Nitrous Oxide and Post-Operative Nausea and Vomiting: A Randomized Controlled Trial

Thesis

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Abstract

Purpose: To investigate the degree of postoperative nausea and vomiting (PONV) experienced in two different groups of patients having general anesthesia, one with 50% nitrous oxide in the administered gas mixture and one without nitrous oxide.

Methods: Twenty adult volunteers, American Society of Anesthesiology (ASA) physical classification I-II and aged 18-32 years, who had previously consented to oral & maxillofacial surgery with general anesthesia at The Ohio State University Oral & maxillofacial Surgery Department, were invited to participate in this clinical research study. Two general anesthesia groups were used: Nitrous Oxide Group – 50% nitrous oxide, sevoflurane, and oxygen; and Control Group – oxygen and sevoflurane. Subjects were divided into the 2 groups via systematic random assignments. Patients were induced for general anesthesia with propofol 2mg/kg IV, fentanyl 0.5mcg/kg IV, and succinylcholine 1 mg/kg IV. Following induction, all subjects were intubated and administered dexamethasone 4 mg IV. Following emergence from general anesthesia, the patients were transferred to the Post Anesthesia Care Unit (PACU). No additional antiemetics were administered prior to arrival and assessment in the PACU. Patients’ incidence of vomiting and self-reported nausea scores were recorded using a Verbal Numeric Rating Scale (VNRS) with a range of 0-10 every 15 minutes from the arrival to PACU until discharge, for a minimum of 60 minutes. A rescue antiemetic was
administered for any episode of vomiting or nausea score equal to or greater than 5 out of 10.

Results: Demographic data and duration of anesthesia were analyzed between groups and found to have no statistically significant difference. There was a significantly higher maintenance concentration of sevoflurane (p=0.015) required in the Control Group when compared with the Nitrous Oxide Group. There was no statistical difference in the patient’s VNRS scores between groups at any 15 minute time interval during the 60 minute recovery period (p=0.098).

Conclusion: The addition of 50% nitrous oxide to an inhalational anesthetic of sevoflurane and oxygen showed no increased incidence of PONV in patient’s having a general anesthetic for routine oral & maxillofacial out-patient surgical treatment (p=0.098). As expected, there was an increased requirement of sevoflurane in the Control Group (p=0.015). There was no difference in duration of anesthesia or demographics between groups. The data collected in this study indicates there may be no detrimental increase in PONV following general anesthesia maintained with volatile inhalational agents and nitrous oxide.
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Introduction

Nitrous oxide is an inhalational agent that has long been used to produce analgesia, anxiolysis, and sedation, either as a lone standing agent or as an adjunct to other general anesthetic agents, without producing the significant vasodilatory and cardiac depressant effects of other inhalational anesthetics (Barash et al., 2013). Nitrous oxide has the benefit of decreased solubility in the blood, fat, and other body tissues, allowing for faster onset of and emergence from anesthesia. This is particularly helpful in decreasing anesthesia time and reducing the incidence of post-operative sedation due to inhalational anesthetic that remains in the body.

Post-operative nausea and vomiting (PONV) is one of the most common side effects following general anesthesia, affecting 20-30% of all surgical patients (Apfel et al., 2012; Lee et al., 2015) and up to 40% of patients undergoing orthognathic surgery (Silva et al., 2006) experiencing PONV in the first 24 hours following surgery. It is important to note, that patients in both studies received significant levels of narcotic pain medication during this 24 hour period. No literature was able to be found on the incidence of PONV and dentoalveolar procedures. Several risk factors for PONV have been identified in the literature including previous PONV, history of motion sickness, young adult and middle aged patients, female gender, and non-smoking status (Apfel et al., 2012). Several anesthetic factors can also increase incidence of PONV, including use of inhalational anesthetics, narcotics, and psuedocholinesterase inhibitors for reversal of paralytic agents.
The surgical procedure can also greatly influence the rate of PONV; procedures that involve the intracranial fossa, the inner ear, manipulation of the bowels (Barash et al., 2013), or procedures that lead to ingestion of significant amounts of blood (Tolasov et al., 2016) can increase the incidence of PONV. In addition to a negative patient experience, it can lead to prolonged PACU stays and overnight hospitalizations, decreased ambulation following surgery, decreased nutritional intake, and electrolyte imbalances.

Current research is divided on whether or not nitrous oxide causes PONV, particularly at concentrations of 50% or less (Apfel et al., 2012; Barash et al., 2013; Fernandez-Guisasola et al., 2010; Ichinohe & Kaneko, 2007; Leslie et al., 2008; Park & Cho, 2011). Very little research has been completed comparing PONV between volatile inhalational agents with and without 50% nitrous oxide. A recent research study compared PONV levels following the administration of 50% nitrous oxide with a propofol infusion to a propofol infusion alone and found no statistically significant difference in the incidence of PONV (Ichinohe & Kaneko, 2007). This study only included 24 total patients and stated that a power analysis should be conducted to find a population large enough to confirm this conclusion (Ichinohe & Kaneko, 2007). It should also be noted that propofol has known antiemetic effects and may have masked the influence of nitrous oxide on the incidence of PONV. In addition, this study did not investigate the use of nitrous oxide in conjunction with other inhalational anesthetics; a commonly practiced anesthetic technique. Many anesthesiologists now avoid the use of nitrous oxide due to the increased risk of PONV, despite the paucity of evidence supporting this assertion. The depth of anesthesia is then maintained by increasing the concentration of other
inhalational agents, or administering higher doses of narcotics- which are known to increase PONV.

Particularly unclear is the impact of nitrous oxide on PONV during procedures not involving the manipulation of abdominal structures. Such manipulation finds a high association with an increased incidence of PONV (Barash et al., 2013). Additionally, the majority of these studies administered 70% nitrous oxide, the highest concentration of nitrous oxide that can be administered in modern anesthetic machines, and did not investigate the impact a lower concentration may have on PONV (Fernandez-Guisasola et al., 2010). The ENIGMA-I study investigated the levels of PONV in patients of various health status and age undergoing a wide variety of procedures including abdominal surgery. This study did not control for the concentration of nitrous oxide used, the administration of antiemetic treatment, either intra- or post- operatively, the administration of narcotics, a class of medications well known to cause nausea and vomiting, or the administration of neuromuscular blockers requiring reversal agents (Leslie et al., 2008). While many procedures require titration of these medications known to increase PONV, dentoalveolar and oral & maxillofacial surgeries are optimal procedures to study PONV as they do not require paralysis, are of similar procedure duration, and can readily incorporate local anesthesia into the surgical technique, thereby reducing the need for intraoperative and postoperative opioid administration for pain control.

Finally, the ENIGMA-II study is currently investigating the perioperative cardiac risk of patients undergoing non-cardiac surgery with and without nitrous oxide. Preliminary
data suggests that the addition of nitrous oxide to general anesthesia does not increase the risk of adverse cardiac events in patients with a history of cardiac disease, and may in fact have cardio-protective effects (Leslie et al., 2015). The benefits provided by nitrous oxide include that it permits an easily adjustable level of anesthetic, it is easily administered and rapidly titratable to variable levels of anxiolysis and analgesia, it has a faster onset and wake up without the excessive and negative cardiovascular side effects seen in other inhalational agents, and it is cost effective. Combined, these attributes make nitrous oxide an excellent adjunct to general anesthesia and warrant further investigation of its role in PONV in dentoalveolar and oral & maxillofacial procedures.

This study compared the degree of patient’s self-reported PONV following intubated general anesthetics maintained with inhalational agent with or without 50% nitrous oxide in oral & maxillofacial procedures. The following parameters were investigated:

- Subject’s self-reported degree of nausea
- Occurrence of vomiting
- Post-operative rescue antiemetic requirement
- Post-operative opioid administration
- Required maintenance concentration of sevoflurane

The following statements comprise the null hypotheses:

- There is no difference in subjects’ self-reported degree of nausea or episodes of vomiting between the Control Group - general anesthesia maintained with sevoflurane and oxygen alone - and the Nitrous Oxide Group - general anesthesia maintained with sevoflurane, oxygen and 50% nitrous oxide.
The Control Group requires a maintenance concentration of sevoflurane greater than or equal to the Nitrous Oxide Group to maintain general anesthesia.
Methods

Study Procedure

After approval from The Ohio State University Human Subjects Review Committee, 20 patients were enrolled to participate in this single-blinded randomized controlled clinical investigation. All patients were aged 18-32 years old, able to consent for themselves, American Society of Anesthesiologists (ASA) classification I or II, and scheduled to receive oral & maxillofacial treatment under general anesthesia. Patients who received antiemetics, psychoactive drugs, steroids, or opioids in the preceding 24 hours were excluded from the study due to their potential to affect the incidence of nausea and vomiting. Additionally, patients who were pregnant, receiving procedures involving the inner ear or intracranial fossa, prisoners, and patients who were unable to consent for themselves were excluded from participating.

Patients at The Ohio State University Department of Oral & Maxillofacial Surgery, already consented for necessary oral & maxillofacial surgery with general anesthesia, were screened by the investigator following their consultation appointment. Those who met the inclusion criteria were introduced to this study and offered the opportunity to participate in this research project. Patients expressing interest in being involved in this study were given the opportunity to read the IRB approved consent form and have any questions they asked fully answered. Patients who volunteered to participate in this study
were then given the IRB approved consent forms to review and sign to document their active study participation. Patients were able to withdraw their participation at any time without affecting their surgery schedule or general anesthesia treatment. There were no incentives for participation in this study.

To minimize systematic error and bias, the subject and the researcher collecting data were blinded to the anesthesia group assignment. A study size of 88 was recommended to evaluate the degree of PONV following general anesthesia with nitrous oxide for oral & maxillofacial procedures. The sample size was recommended following the performance of a power analysis based on data from similar study models found in the literature. It was calculated that a study size of 88 was needed to detect a difference of 2 on the VNRS scale with alpha set at 0.05.

On the day of surgery, consents were reviewed and willingness to participate confirmed. The past medical history was reviewed and updated as needed. Patients were then asked to complete a short questionnaire (Figure 1) to identify common risk factors cited in the literature for PONV (Apfel et al., 2012). Following completion of this paperwork patients were escorted to the operating room (OR) for treatment.

Venipuncture was performed to obtain peripheral intravenous (IV) access. Standard ASA monitors were placed, including pulse oximeter, electrocardiogram, end-tidal gases, non-invasive blood pressure monitoring, and temperature. Patients were pre-oxygenated and IV induction was performed with fentanyl 0.5 mcg/kg IV, propofol 2 mg/kg IV, and succinylcholine 1 mg/kg IV. An appropriately sized cuffed nasal endotracheal tube was placed and secured. Proper tracheal positioning of the tube was confirmed by bilateral
auscultation of lung sounds and end-tidal CO₂ sampling. General anesthesia was maintained based on group assignment according to the following protocols:

- **Nitrous Oxide Group**: General anesthesia maintained using 50% nitrous oxide and oxygen as a carrier gas and sevoflurane.
- **Control Group**: General anesthesia maintained using 100% oxygen as a carrier gas and sevoflurane.

Each group received dexamethasone IV 4 mg immediately following induction. Appropriate antibiotics were given and recorded on the Pre-PACU Data Collection Form (Figure 2) as required for the procedure and determined by the oral surgery team.

Surgical procedures included third molar extractions, full mouth extractions, Tori removal, dentoalveolar cyst biopsies and decompression or removal, and dental implant placement. Local anesthetic at the surgical site was given at the discretion of the surgical team, as required by the procedure, and the planned treatment was then completed. The amount and type of local anesthetic was recorded on the Pre-PACU Data Collection Form (Figure 2).

Following completion of treatment, patients were extubated and then transported to the PACU under continuous pulse oximetry monitoring, until adequately recovered.

Supplemental oxygen was delivered for patients with pulse oximeter oxygen saturation levels <95%. A pain management protocol was established for use in the PACU if required. This consisted of 5 mcg/kg IV hydromorphone bolus, a minimum of 15 minutes apart, as needed. Amounts and times of rescue pain medication administration in the PACU were also recorded on the PACU Data Collection Form (Figure 3).
The occurrence of vomiting and the self-reported degree of nausea were recorded on the PACU Data Collection Form (Figure 3) using a Verbal Numeric Rating Scale (VNRS) (Figure 4) upon arrival to PACU and every fifteen minutes thereafter, for a minimum of 60 minutes. The scale was anchored at 0 corresponding to no nausea and 10 corresponding to severe nausea.

To ensure a more homogenous treatment of nausea and vomiting, to enable a better assessment and understanding of the potential improvement the tested regimen may have offered, and to permit optimal comparison of medication efficacy between test groups, the antiemetic medications administered in the post-operative period followed a set protocol. For all rescue antiemetics administered in the PACU, the dose, time of administration, and number of antiemetic doses needed were recorded on the PACU Data Collection Form (Figure 3).

This simplified protocol was developed to follow very common approaches used in hospital PACU environments as follows:

1. Ondansetron 4 mg IV given as the initial rescue antiemetic for a score of 5 or higher on the VNRS.

2. Promethazine 6.25 mg IV was given as the second rescue antiemetic for a VNRS score of 5 or higher, at any time point 15 minutes or longer following the initial rescue antiemetic treatment.
Post anesthesia care adhered to standard PACU recovery guideline, and after meeting standard discharge criteria assessed by achieving a modified Aldrete score of 9 out of 10, patients were permitted to return home in the charge of an approved care giver.

Data Analysis

To minimize systematic error or bias in this experiment, the subject was blinded to the anesthetic technique. The researchers collecting the VNRS data was also blinded to the anesthetic technique used. It was not possible to blind the anesthesiologist to the anesthetic technique. For calibration purposes, one anesthesiologist performed the general anesthetic for all subjects, and the VNRS data was collected by 3 trained and calibrated data collectors. All data was decoded prior to sending to the statistician for analysis.

Measurements collected and used for statistical analysis included: anesthesia start time, anesthesia stop time, procedure start time, procedure stop time, maintenance concentration of sevoflurane required for each subject, amount and type of local anesthetic administered, amount and type of antibiotics administered, nausea score and occurrences of vomiting in the PACU at entry and every 15 minutes thereafter until discharge, for a minimum of 60 minutes, need for administration of rescue antiemetic, number of rescue antiemetics doses required, need for postoperative opioid administration, and number of postoperative opioid doses required.

The degree data from the VNRS was analyzed with a repeated measures ANOVA using the methods of maximum likelihood estimation (Hartley & Rao, 1967) and the Satterthwaite degrees of freedom (SAS Mixed Procedure, SAS (R) Proprietary Software
9.3, SAS Institute, Inc., Cary, NC, USA) (Satterthwaite, 1946; Welch, 1947) in order to account for any violations of normality or of assumed equality of variances. The factors analyzed were the anesthesia group, time, and the interactions of these two main factors, where time was treated as a repeated measure. A post hoc G*Power Statistical Analysis power analysis was completed on the VNRS data to determine the sensitivity of this study (Faul et al., 2007). The duration of anesthesia and mean maintenance concentration of sevoflurane, both recorded by the anesthesiologist on the Pre-PACU Data Collection Form (Figure 2), were analyzed using the Student’s T-test. The demographic data the subjects provided on the Nausea and Vomiting Questionnaire (Figure 1) was analyzed in the following ways: sex, smoking status, and history of PONV were analyzed using an Exact Chi-square test; history of motion sickness was analyzed with an Exact Mantel-Haenszel Chi-square test; and age, height and weight were analyzed using a Student’s T-test. An alpha value of 0.05 for any parameter test was considered statistically significant.
Results

Twenty patients completed this randomized controlled trial. The study population consisted of ten females and ten males, five of each per group. The mean age of the study population was 21.5 years with a range of 18-32 years of age. The mean weight for the subjects was 75.2 kg with a range of 51.3-118.3 kg. The mean height was 66.9 inches with a range of 59-74 inches. The procedures included dentoalveolar and oral & maxillofacial procedures not involving the inner ear or intracranial fossa. All patients received local anesthetic for their procedure, which was administered by the surgeon, as appropriate for the procedure, at the surgical site. The mean duration of anesthesia time was 55 minutes with a range of 25 – 92 minutes. Of the 20 subjects, 3 were smokers, 1 reported a history of mild motion sickness, 2 reported a history of moderate motion sickness, and 1 person reported previous PONV with general anesthesia. It is interesting that 2 of the 3 subjects reporting motion sickness, and the subject who reported previous PONV, all reported a score of 0 on the nausea VNRS for all time periods, and were test subjects of the Nitrous Oxide Group.

Each of the demographic data was analyzed between the Nitrous Oxide Group and the Control Group using the Exact Chi-square test to confirm homogeneity of subjects. This analysis found no significant difference in sex, smoking habits, or history of PONV following general anesthesia. The Exact Mantel-Haenszel Chi-square test was used to analyze the history of motion sickness between groups and no difference of statistical
significance was found. A Student’s T-test was used to analyze age, height, and weight, and no significant difference was found between groups in these parameters. A breakdown of all demographic data and their p-values can be found in Table1, and represented graphically in Figure 5 and Figure 6.

The duration of anesthesia, measured from anesthesia start to anesthesia stop, was analyzed using a Student’s T-test and demonstrated no statistical difference between groups (p= 0.626)(Table 2, Figure 7). The required maintenance concentration of sevoflurane was titrated to achieve a 10-20% decrease in preoperative mean arterial blood pressure (MAP) and no movement to painful stimulus. This value was measured from the expired sevoflurane concentration using a Datascope Gas Module SE end tidal gas analyzer. The same anesthesia machine, vaporizer, and gas analyzer was used for all subjects. The results of the Student’s T-test analyzing the required maintenance concentration of sevoflurane indicated that the Control Group required a significantly higher concentration of sevoflurane to maintain general anesthesia (p=0.015) (Table 3, Figure 8).

A total of 7 subjects experienced PONV, 2 patients in the Nitrous Oxide Group and 5 patients in the Control Group. The degree of post-operative nausea experienced was measured five separate times postoperatively: upon arrival to the PACU where the VNRS scores averaged 0 (Nitrous Oxide Group) and 0.5 (Control Group), at 15 minutes after arrival to PACU where the VNRS scores averaged 0.2 (Nitrous Oxide Group) and 0.5 (Control Group), at 30 minutes after arrival to PACU where the VNRS scores averaged 0.3 (Nitrous Oxide Group) and 1(Control Group), at 45 minutes after arrival to PACU.
where the VNRS scores averaged 0 (Nitrous Oxide Group) and 0.2 (Control Group), and finally at 60 minutes after arrival to PACU where the VNRS scores averaged 0.2 (Nitrous Oxide Group) and 0.2 (Control Group). Only one subject stayed in the PACU for longer than 60 minutes; this subject recorded a value of 0 on their VNRS score at 75 minutes. Because there is no other data at 75 minutes for comparison, this data was not analyzed and has been omitted from tables and graphs included in this report. There is large variability of VNRS scores within each group at each measured time, resulting in large standard deviations. It should also be noted that 0 values represent true means of 0. The VNRS data organized by time can be found in Table 4, and is represented graphically in Figure 9. There were no significant differences in the self-reported VNRS nausea levels between the Nitrous Oxide Group and the Control Group (p=0.098), the Times for collection of degree data in PACU (p=0.122), and no interactions between Group and Time were found (p=0.490) (Table 5).

No subjects required rescue antiemetic or rescue pain medications in the PACU. There were no occurrences of vomiting in either group. No patients were required to stay for a prolonged recovery period, or admitted to a hospital.
Nitrous oxide has been used in dentistry for over 150 years. The drug has been well studied as an agent for sedation and anesthesia. Nitrous oxide has many benefits as an adjunct to general anesthesia, including analgesic properties, increased hemodynamic stability, decreased solubility in blood and body tissues which may allow for a faster recovery, and cost effectiveness. The literature has published a number of papers investigating the role of nitrous oxide on PONV. These studies have rarely included dentoalveolar or oral maxillofacial procedures and have often poorly controlled for many factors that could affect PONV and confound the data. We were also unable to find studies that compared maintenance of anesthesia with modern volatile inhalational agents (such as sevoflurane) to maintenance with nitrous oxide in addition to volatile inhalational agents with nitrous oxide administered at 50%. Additionally, the majority of studies have investigated nitrous oxide delivered at a concentration of 70%, the highest concentration available to administer to patients and significantly higher than many practitioners use on a daily basis. This study examined the degree of PONV following intubated general anesthesia using volatile inhalational agents with and without nitrous oxide at a concentration of 50%, a commonly used ratio, while controlling for induction technique, narcotic administration, and antiemetic administration. This study also eliminated the need for short term postoperative narcotic administration and reversal of paralytic agents by administering local anesthetic at the surgical site for pain control.
utilizing a short acting paralytic (succinylcholine) that does not require reversal. This study aimed to eliminate many of the confounding variables that were found in previous studies published in the current literature.

There are many risk factors associated with PONV (Apfel et al., 2012; Lee et al., 2015). This study relied on a self-reported patient questionnaire to identify each subject’s risk factors (Figure 1). The risk factors assessed included patients’ age, gender, smoking status, history of motion sickness, and history of PONV following general anesthesia, all of which are known affect incidence of PONV. This study did not set out to control for preoperative risk factors, however post hoc data analysis showed there was no demographic factor found to be significantly different between groups.

A limitation to this study was that it only monitored patients for 60 minutes following their surgery and anesthetic, a relatively short time frame in which to observe possible incidences of PONV. It is, however, a typical PACU observation time following outpatient general anesthesia, and a time period during which a significant amount of PONV is experienced. This limited time period permitted a more controlled data collection environment, preventing confounding factors such as consumption of the patient’s first meal or home narcotic containing pain medication, both of which may increase the degree and incidence of nausea or vomiting. Although many patients were appropriately recovered prior to the conclusion of the required 60 minute observation period, time for emergence from anesthesia and time when the subjects were initially ready to be discharged from PACU was not recorded or compared between groups. In a future study, it would be interesting to measure recovery using an acuity test, such as a
Trieger test, periodically in the PACU to assess differences in emergence from anesthesia that may be present between groups.

Although the average length of procedure was 55 minutes, it is important to note that the range was quite large, from 25-92 minutes. While this time range is typical for outpatient general anesthetics in the dental field, this is a fairly short time frame for general anesthetics and procedures that occur in other surgical specialties. The current literature suggests that PONV related to nitrous oxide is influenced strongly by the length of exposure to the medication (Peyton & Wu, 2014); therefore this data cannot necessarily be extrapolated to apply to longer procedures. However, it may be interesting and possible to alter this study protocol in the future to use for orthopedic procedures where regional anesthetic blocks are also frequently performed to decrease and possibly eliminate the need for intraoperative and postoperative narcotic administration in the PACU. These procedures, while very similar to those studied in this project, are typically of longer surgical duration and require a longer PACU stay while monitoring recovery from the regional nerve block. This data could possibly be applied to procedures in the medical field of similar duration.

Another major limitation of this study was the sample size. An a priori power analysis of current literature was performed and suggested a study population of 88 subjects, 44 per group, would be required to detect an intergroup difference of 2 on the VNRS at a power of 95% and alpha equal to 0.05. Given time constraints associated with this study it was only possible to recruit 20 subjects. A post hoc sensitivity power analysis was completed and confirmed this study, with a total number of 20 subjects, had a power of 95% at an
alpha of 0.05 and could detect a difference of 0.612 on the VNRS between the 2 groups (Faul et al., 2007). For patients a difference of this magnitude may be clinically significant, with many people opting for the general anesthetic technique with slightly less chance of nausea (~6%). With this study, a difference between groups of 0.612 could be detected if it existed, however, because our p-value is 0.098 there is no statistically significant difference between the groups and no difference of this magnitude or greater was detected. This indicates that the evidence is sufficient to make the conclusions we have drawn, that there is no statistical difference in PONV between the Nitrous Oxide Group and the Control group (p=0.098). As an improvement for the future, it would be recommended to use a much larger sample size in order to see a difference between groups. While there is no statistically significant difference now, there is the possibility that the difference between groups may become significant with a much larger data set. Further research in this area with a larger patient population would be of interest following the results of this study which suggest nitrous oxide at 50% can be used in addition to inhalational anesthetic agents without fear of contributing to an increase in PONV.

One difficulty for the anesthesia provider was that they were faced with following a fairly stringent induction and anesthetic protocol, which may not be appropriate for every patient. The study design and anesthetic protocol, however, was aimed to minimize as many confounding variables as possible. Each patient received only one narcotic, fentanyl 0.5 mcg/kg, just prior to intubation, a very common anesthetic practice used to blunt the physiologic response to direct laryngoscopy. Each patient also received succinylcholine, a depolarizing muscle relaxant that does not require reversal with
psuedocholinesterase inhibitors; this latter medication may also increase the incidence of PONV. As expected, the maintenance concentration of sevoflurane required was significantly higher in the Control Group (p=0.015), compensating for the loss of anesthetic effect that would have been offered by nitrous oxide. A decrease in the concentration of volatile inhalational agents of this magnitude allows for improved hemodynamic control and a less expensive general anesthetic. This value was, however, recorded by the anesthesiologist who was not blinded to the anesthetic technique and it is possible that bias occurred based on the subject’s group assignment. In the future, it would be ideal to blind the anesthesiologist to the anesthetic technique to decrease any systematic bias and to improve the data for the required maintenance concentration of sevoflurane. The anesthetic technique for the Control Group used a carrier gas of 100% oxygen because the anesthesia machine used in this study could only supply oxygen and nitrous oxide. In typical anesthetic practice the carrier gas is a combination of oxygen and medical air, which contains nitrogen and oxygen to imitate air in the atmosphere. In the future it would be ideal to design a study where the carrier gas in the Control Group includes nitrogen or medical air to more closely replicate the anesthetic used in daily practice. Each patient also received dexamethasone 4 mg IV, a common medication used in oral & maxillofacial procedures used to decrease inflammation and postoperative pain, incidentally, a medication that is also known decrease the incidence of PONV. No other antiemetics were administered to the subjects, although there was a protocol in place in the event a subject required a rescue antiemetic in the PACU. While a single antiemetic was administered, commonly a multimodal approach is used to prevent PONV. Decreasing the antiemetic protocol to a single agent was intentional, with the aim of
providing a clearer implication of the role nitrous oxide plays in PONV when used with an inhalational agent to produce general anesthesia. Local anesthetic was administered at the surgical site to control pain in the immediate postoperative period, allowing elimination of postoperative and long-acting opioid administration. Additionally, patients who had received antiemetics, psychoactive drugs, steroids, or opioids – all agents known to affect levels of PONV – in the preceding 24 hours were excluded from participation. These restrictions resulted in the randomly chosen groups having very similar demographics and anesthetics that revealed no significant differences in the attributes assessed. It was very fortunate in that chance delivered two very similar groups in this small population.

Overall this study design proved to be an appropriate model with which to analyze the possible association between nitrous oxide and PONV and was incorporated easily into an outpatient surgical environment. While there was no statistically significant difference in the degree of nausea or incidence of vomiting between the study groups, there was a clear tendency of increased nausea being experienced by the Control Group (sevoflurane only) (p=0.0983). With a larger study population the difference between groups may well have reached statistical significance or been able to detect a smaller difference between groups. Further investigation of this difference is warranted with a much larger sample size. Interestingly, it is possible that nitrous oxide, at the concentration used in this study, may be a beneficial adjunct to inhalational anesthetics to improve patients’ experience of PONV. This may simply be due to the reduction in required concentration of potent inhalational anesthetic agents, a known contributing factor in the complex area of PONV.
Conclusion

This single blinded randomized controlled trial evaluated the incidence and degree of patient’s self-reported PONV, post-operative rescue antiemetic requirements, and post-operative opioid requirement following general anesthesia for oral & maxillofacial procedures with and without nitrous oxide that was maintained with sevoflurane and oxygen. It also evaluated the concentration of sevoflurane required to maintain general anesthesia for each subject. 20 subjects with an ASA physical classification I or II between the ages of 18-32 completed this study. The addition of 50% nitrous oxide to an inhalational anesthetic of sevoflurane and oxygen showed no increased incidence of PONV in patient’s having a general anesthetic for routine oral & maxillofacial out-patient surgical treatment (p=0.098). As expected, there was an increased requirement of sevoflurane in the Control Group (p=0.015). There was no difference in duration of anesthesia or demographics between groups. The data collected in this study indicates there may be no detrimental increase in PONV following general anesthesia maintained with volatile inhalational agents and nitrous oxide. A post hoc power analysis revealed this study had a power of 95% at an alpha of 0.05 and could detect a difference of 0.612 on the VNRS scale of 0-10 if a difference existed. With a p-value of 0.098, no statistically significant difference existed between groups. The data from this study does, however, warrant further investigation with a larger sample size to confirm that no difference exists in the incidence of PONV following general anesthesia maintained with
volatile inhalational agents alone or with the addition of 50% nitrous oxide. There are many benefits to be gained by incorporating nitrous oxide into a general anesthetic including decreased expense for anesthesia, cardiovascular stability, and analgesic affects, and further evidence as to its role in PONV may alter patients’ anesthetic plans in the future. There are currently plans to continue this study with an increased sample size.
Appendix A: List of Figures

Nausea and Vomiting Questionnaire

1. What is your age?

2. What is your height?

3. How much do you weigh?

4. What is your sex? (circle one) Male or Female

5. Do you smoke? (circle one) Yes No

6. Do you experience motion sickness? (circle one) Yes No
   a. If yes, what is the severity? (circle one) Mild moderate severe

7. Have you ever received general anesthesia? (circle one) Yes No
   a. Have you experienced nausea or vomiting following general anesthesia? (circle one) Yes No
   b. If yes, what was the severity? (circle one) Mild moderate severe

Figure 1 - Nausea & Vomiting Questionnaire
Pre-PACU Data Collection Form

Subject #: __________
Study Group: __________
Anesthesia Start Time: __________
Procedure Start Time: __________
Procedure Stop Time: __________
Anesthesia Stop Time: __________
Concentration Sevoflurane during Procedure: __________
Antibiotics given? Yes or No
Type and amount: __________
Amount and Type of Local Anesthesia Administered: __________
Time of Arrival to PACU: __________

Figure 2 - Pre-PACU Data Collection Form
PACU Data Collection Form

Subject #

Post-Operative Nausea and Vomiting Score:

*Please circle if vomiting occurs at each time, and if no vomiting occurs, record the self-reported severity of nausea from 0-10 every 15 minutes beginning at arrival to PACU and ending at discharge, for a minimum of 60 minutes. If additional time is spent in the PACU please continue to monitor and record the patient's nausea score every 15 minutes until discharge.

0 Minutes/arrival to PACU: Vomiting? Yes or No

Level of nausea: __________ Time: __________

15 Minutes after arrival to PACU: Vomiting? Yes or No

Level of nausea: __________ Time: __________

30 Minutes after arrival to PACU: Vomiting? Yes or No

Level of nausea: __________ Time: __________

45 Minutes after arrival to PACU: Vomiting? Yes or No

Level of nausea: __________ Time: __________

60 Minutes after arrival to PACU: Vomiting? Yes or No

Level of nausea: __________ Time: __________

75 Minutes after arrival to PACU: Vomiting? Yes or No

Level of nausea: __________ Time: __________

Need for Rescue antiemetic?: Yes No

Rescue antiemetic and dose given: ________________ Time: __________

Additional Rescue antiemetic and dose given: ________________ Time: __________

Need for Pain medication?: Yes No

Pain medication and dose given: ________________ Time: __________

Pain medication and dose given: ________________ Time: __________

Pain medication and dose given: ________________ Time: __________

Discharge Time: ____________________

Figure 3 - PACU Data Collection Form
Figure 4 - Verbal Numeric Rating Scale

Figure 5 – Demographics by Group
Figure 6 – Demographics by Group Continued

Demographics by Group

- Age (Years)
- Height (Inches)
- Weight (Kilograms)

Nitrous Oxide Group
Control Group

Figure 7 – Duration of Anesthesia by Group

Duration of Anesthesia

- Minutes

Nitrous Oxide Group
Control Group
Figure 8 – Required Mean Maintenance Concentration of Sevoflurane

Figure 9 – VNRS by Time
Appendix B: List of Tables

<table>
<thead>
<tr>
<th>Drug</th>
<th>Male</th>
<th>Female</th>
<th>Smoking Status</th>
<th>History of PONV Following General Anesthesia</th>
<th>History of Motion Sickness</th>
<th>Age (Years)</th>
<th>Height (In)</th>
<th>Weight (Kg)</th>
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<tbody>
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<td>5</td>
<td>2</td>
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<td>2</td>
<td>21.5</td>
<td>67.5</td>
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<td>Control Group</td>
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<td>1</td>
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Table 1 - Mean Population Demographics

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<th>Drug</th>
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<tbody>
<tr>
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<td>58.2 ± 13.784</td>
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<td>P-Value</td>
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Table 2 - Anesthesia Duration
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<td>Mean</td>
<td>Standard Deviation</td>
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<tr>
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<td>0</td>
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<td>30 Minutes</td>
<td>0.3</td>
<td>0.675</td>
</tr>
<tr>
<td>45 Minutes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60 Minutes</td>
<td>0.2</td>
<td>0.632</td>
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Table 3 - Mean VNRS Ratings

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<th>Mean Concentration Sevoflurane</th>
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<tbody>
<tr>
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<td>Control Group</td>
<td>2.66 ± 0.349</td>
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Table 4 - Maintenance Sevoflurane Concentration

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<td>Time</td>
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<td>Group*Time</td>
<td>0.86</td>
<td>0.490</td>
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Table 5 - VNRS statistical analysis
References


Ichinohe, T., & Kaneko, Y. (2007). Nitrous oxide does not aggravate postoperative emesis after orthognathic surgery in female and nonsmoking patients. *Journal of*


Welch, B. L. (1947). The generalisation of student's problems when several different population variances are involved. *Biometrika, 34*(1-2), 28-35.