Guanfacine for PONV and Pain After Sinus Surgery

Version: March 10, 2016

NCT #: NCT02882854

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STUDY SCHEMA

PRE-OP	SURGERY	EMERGE	PACU
Consent	Tot GA time	Extubate	Max nVRS
Demographics	#pressors	Transport	PONV Tx
Study Drug/placebo			Max pVAS
			Total ME
			PACU LOS

After meeting I/O criteria pre-operatively, patients will hear a brief description of the study (guanfacine for PONV). If they are interested, potential participants will be given a consent to read and ask questions. After all their questions have been answered, they will sign the consent if they wish to participate. Study drug will be administered with a few sips water. IV pre-med should consist of no more than 2 mg midazolam.

Total time under general anesthesia (induction to extubation) will be recorded along with the number of times pressors are administered. No non-depolarizing muscle relaxant will be administered to avoid the need for reversal agents and the associated confounding factor.

In PACU, the maximum nausea score (nVRS) 0-10 will be recorded, where 0 = none and 10 = maximum, along with the number of times an anti-emetic is required. Maximum pain score (VAS) along with morphine equivalents will also be recorded. PACU length of stay (LOS) will also be recorded. PACU times may be obtained from the PACU records.

Abstract

Postoperative nausea and vomiting (PONV) and post-op pain are the most common problems after all types of surgery and the two major factors delaying post-anesthesia care unit (PACU) discharge. PONV has an incidence of 20-30% if untreated. Pain after surgery is commonly treated with narcotics which can potentiate PONV, further delaying PACU discharge. In multiple studies, alpha-2 agonists such as clonidine and dexmedetomidine reduce both the incidence of PONV and post-op pain, as well as requirements for postoperative analgesics. These actions are mediated via central alpha-2A receptors (A2AR). Of the A2AR agonists, guanfacine (GF), though a weak antihypertensive agent, has the highest selectivity for the A2AR, but to date is untested for its potential to treat either PONV or post-op pain. In this double blind, placebo-controlled study, we will evaluate oral guanfacine versus placebo in patients undergoing sinus surgery for its potential to reduce PONV and pain in the PACU.

Background

Postoperative nausea and vomiting (PONV) and pain are the most common causes of Post Anesthesia Care Unit (PACU) discharge delay, with untreated PONV occuring in 20-30% of post-surgical patients. [1] In addition to the immediate discomfort, patients who suffer with these symptoms may develop maladaptive behavioral changes. Furthermore, managing PONV and pain increases PACU staffing requirements and the direct cost of care.

Because of the published efficacy of alpha-2 agonists in reducing PONV and pain, anesthesiologists at Vanderbilt University Medical Center commonly employ oral, generic off-label guanfacine (GF) pre-operatively with a perceived reduction in these symptoms.

1.0 Rationale and Specific Aims

In efforts to improve the postoperative course of their patients, anesthesiologists have administered several medications with mixed results. Propofol, ketamine, lidocaine, and opioids have been shown to have varying effects in reducing (and sometimes increasing) PONV and pain in the PACU. Over the last few years, alpha-2 adrenergic receptor (A2-AR) agonists have gained popularity as effective agents for reducing these symptoms. By more selectively targeting the A2AR, Dexmedetomidine (DEX) reduces PONV, pain and anxiety with greater hemodynamic stability, but at significantly greater cost. Guanfacine (GF) is the oldest A2-AR agonist in clinical use in this class and the least expensive (10¢/mg). Also, GF is the most highly selective for the

alpha-2A receptor subtype [2] and the least sedating. [3] GFs effects on PONV and pain are unstudied, but it has been used orally for more than 35 years for hypertension, and more than 20 years for managing ADHD. [4]

2.1 PONV

In preventing PONV, [5] the mechanism of the A2-AR agonists is not perfectly clear, though both CL and DEX have vagolytic, anti-dysrhythmic effects [6] as well as concomitant anti-sialagogue and airway drying actions. These effects likely arise from brainstem actions at A2-AR in the dorsal motor nucleus of the vagus, the area postrema, and the nucleus tractus solitarius. [7]

2.2 Pain

Both CL and DEX are well studied for pain management, with actions on brainstem and spinal dorsal horn A2-AR. Mechanisms [2] include a reduction of central sensitization and upregulation of NO synthase. [8] Furthermore, as a result of the presence and similarity of mu opioid and A2-AR (both Gi/o GPCRs) in locus coeruleus, cross reactivity of the natural ligands at these receptors in LC likely confers (via GIRK channels) the A2-AR descending central analgesic effects. [9]

2.4 Previous Studies

Zhao, *et al*., [18] recently studied 90 patients, 30/group, undergoing thyroidectomy and receiving intraoperative infusions of either 0.4 or 0.8 mcg/kg/hr DEX vs placebo. The DEX groups had ~1-3-fold lower pain scores (VAS: 0.4 group: 1.50+/-0.52; 0.8 Group: 0.80+/-0.63 vs. Placebo 2.50+/-0.52) in the PACU, as well as a substantially lower incidence of PONV (0.4 Group: 3.3%; 0.8 Group: 0%; Placebo: 13.3%). In a systematic review and meta-analysis of 30 studies of perioperative A2-AR agonist use (aggregate 1,792 pts, 933 receiving DEX or clonidine), Blaudszun et al. validated the use of alpha-2 agonists in the reduction of postoperative pain (and reduced opioid requirements) and PONV at one hour, without prolonging PACU times. [19] Tufanogullari et al. also showed that dexmedetomidine reduced total morphine equivalents as well as nausea based on an 11-point verbal rating scale (VRS).

The effectiveness of GF in reducing Post-op pain and PONV has never been studied. However, since GF is the most selective A2-AR agonist in clinical use, we believe the reduction of postoperative pain and PONV seen with clonidine and dexmedetomidine can be reproduced (and potentially surpassed) with GF.

2.5 Hypothesis

As a primary endpoint, we hypothesize that patients undergoing a standardized general anesthetic for sinus surgery and are randomized to receive GF vs Placebo will have 20-30% lower PONV scores in PACU, as measured by the 10-point nausea scale (nVRS) previously used in other studies. Secondarily, we hypothesize that patients receiving GF will have less pain as measured by visual/verbal analog (VAS) scores and total morphine equivalents (ME) administered in PACU than patients receiving placebo, without significant hemodynamic instability.

3.0 Inclusion/Exclusion Criteria

3.1 Inclusion Criteria

- VUMC patients undergoing sinus surgery in MCE OR.
- Adults aged 18 and older

3.2 Exclusion Criteria

- Patients who do not meet the inclusion criteria
- Inability to read and freely consent
- Patients who take alpha-2 agonists routinely (guanfacine, clonidine, tizanidine)
- Patients undergoing sinus surgery planned for greater than 3 hours
- Patients with significant pre-existing pain, on chronic pain (opioid, methadone) therapy, severe fibromyalgia or other pre-existing pain condition in any body part
- Patients with pre-op nausea/vomiting at baseline.
- Pregnant or lactating women.

4.0 Enrollment

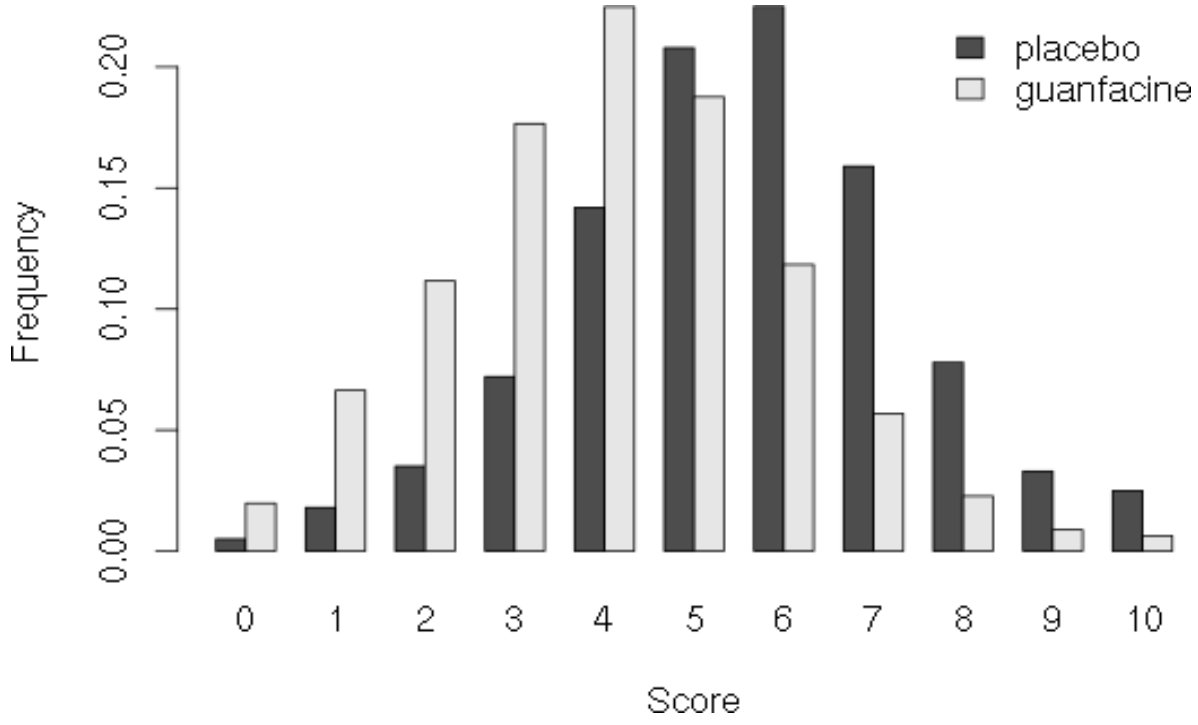
Patients identified as candidates by primary criteria (above inclusion/exclusion listing) will be interviewed immediately prior to surgery to determine suitability and patient willingness to participate in the study. After receiving complete information and a description of the study, patients accessioned will give written consent. On pre-op administration, Pt. Name, MRN and Study Drug Envelope Number (SDE#) will be logged into the Study Database in REDCap and reported directly to IPS with a completed Study Drug Administration Sheet, either by hand or by FAX.

5.0 Study Procedures

5.1 Statistical Analysis and Power

The effect of guanfacine administration on pain and nausea scores will be assessed using proportional odds logistic regression. The odds of greater pain or nausea associated with guanfacine administration will be summarized using the odds ratio and Wald-type 95% confidence interval and Wald test against the null hypothesis of no effect (odds ratio equal to one).

The study design and testing procedure were simulated to study the statistical power. The distribution of pain and nausea scores in the placebo and guanfacine groups were assumed to have the distributions illustrated in the figure below, which correspond to a difference in mean score of 1.5 points, or an (ordinal) odds ratio of 0.25. Taking this as the minimum detectable effect, **80** randomized subjects are needed to achieve 90% power.



5.2 RANDOMIZATION

Subjects will be randomized to one of TWO GROUPS: **Group A**: Forty (40) patients will receive GF 1 mg orally; OR, **Group B**: Forty (40) patients will receive a similar appearing placebo (containing no drug) from numbered study drug envelopes (SDE) prepared by Vanderbilt's Investigational Pharmacy Service (IPS) which will independently randomize the drug envelopes and maintain the Master Drug Study Log.

5.3 POWER ANALYSIS

5.4 STUDY METHODS

5.41 PRE-OP

a. Consent; Demographics; [25]

b. NO PRE-OP ADJUNCTS

Ketamine, gabapentin, acetaminophen, droperidol, promethazine, haloperidol, other buterophenones or phenothiazines **will not be administered**.

5.42 ANESTHESIA MANAGEMENT

The general anesthetic administered will be standardized as follows:

a. **Premedication**: Midazolam 0 - 2 mg IV
b. **Induction:** Fentanyl: 0.5-2 mcg/kg; Lidocaine: 1-2 mg/kg; Propofol: 1-3 mg/kg; SUX: 0.5-1.5 mg /kg
c. **Maintenance:** with inhalational agent and hydromorphone.
d. **Emergence**: Hydromorphone in 0.25 mg increments as deemed appropriate by anesthesia team and a standardized dose of ondansetron (4 mg) in keeping with routine practice.

5.43 PACU: Hydromorphone for pain and ondansetron for PONV per standardized order set will be administered and documented. IV fluids and oxygen may be continued as long as deemed useful by the PACU and Study staff.

5.5 POST-OP:

A. PONV will be quantified by the maximum nVRS.

B. PAIN will be evaluated by the maximum Verbal Analog Scale (**VAS = 0 – 10: See Fig. 6**).

C. PACU LOS will be the duration of PACU Length of Stay

5.6 DATA COLLECTION (See Data Sheet and Data Dictionary)

A. STANDARD ANESTHESIA PRE-OP ASSESSMENT

B. ANESTHESIA RECORD COPY

C. COPY OF SIGNED PATIENT CONSENT FOR STUDY

D. PATIENT DATA SHEET, (PDS) including Transition Times:

1. Planned Surgical Procedure, Duration
2. Demographics (age, height, weight, etc.)
3. **Nausea score (nVRS) and rescue Tx** in PACU
4. **Pain Scores (VAS) and Tx** in PACU
5. **PACU LOS**

5.7 STUDY CONDUCT:

5.71 PRE-OP: After soliciting interest and enrolling, **written consent** will be obtained and basic patient data and pre-op assessments (Apfel Score **Fig 2**) performed. Patients will receive GF or placebo orally from a numbered envelope prepared by the IPS in a blinded manner. Patients will then undergo a standardized general anesthetic as described above. At the conclusion of the sinus procedure, patients will be extubated as per routine management and assessed immediately with:

5.72 In PACU, assess the following endpoints:

A. Max Nausea score (nVRS)

B. PONV Treatment(s)

C. VAS (Fig 6): Assess Pain score (Verbal Analog Scale rated 1-10) at 10 and 60 min after PACU arrival

D. Pain TX: Total Narcotic requirement in PACU (Tallied in Morphine Equivalents for PACU stay)

E. PACU LOS

6.0 RISKS

Both PONV and post-op pain are expected risks after surgery. The risk of the use of GF include modest hypotension and sedation. Coincident to the study, patients will be undergoing sinus

surgery, but there will be no medical procedures performed on patients as part of the study. To protect the patient's confidentiality, only a limited data set will be created. The PI will check the data for completeness after it's been collected/extracted/collated and verify that all subject identifiers except those listed in the limited data set are destroyed once the study is concluded. All data will be stored on a password-protected server in a locked area of the VUMC Department of Anesthesiology. This data will only be accessible by the PI and KSP.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events will be monitored throughout the study. These may include any occurrence within the study setting (surgery itself or the conduct of the anesthetic), such as unexplained changes in vital signs, unexpected surgical complications, prolonged PACU stay, etc. ***Protocol deviations*** will be reported separately per VHRPP guidelines. The PI of this study will report adverse events to the IRB per VHRPP reporting guidelines.

8.0 Study Withdrawal/Discontinuation

8.1 Withdrawal. After Study Drug administration, this study involves only assessment for nausea and vomiting (nVRS) and pain (VAS) in the surgical setting of sinus surgery. After patients have been enrolled and consented, it is not anticipated that patients will voluntarily withdraw. Nevertheless, patients are free to withdraw at any time, simply by telling one of the study physicians/managers. However, after enrollment and initial pre-op study assessment, patients may withdraw up to the point of anesthetic induction and surgical procedure, and thereafter, may only withdraw when fully awake and alert in PACU.

8.2 Discontinuation. This study is designed as intention-to-treat, so once subjects have taken the Study Drug, they will be followed per protocol through completion, or up to any time they choose to withdraw or any unspecified Adverse Event that would halt normal data collection. In either event, data obtained to that point in the protocol would be included in the total dataset, with reporting of the withdrawal or AE as noted above.

9.0 Privacy/Confidentiality Issues

All reasonable efforts will be made to keep a patient's protected health information (PHI) private and confidential. Patients will be assigned a code to replace names. There will be limited access to medical records and a limited data set created. Federal privacy guidelines will be followed when using or sharing any protected health information.

Data will be stored in secured areas on password protected Vanderbilt PCs conforming to the latest Vanderbilt IS security policies. Computer databases will be maintained on password protected Vanderbilt PCs. REDCap (see below) servers are housed in a local data center at Vanderbilt, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Vanderbilt researchers by both our Privacy Office and Institutional Review Board. All study staff have completed employee education regarding patient confidentiality and have completed Human Subjects protection education (CITI course) as specified by the VHRPP.

10.0 Follow-up

The Perioperative Clinical Research Institute (PCRI) will retain research Records for a period of six (6) years after the submission of the final report and closeout procedures on the research project for which the Research Records were prepared. Paper copies of the research records and/or research consent will be held in a secure access area determined by of the Department of Anesthesia (PCRI) for 6 years. Any research data that is put in the participants medical record will be kept for an unknown length of time.

11.0 Record Retention & Data Management

The retention of the original Research Records will be the responsibility of the Principal Investigator on behalf of PCRI, but at all times shall remain the property of PCRI, unless otherwise specified by law, regulation or agreement. The Vanderbilt University Office of Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) is a secure, web-based application that is

flexible enough to be used for a variety of types of research. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). In addition to traditional data capture functionality, all data collection projects rely on a thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process. This iterative development and testing process results in a well-planned and individualized data collection strategy.

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13.0 Testing Regimens

Fig 3. Verbal/Visual Analog Pain Score (VAS) [29]:

NO PAIN ----------WORST PAIN

0-------1-------2-------3-------4-------5-------6-------7-------8-------9-------10

At 10, 30, and 60 min after PACU arrival ask patient to verbally score their pain on this scale.

Data Dictionary-

1. **Patient Data Sheet**, (PDS) will include all data collected on each individual:
   - **A. Planned Surgical Procedure** (all sinus surgeries not greater than 3 hours)
   - **B. Demographics**: Data identifying characteristics of each patient, including Age, Gender, Height, Weight, MRN, etc.)
2. **POST-OP:**
   - **A. Anesthetic Duration** – Difference between induction and extubation recorded in the Anesthesia Record; PACU Entry Time
   - **B. PONV** will be quantified by a Nausea Verbal Reporting Scale (nVRS), 0-10
   - **C. PAIN** will be evaluated by Verbal Analog Scale (VAS = 0 – 10). (See Fig. 3)
   - **D. PACU LOS**