 as long as they remained admitted and had no reason for study withdraw.

Adverse effects associated with gabapentin, including dizziness, sedation, and nausea or vomiting, were elicited with each VAS score. Participants were followed up for adverse effects for 30 days after enrollment.

Self-reported baseline pain and perceived opioid effectiveness were elicited from participants at enrollment using a short questionnaire asking participants to circle yes or no to the presence of daily pain aside from their head and neck condition and to rate narcotics as not at all effective to extremely effective. Overall severity of comorbidity was captured using the Adult Comorbidity Evaluation-27.

1.4 Sample Size Estimation

Sample size calculations were based on a study of the use of gabapentin in patients undergoing tonsillectomy.20 With use of relevant estimates from that study, it was determined that approximately 46 individuals per group (92 total) were sufficient to detect a difference of 20% or greater in mean morphine dose (effect size d = 0.6) between the placebo and gabapentin groups with an 80% power and a 2-sided α threshold value of .05.

# 2. Analysis Sets

## 2.1 Full Analysis Sets

The main outcome will be performed an intend-to-treat analysis.

## 2.2 Safety Analysis Sets

Safety analysis for adverse effects was undertaken after 50% enrollment was achieved and again at study completion. Masking was maintained for the safety analysis.

# 3. Endpoints

## 3.1 Primary Endpoints

The primary study endpoint is postoperative narcotic consumption. Average daily narcotic use from postoperative admission to the last dose of pain medication on POD 2, or the day of discharge, whichever comes sooner, will be calculated. Total amount of narcotic use in morphine equivalents will be divided by the total hours of inpatient hospitalization, multiplied by 24 hours, to obtain the average daily narcotic consumption.

## 3.2 Second Endpoints

The secondary endpoints include (a) subject satisfaction with pain control, (b) VAS pain scores, (c) patient baseline pain perceptions (d) hospital length of stay, and (e) potential side effects of the medication.

* (a) Subject satisfaction with pain control will be captured in a survey administered at POD 2 after the AM dose administration, or after the AM dose administration on the day of discharge, whichever comes sooner.
* (b) VAS pain scores will be assessed 45min to 1 hour after surgery and then three times a day on POD 1-2 and once on POD 3, or until day of discharge, whichever comes sooner. A standardized VAS form will be given to subjects with verbal instruction to first ―mark on the line the point that you feel represents your current pain level when you’re resting. This is followed by asking the subject to gesture swallowing and ―mark another point on the line that represents your pain level when you swallow. Lastly, the subject will be asked to cough and to ―mark the final point on the line that represents your pain when you cough. The study team member administering the test will annotate what each mark represents (rest, swallow, and cough). The scale contains a 10-cm line from ―no pain on the left to ―extreme pain on the right. The distance in centimeters from the left of the line to the center of the patient’s three marks will be recorded. The results from all available VAS scores for each subject will be averaged and included in the final analysis.
* (c) The subject’s belief in pain medication efficacy and pain tolerance will be assessed from a short survey obtained preoperatively during the office visit.
* (d) Hospital length of stay will be calculated for each subject.
* (e) During the VAS scores, study team members will also collect information about potential medication side effects, including those that are commonly associated with gabapentin or with narcotic medications.

## 3.3 Primary Safety Endpoints

The primary safety endpoints are the rate and severity of drug-related adverse events. Adverse events will be monitored and recorded by study team members during subject inpatient stay. These events will be reviewed by the principal investigator and categorized into drug-related, likely drug-related, and unlikely drug-related. Any significant adverse events determined to be likely drug related will be reported to the OHRP within a 24 hour time period and stopping the study for the subject will be discussed. A safety meeting will be held half way through the study with the PI and all involved faculty mentors to determine if an interim analysis is necessary. This analysis would be considered necessary if a significant number of adverse events likely related to the study medication were occurring, and an analysis to make sure the study was not causing harm to the treatment group was needed.

# 4. Hypotheses

# For parametric data, mean differences and 95% CIs were calculated, the hypothesis is: the mean difference equals to 0.

# For nonparametric data, median differences and 95% CIs were calculated, and the hypothesis is: the median differences equals to 0.

# All statistical tests were 2-sided and evaluated at an α level of .05. SAS statistical software, version 9.4 (SAS Institute Inc) was used for all statistical analysis.

# 5. Handling of Missing Values

# For the subjects who do not complete the trial, we would use the last observation carried forward (LOCF) method.

# 6. Statistical Analyses

## 6.1 Statistical Methods

Descriptive statistics will be used to describe distribution of demographics. Bivariate analysis using independent samples t-test for continuous variables and chi square test for categorical variables will be used to compare distribution of characteristics between treatment groups to ensure successful randomization.

The primary and secondary outcome measures will be compared between the two treatment groups via bivariate analyses. In addition, a General Linear Model (GLM) approach will be used to explore the impact of gabapentin as compared to placebo on each of the outcomes of interest after controlling for potential cofounders that were unevenly distributed between the two groups. The estimated mean difference and 95% confidence interval will be reported.

## 6.2 Primary Analyses

Primary outcome was the difference in mean per participant per group narcotic use per hour in oral morphine equivalents. Mean differences and 95% CIs were calculated for parametric data, and median differences and 95% CIs were calculated for nonparametric data.

## 6.3 Secondary Analyses

Secondary outcomes included VAS scores, patient satisfaction with pain control, and adverse effects. A hierarchical mixed model analysis with participant as the random factor was used to analyze VAS scores. This analysis makes maximum use of the data available at any time point without using a list-wise exclusion approach and allows for exploration of the time by group interaction both within and between participants. That is, this analysis explored changes in VAS scores between the 2 treatment groups across different time points.

# 7.Reference

https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2678656