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Studying the Effectiveness of Triple Therapy with Palonosetron, Dexamethasone and Promethazine for Prevention of Post Operative Nausea and Vomiting in High Risk Patients Undergoing Neurological Surgery and General Anesthesia

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Abstract

Post operative nausea and vomiting (PONV) occurs in as many as 70%-80% of high risk surgical patients. The latest prophylactic treatment recommended in the Society of Ambulatory Anesthesia Guidelines for the management of Postoperative Nausea and Vomiting for high risk patients is a combination of 2 or more interventions (multimodal therapy). A combination of a 5-HT_3 receptor antagonist with dexamethasone and/or droperidol, or a 5-HT_3 receptor antagonist with droperidol alone, or dexamethasone with droperidol, have been the pharmacologic combination therapies suggested in these guidelines. Palonosetron is a fairly new 5-HT_3 receptor antagonist recently approved by the FDA for PONV prophylaxis. The use of this novel drug in a triple therapy combination with Dexamethasone and/or Droperidol could be an effective treatment for the prevention of PONV. However, since the FDA issued a warning stating that droperidol may cause life – threatening arrhythmias as well as a prolongation of the QTc interval, the need to discover new combination therapies for PONV prevention in high risk patients is still in demand. Therefore, we hypothesize that the use of this novel drug Palonosetron in a triple therapy combination with Dexamethasone and Promethazine will be an effective treatment for the prevention of PONV in patients at a high risk for developing PONV during the first 120 hours after neurosurgery.

Introduction and Background

Postoperative Nausea and Vomiting (PONV) continues to be a common and undesirable complication of surgery. It is a problem concerning both patients and clinicians. Prevention and treatment of PONV are key patient care issues that greatly affect comfort and satisfaction with care. Nausea and Vomiting are frequently listed by patients as their most important perioperative concerns. In a survey of 101 patients, the most undesirable surgical outcome reported was vomiting, which ranked higher than pain [1]. PONV is a post operative complication that increases morbidity by threatening wound dehiscence, hematoma formation, aspiration, esophageal rupture, dehydration and increases in intraocular and intracranial pressures due to acute blood pressure elevations [2,3].

Currently, the overall incidence of PONV is estimated to be 20-30% of all surgical patients [4]. If untreated, PONV occurs in as many as 70%-80% of high risk surgical patients [4]. The incidence of post operative nausea and vomiting (PONV) in neurosurgery is considered separately 50% for nausea and 39% for vomiting [5]. Postoperative nausea or vomiting was the most common complication observed following neurosurgery with an overall incidence of 39% in the first four hours after surgery in a study of postoperative complications [6]. A higher prevalence of 70% nausea and 55% vomiting was observed during the first 48 hours following neurosurgery in a study examining patients given a placebo (no prophylactic anti-emetic treatment) prior to undergoing supratentorial craniotomies [3].

Several baseline risk factors that are independent predictors of PONV have been identified to determine which patients are candidates for prophylaxis. These can be classified into 3 categories: (a) patient specific, (b) anesthetic, and (c) surgical.

The most prevalent patient specific risk factors for PONV are female gender, nonsmoking status, and history for PONV or motion sickness [4]. Other potential risk factors considered of relevance include migraine, young age, anxiety, and an American Society of Anesthesiologists (ASA) low-risk classification [4]. Anesthetic risk factors include use of general anesthesia with volatile anesthetics, use of nitrous oxide, and postoperative use of opioids [4]. Surgical risk factors are related to the duration of surgery, each 30-minute increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased to 16% after 30 minutes; and type of surgery: laparoscopy; laparotomy; breast; strabismus; plastic; maxillofacial; gynecologic; abdominal ophthalmologic; urologic and neurologic surgery [4].

A single risk factor for PONV is not sensitive or specific enough to be used to assess risk for PONV. According to the simplified risk score model from Apfel et al. [7], the greater the number of independent predictors, the higher the risk for PONV. Specifically, the presence of 1 risk factor correlates with 20% risk for PONV, and as each subsequent risk factor is added, risk increases by 20%, resulting in an 80% risk when all 4 risk factors are present [7]. This model includes as risk factors: female gender, nonsmoker status, history of PONV and use of postoperative opioids. Each factor has a punctuation value of 1, which added will equal 0 – 4. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present; the corresponding risk for PONV is approximately 10%, 20%, 40%, 60%, or 80% [4].

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Patients undergoing neurosurgery with opening of the cranium and dura mater under general anesthesia are at high risk for developing PONV. The Society for Ambulatory Anesthesia guidelines for PONV management provide risk factors associated with an increased likelihood of PONV [4]. The nature of the neurological surgery to be studied is associated with several of these risk factors such as, the use of volatile anesthetics, the likely extended duration of the surgery, the nature of neurological surgery, and the likely use of postoperative opioids. This creates an elevated level of PONV risk for all patients undergoing this type of neurosurgery. This risk level is further elevated in many of these patients by the common patient characteristics associated with increased risk of PONV mentioned above (female gender, non-smoker, etc).

According to the Society for Ambulatory Anesthesia the current guidelines for postoperative nausea and vomiting include assessing the patient's risk for PONV, reducing the baseline risk factors for PONV, and prophylactic treatment. Some ways to reduce the baseline risk for PONV include avoidance of general anesthesia, use of propofol for induction and maintenance of anesthesia, avoidance of nitrous oxide and other volatile anesthetics, and minimizing the use of opioids during and after the surgery [4]. However, these PONV risk elevating techniques cannot be avoided during this type of neurological surgery. Therefore, while prophylactic treatment is not recommended for all patients, it should be used when a patient's risk of developing PONV is adequately high or when it is advantageous to prevent vomiting such as when patient's have wired jaws, increased intracranial pressure, or gastric surgery [4]. The Society for Ambulatory Anesthesia recommends the use of one or two antiemetic in combination in adults with moderate risk; and two or more in combination for adults at high risk [4]. Specifically, patient's at high risk for PONV are recommended to receive two or more prophylactic antiemetic drugs from different classes [4]. Vomiting can be induced through multiple pathways which ultimately activate the vomiting center in the lateral reticular formation of the medulla, activation of this center leads to the visceral and motor output involved in vomiting [8]. Since there are multiple pathways of activation, a multi-modal approach should be used to prevent PONV [9]. Correspondingly, it has been proven that a combination multi-modal prophylactic therapy is more effective at preventing PONV than single drug therapy [9]. Furthermore, in using a combination of drugs, the dosage of each drug could be reduced, decreasing side affects [10]. Overall, the guidelines state that patients at moderate risk should receive one or more prophylactic drugs from different classes and those at high risk, two or more [4].

The Society for Ambulatory Anesthesia guidelines suggest the use of several drugs for the prophylactic treatment of PONV [4]. They recommend the use of 5-hydroxytryptamine (5-HT_3) receptor antagonists: (ondansetron, dolasetron, granisetron, and tropisetron; Palonosetron is also a 5HT_3 receptor antagonist that has recently received FDA approval for PONV prophylaxis), steroids (dexamethasone), the dopamine (D_2) receptor antagonists (droperidol, haloperidol), an antihistamine drug (dimenhydrinate), and an anticholinergic drug (scopolamine) [4].

These guidelines recommend the use of combination therapy with two or more interventions for those at high risk for developing PONV [4]. They also mention the superior efficacy of combining different classes of prophylactic drugs in the prevention of PONV. Specifically the guidelines recommend the use (in adults) of the following combination therapies: droperidol and dexamethasone, 5-HT_3 receptor antagonist and dexamethasone, 5-HT_3 receptor antagonist and droperidol, and a triple therapy of a 5-HT_3 receptor antagonist, dexamethasone, and droperidol [4]. Droperidol is no longer recommended as prophylactic treatment for PONV because of a recent black box FDA label indicating that droperidol may cause prolongation of the QT interval and dangerous heart arrhythmias.

With the elimination of droperidol from the prophylactic PONV drug armament many of the recommended combination therapies mentioned above are eliminated. Remaining is therapy with a 5-HT_3 receptor antagonist and dexamethasone and there are indications that this therapy is as effective as a 5-HT_3 receptor antagonist and droperidol [11]. Due to the high risk of PONV from undergoing neurological surgeries, prophylactic treatment with a combination of three interventions is warranted and indicated by the most recent guidelines [4]. According to Khalil et al. there is a significant reduction in both vomiting and nausea seen in a combination prophylactic therapy of a 5-HT_3 receptor antagonist and promethazine [12]. This indicates that the addition of promethazine to the triple prophylactic therapy used in this study is appropriate and will prove beneficial in the prevention of PONV.

With the recent approval of the 5-HT_3 receptor antagonist Palonosetron for use in the prophylactic treatment of PONV; the use of a combination therapy of palonosetron, dexamethasone and promethazine would be appropriate as a treatment for patients with a high risk of PONV. Palonosetron is unique among 5-HT_3 receptor antagonists because it has a longer half life, more than 3 times longer than other 5-HT_3 receptor antagonists, and also has a 100 fold higher 5-HT_3 receptor affinity than the other 5-HT_3 receptor antagonists [13,14]. These specific pharmacodynamic properties suggest that palonosetron may be a superior agent for preventing PONV and that it may continue to work over a longer period of time when compared to the other 5-HT_3 receptor antagonists. A more recent evaluation of Palonosetron's interactions with the 5-HT_3 receptor indicates that Palonosetron has unique binding properties among 5-HT_3 blockers, in addition to its higher affinity and longer half life [15]. Palonosetron appears to have a different binding site and unique mechanisms of action when compared to the other 5-HT_3 receptor antagonists. Specifically, Palonosetron was shown to have significant impact on cell functioning even after it was no longer bound to the 5-HT_3 receptor, providing a plausible mechanism for Palonosetron's prolonged action [15]. When all of these unique pharmacological properties are considered together, they illustrate reasonable mechanisms for Palonosetron's efficacy as a prophylactic treatment for PONV.

Palonosetron was found to be significantly superior to another 5-HT_3 receptor antagonist as prophylactic therapy for the prevention of chemotherapy induced nausea and vomiting (CINV), particularly in the delayed phase after chemotherapy, while having a similar adverse reaction profile [16]. Another trial examining CINV found that palonosetron was superior to another 5-HT_3 receptor antagonist in the prevention of CINV over a five day period following chemotherapy and that a combination therapy of palonosetron and dexamethasone was also superior to a combination therapy of another 5-HT_3 receptor antagonist and dexamethasone in preventing CINV [17]. The same study found no difference between the adverse reaction profiles of palonosetron and the other 5-HT_3 receptor antagonist.

The use of palonosetron specifically for the prevention of PONV has also been recently examined. A study by Candiotti et al. [18], examined single prophylactic treatment with Palonosetron in female

patients undergoing elective laparoscopic abdominal or gynecological surgery. This study found significant reduction in PONV during the first 72 hours after surgery when comparing 0.75 mg Palonosetron with a placebo [18]. Additionally, Palonosetron was found to have a significant effect leading towards less intense nausea during the first 72 hours [18]. These reductions in PONV were found to decrease the level of functional interference in the Palonosetron treatment group when compared to the placebo in several domains of functional activities. Another similar study by Kovac et al. examined Palonosetron compared with a placebo as a single prophylaxis treatment for PONV in female patients undergoing gynecological surgery or breast surgery [19]. They found similar significant reductions in PONV in the first 72 hours and also found significant differences in the specific reduction of emesis and nausea between the Palonosetron 0.75 mg treatment group and a placebo [19]. Both of these studies found no significant differences in adverse events between the Palonosetron treatment groups and the placebo treatment groups [18,19]. Altogether, these two studies indicate that Palonosetron is a safe and effective prophylactic treatment for PONV.

The studies of Palonosetron for the prevention of CINV suggest that Palonosetron is superior to other 5-HT_3 receptor antagonists for preventing CINV, particularly in the delayed phase. The very recent studies of Palonosetron for the prevention of PONV suggest that Palonosetron has significant and meaningful effects for the prevention of PONV. This study will be the first to evaluate Palonosetron's efficacy and clinical relevance as a part of a triple prophylactic combination therapy in a high risk patient population. This proposed study would further examine the efficacy and value of using Palonosetron for the prophylactic treatment of PONV by: 1) expanding the study participants to include both men and women, 2) evaluating Palonosetron's efficacy in a new patient population (neurosurgical patients who are at very high risk for developing PONV), 3) evaluating Palonosetron's effects up to 120 hours post surgery, and 4) employing a triple prophylactic combination therapy which includes dexamethasone and promethazine in addition to Palonosetron. These aspects of the study will allow for a better evaluation of Palonosetron's efficacy over a longer time period (as indicated by Palonosetron's unique pharmacological characteristics), in a new patient population, and as a part of a triple therapy indicated by the latest Society for Ambulatory Anesthesia guidelines. These unique study attributes will allow the study's findings to help establish the future role of Palonosetron as a part of the PONV prophylactic treatment plan and determine the efficacy of the triple prophylactic therapy of Palonosetron, dexamethasone, and promethazine for the prevention of PONV.

Hypothesis

The use of a triple prophylactic therapy consisting of Palonosetron, Dexamethasone, and Promethazine will be an effective treatment for the prevention of PONV in patients at a high risk for developing PONV during the first 120 hours after neurosurgery.

Primary objective

To evaluate the efficacy of triple therapy with Palonosetron, Dexamethasone and Promethazine for prevention of post operative nausea and vomiting in high risk patients after neurological surgery and general anesthesia.

Secondary objective

To assess the safety of triple therapy with Palonosetron, Dexamethasone and Promethazine for prevention of post operative nausea and vomiting in high risk patients after neurological surgery and general anesthesia.

Primary endpoint

Proportion of patients with a complete response (no emesis and no rescue medication) during the first 24 hours after neurological surgery and general anesthesia.

Secondary endpoint

Proportion of patients with a complete response during a delayed period (24 – 120 hours; days 2 – 5) and overall (0-120 hours; days 1 -5) after neurological surgery and general anesthesia.

- Proportion of patients with complete control, defined as no emetic episode, no need for rescue medication and no more than mild nausea overall (nausea rated ≥ 4 on a 0 to 10 verbal response scale or nausea that required rescue therapy) (0-120 hours; days 1 - 5) after neurological surgery and general anesthesia.
- Assess the severity of nausea and vomiting during acute (0 - 24 hours), delayed (24 - 120 hours) and overall (0 - 120 hours) intervals after neurological surgery and general anesthesia.
- Assess the time to treatment failure (defined as time to first emetic episode and/or to first use of rescue medication).
- Assess the time to first emetic episode.
- Assess the time to significant nausea (defined as nausea rated ≥ 4 on a 0 to 10 verbal response scale or nausea that required rescue therapy).

Study population

Adult patients, 18 to 85 years of age, scheduled to undergo neurological surgery and general anesthesia requiring opening of the cranium and Dura mater at Ohio State University Medical Center.

Sample size

44 subjects meeting the inclusion and exclusion criteria and who give written informed consent to participate in the study distributed in one single treatment group.

What is the study question?

Is triple therapy with Palonosetron, Dexamethasone and Promethazine effective in preventing post operative nausea and vomiting in high risk patients undergoing neurological surgery and general anesthesia?

Study design

Prospective, Non Randomized, Open Label, Single-Arm, Single-Center, Phase IV Trial.

Drug regimen / treatment plan: Triple therapy

1. Palonosetron (Aloxi), 0.075 mg, IV as a single dose immediately before induction of general anesthesia.
2. Dexamethasone, 10 mg, IV as a single dose at induction of general anesthesia.
3. Promethazine 25 mg, IV as a single dose at induction of general anesthesia.

Rescue medication

Ondansetron will be administered as rescue medication. Intravenous Ondansetron 4mg may be given as rescue medication. Following an emetic episode, rescue medication may be given on subject request or on the recommendation of the treating medical staff, treating surgeon or principal investigator, according to the standard of care practices at The Ohio State University Medical Center. A subject may be offered rescue medication for nausea if he or she complains of nausea and/or emesis occurs. The patient will not be administered additional antiemetic treatment as prophylaxis for PONV after surgery or at any time during the study period or treatment phase. Subjects who do not respond to this initial treatment will be given intravenous Promethazine 12.5 mg - 25 mg as a second line of therapy. Patients with intractable post operative nausea and vomiting will have a nasogastric tube inserted into their stomach as per standard of care practices at The Ohio State University Medical Center.

Length of washout period will be the 24 hours immediately preceding the induction of anesthesia. Any patients who have taken medication with antiemetic properties during this time period will be excluded.

Duration of treatment

- Screening period will consist of up to 30 days before study treatment is given.
- Treatment phase (including Baseline) duration of 5 days.
- Additional telephone contact at 30 days will be used to further assess any longer term complications or adverse events.

Demographic and preoperative baseline data will be collected

1. Gender
2. Age
3. Race
4. Height
5. Weight
6. History of Post Operative Nausea and Vomiting
7. Medical History including reason for surgery
8. Scheduled surgical procedure
9. Surgery scheduled length
10. Baseline, 24 hours and discharge ECG.
11. Baseline and 24 hours Laboratory Analysis:
    - Liver Function Tests
    - Chemistry
    - Hematology
    - Urinalysis
12. Vital Signs
13. Systolic, Diastolic and Median Blood Pressure
14. History of Smoking and alcohol consumption
15. History of Motion Sickness or Migraines
16. Allergies
17. Anesthesia modality
18. Serum or urine pregnancy test

The start and end time of the procedure and anesthesia will be recorded. End of surgery time and extubation time will be recorded as will total anesthesia time. Admission and discharge time from the PACU will also be recorded. Patients will be continuously monitored in the post anesthesia care unit (PACU), surgical intensive care unit (SICU) and the medical floor for a total of 120 hrs postoperatively or until discharge. Nausea and vomiting will be assessed every 24 hours for 5 days via direct patient interview and chart review. If the patient is discharged before this 5 day time period, the patient will be then contacted via phone call by a co-investigator or key personnel to complete assessments. Episodes of nausea, vomiting and administration of rescue therapy for either nausea or vomiting will be recorded. In addition, the severity of each nauseous or emetic episode will be recorded. Nausea will rated by the patient utilizing a verbal response scale (0-10). Vomiting will be evaluated by the investigator or nursing staff numerically as either 0 (no vomiting), 1 (mild vomiting), 2 (moderate vomiting) or 3 (severe vomiting). Following the first 24 hours after administration of the prophylactic triple therapy an ECG will be given and blood will be drawn for analysis. At patient's discharge a final ECG will be performed.

Inclusion / Exclusion Criteria

Inclusion criteria

1. Adult patients, 18 to 85 years of age, of any race or gender. With an American Society of Anesthesiologists (ASA) physical status of I to III who are scheduled to undergo neurological surgery requiring opening of the cranium and Dura matter under general anesthesia, at Ohio State University Medical Center and who consent in writing to participate in this study are eligible.
2. Post operative hospitalization expected to last at least 72 hours.
3. Subjects whose surgery is expected to require at least 1 hour of general anesthesia.
4. Subjects who have a negative serum or urine pregnancy test within 1 day of surgery or who have been surgically sterilized or are postmenopausal.

Exclusion criteria

1. Subjects who are prisoners, pregnant, mentally ill, under the age of 18 or over the age of 85, ASA classification or V, alcohol or drug abusers.
2. Subjects with known hypersensitivity to any 5-HT_3 antagonist, to any agent that is part of the anesthesia regimen, or to other medications to be administered under this protocol.
3. Subjects who are breastfeeding.
4. Subjects who have had retching/vomiting or moderate to severe nausea in the 24 hours prior to anesthesia or suffer chronic nausea and/or vomiting.
5. Subjects who have been treated with any drug or other treatment with antiemetic efficacy within the last 24 hours prior to the start of treatment.
6. Subjects who have participated in a clinical trial of an investigational drug within 30 days prior to surgery.

7. Subjects who are participating in any other clinical study.

Safety assessments

Safety will be assessed by monitoring vital signs, adverse events, assessing baseline and 24 hour laboratory results and baseline, 24 hours and discharge ECG. A physical exam will be performed at screening and at the end of treatment phase.

Liver function tests, chemistry, hematology, urinalysis and ECG's will be obtained at screening or baseline and 24 hrs after surgery end time. Vital signs will be obtained from the patient's medical record nurses flow charts on a daily basis. Extubation time and duration of recovery from anesthesia time will be recorded.

All study medications and study procedures required by the protocol that are not considered as part of the standard of care, and that will be obtained solely for research purposes, will be provided by the study at no cost to the subjects.

The occurrence of adverse events (AE) or serious adverse event (SAE) will be recorded during the 5 day treatment period and followed until resolution. Additional telephone contact at 30 days will be used to further assess any longer term complications or adverse events. For each adverse event the relationship to the study medication, severity, expectedness of an adverse event and outcome will be determined by the Principal Investigator and recorded in the study source accordingly.

In the case a subject is withdrawn from the study because of a serious adverse event (SAE) the FDA will be notified within 7 working days of the occurrence of the SAE and local IRB will be notified within 10 days.

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign, symptom, abnormal laboratory finding or a temporally disease associated with the use of a study drug, whether or not considered related to the study drug.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the subject was enrolled in a clinical study are not to be considered AEs.

Serious adverse event definition

A SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Results in persistent or significant disability/incapacity.
- Requires in-subject hospitalization or prolongs hospitalization.
- Is a congenital anomaly/birth defect.
- Is another medically-significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Withdrawal criteria from the study

According with the Declaration of Helsinki, participants have the right to withdraw from the study at any time for any reason. The principal investigator also has the right to remove subject from the study. Reasons for which a subject may be removed from the study include:

- An adverse Event
- The request of the subject, his/her legal representative or caregiver, investigator or Sponsor, whether for administrative or other reasons.
- Non - compliance with medication, protocol violation or unreliable behavior.
- Any clinically significant abnormal laboratory values, or other clinically significant abnormalities identified by the principal investigator according to his clinical judgment, will be followed by appropriate tests and/or procedures until these values have returned to normal or to clinically acceptable levels or can be attributed to other causes other than study drug.

The principal Investigator may withdraw an enrolled and treated subject from the study for any of the following reasons:

- Occurrence of a serious or intolerable adverse event
- Emergence of a clinically significant change in a laboratory parameter(s)
- The subject requests to be discontinued from the study
- A protocol violation sufficiently serious as to require subject withdrawal
- General or specific changes in the subject's condition that render further treatment unreasonable or unsafe within the standards of clinical practice in the judgment of the Principal Investigator or treating physician.

Any subject may leave the study at any time. If a subject decides to stop participating in the study, there will be no penalty. The subjects will not lose any benefits to which they are otherwise entitled. Their decision will not affect their future relationship with The Ohio State University.

Efficacy Assessments

Efficacy parameters will be collected at each 24 hour time interval throughout the 120 hours of the treatment phase. These measures include the number and severity of emetic episodes experienced, the use of rescue medication, and the intensity of nausea experienced post operatively. Nausea severity will be assessed with the use of a verbal response scale on a 0 to 10 verbally elicited scale. The 11 point categorical scale to be used to rate severity of nausea ranges from 0 (no nausea) to 10 (nausea as bad as it could be). Vomiting will be evaluated by the investigator or nursing staff numerically as either 0 (no vomiting), 1 (mild vomiting), 2 (moderate vomiting) or 3 (severe vomiting).

Primary efficacy assessment

The percentage of patients with no emetic episodes over 0 – 24 hrs post operatively.

Secondary efficacy assessment

- No emetic episodes for the following time intervals: 24 – 48, 24 – 96, 24 – 72 and 24 – 120 hours.

- Number of rescue therapy treatments administered over 0 – 24,

0 – 48, 0 – 96, 0 – 72 and 0 – 120 hours postoperatively.

- Percentage of patients achieving complete response (no emetic episodes and no use of rescue medication) over 0 – 48, 0 – 96, 0 -72 and 0 – 120 hrs.
- Percentage of patients with no nausea over 0 – 48, 0 – 96, 0 – 72 and 0 – 120 hrs post operatively.
- Time to first rescue medication.
- Time to first emetic episode.
- Time to significant nausea.
- Number of emetic episodes at 0 – 24, 0 – 48, 0 – 96, 0 – 72 and 0 – 120 hrs.

Statistical plan

The efficacy data will be analyzed based on the intention-to-treat principal. The intent-to-treat cohort will consist of all patients given triple therapy with palonosetron, dexamethasone and promethazine with at least one post operative efficacy assessment. The safety cohort will consist of all patients given triple therapy with palonosetron, dexamethasone and promethazine who had at least one post dose assessment. Patients who withdraw from the study will be considered nonresponders on and after the day of withdrawal. Baseline patient demographics, clinical characteristics, and safety data will be summarized with descriptive statistics, such as mean, median, standard deviation, etc.

The proportion of patients experiencing a complete response (no emesis and no rescue medication required) will be evaluated at 24 - hour intervals from 0 - 120 hours post operatively, including the acute (0 - 24 hours), delayed (> 24 - 120 hours), and overall (0 - 120 hours) intervals. Efficacy data will be summarized using descriptive methods with confidence intervals determined for mean values and proportions. We will examine the comparability of the treatment group with respect to important preoperative factors.

Logistic regression will be used to test the primary hypothesis with demographic characteristics as potential covariates in the model.

For the number of rescue therapy treatments used during the 24, 48, 96, 72 and 120 hour postoperative period, Chi-square or exact test for proportions will be performed. Adjustments for multiple comparisons will be performed (Bonferroni or Holm's methods). For other secondary endpoints, the analysis plan will be similar to the one for the primary endpoints.

With a sample size of 40 patients we will have 80% power to detect a reduction of 30% from expected incidence of nausea and vomiting (~ 80%) in this patient population (alpha level 0.05 and 1-sided test for proportions were assumed). This sample size will allow us to construct 95% confidence interval with limits of 0.47 to 0.77. We will seek n=44 subjects to account for screening and attrition in the study.

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