The Incidence of Dysesthesia When Droperidol is Used for Prophylaxis of Post Operative Nausea and Vomiting

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Dedication

To Azar, the smartest and kindest person I know
Acknowledgements

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Abstract:

**Background:** Multiple therapeutic regimens are used in an effort to attenuate the incidence of postoperative nausea and vomiting (PONV). Some drugs (e.g. dexamethasone, droperidol and scopolamine) are given preoperatively for prophylaxis in patients who are at increased risk of developing PONV. The use of droperidol has been associated with a relatively high incidence of dysesthesias (30% to 70%) in the outpatient setting, but we have not observed dysesthesias in most patients who receive it perioperatively.

**HYPOTHESIS:** The incidence of dysesthesias in the perioperative period is less than that reported in the outpatient environment.

**Purpose:** The primary goal was to determine the incidence of dysesthesia in patients treated with droperidol perioperatively for PONV. Secondary goals were to determine efficacy of droperidol for preventing PONV and the effect of droperidol on anxiety.

**Methods:** 30 patients who were at moderate to severe risk of developing PONV and met no exclusion criteria were asked to participate in the study. The consented patients completed a survey just prior to the intravenous administration of 0.625 mg of droperidol.
The survey was repeated 1 hour after the patient was admitted to the PACU.

**Results:** None of the patients reported dysesthesia (0%, p<.001).

Patients also reported an average 2.2 point reduction on their 1-10 anxiety level after surgery and no patients complained of PONV.

**Conclusion:** Dysesthesia from droperidol is much less common in the perioperative setting than has been reported in the outpatient setting. Based on result, low dose droperidol is expected to prove less likely to cause dysesthesias when used in the intraoperative setting for prophylaxis of PONV than reported in emergency departments and oncology clinics.
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Introduction

Background

**Nausea** is a subjective symptom defined as an unpleasant awareness of the urge to vomit [1]. Intestinal contractions accompanied by loss of gastric tone allow reflux of intestinal contents into the stomach [2]. **Vomiting**, or emesis, is the forceful eviction of gastric contents cephalad through the esophagus and out the mouth caused by abdominal muscle contraction, lowering of the diaphragm and gastric cardia release [1,2].

**Postoperative Nausea and Vomiting (PONV)** is a major sequelae of anesthesia and surgery and, with an incidence of ~30%, is 1 of the major morbidities experienced by patients in the perioperative period [1]. In the ambulatory setting patients may experience nausea and vomiting after arriving home, so called postdischarge nausea and vomiting. PONV is certainly unpleasant for the patient and equally concerning to health care providers because patients recovering from anesthesia are at increased risk for aspiration of gastric contents into the trachea and bronchi. The strain on the abdominal cavity in a
patient who may have had a laparotomy, or the release of catecholamines in a patient who may have coronary artery disease are additional adverse events associated with vomiting.

PONV delays patients’ discharge from the postanesthesia care unit (PACU), consequently slowing patient turnover from the operating room, decreases operating room efficiency [3]. Multiple therapeutic regimens have been tried in an effort to attenuate the incidence of PONV [4]; in most hospitals, PONV is treated with a multistep regimen that includes the prophylactic administration of drugs such as dexamethasone, scopolamine, or droperidol; administration at the end of the procedure of a 5-HT₃ blocker; and, on an as-needed basis, intravenous administration of promethazine or intramuscular administration of hydroxyzine as rescue medications in the PACU.

**Droperidol** is a butyrophenone known for its potent antiemetic properties with anti-dopaminergic activity as a D₂ receptor antagonist [5]. Since its approval in 1970, droperidol has been widely used in the treatment of PONV in doses of 0.625 or 1.25 mg administered via intramuscular (IM) or intravenous (IV) routes. Droperidol’s anti-emetic effects are exerted usually within 5 minutes, with a half-life of less
than 3 hours [5]. Droperidol is hailed for its clinical effectiveness, short half-life, and quick onset of action. In addition to its antiemetic properties, many anesthesiologists argue it a safe and potent medication for agitation. In a randomized, double-blinded study conducted by Rosen et al., paramedic-administered droperidol compared to placebo was found to reduce agitation within 5 minutes and also have a significant reduction in requirement for sedation in the ED after transport [6].

In, 2001 the US FDA issued a Black-box warning for the proarrhythmic effects of droperidol noting QT prolongation leading to Torsades de Pointes in some patients [7]. Many anesthesiologists argue that the black-box warning is unjustified claiming inadequate causative evidence. Nevertheless, in the 10 years since the warning, utilization of the drug has fallen 90% [7]. 207 ED physicians responded to a multicenter survey conducted by Jacoby et al. 73% had used droperidol at least once per week before the black-box warning and 71% reported never using droperidol after the warning. Of those using alternate sedative agents, 92% did not think the alternative agent was more effective than droperidol [5].
**Significance**

In addition to its cardiac effects droperidol has also been associated with neurologic side effects. For many years droperidol has been rumored to cause akathisias and dysesthesias resembling the symptoms of Restless Legs Syndrome. **Dysesthesia** is a general term for unusual and unpleasant sensations in the extremities, while **parasthesias** are any unusual sensations experienced, not necessarily unpleasant or painful in nature. **Akathisia** is a term to describe a deep sensation typically in the legs or arms. Some descriptive words that patients commonly use to explain the sensation are: crawling, creeping, pulling, itching, drawing, or stretching, all localized to deep structures rather than superficially to the skin. Akathisia is incorrectly thought to be synonymous with Restless Legs Syndrome because the akathisia sensations are experienced at rest and typically alleviated with movement.

The incidence of droperidol-induced dysesthesias is typically reported to be 30% in Emergency Medicine literature. In a multi-center, double-blinded study the incidence was found to be as high as 71.4% [8].
Aims/Goals/Hypothesis

The purpose of this study was to determine the incidence of dysesthesia with low-dose droperidol in the perioperative setting. This is hypothesized to be less frequent than seen in outpatient settings based on expert opinion and experience of the researchers. Better understanding of the drug and its adverse events will improve medical care and patient outcome. Secondary goals of the study are determining efficacy of the drug in preventing PONV and reducing anxiety.
Research Materials and Methods

a. Study Design: This was prospective minimal-risk study in which 30 subjects completed a short questionnaire (Appendix I) before and after administration of IV droperidol.

b. Study Subjects

Inclusion Criteria

- Adult men and women ≥ age 18 who were at moderate to high risk of having PONV (Appendix II).

Exclusion Criteria

- Lack of consent (Appendix III)
- Allergy to droperidol
- An ECG was not required to participate in the study, but, if the patient had an ECG within the last 12 months demonstrating a QTc > 470 msec.
- A history of Parkinson disease, Restless Leg Syndrome, or other movement disorder in which the use of an antidopaminergic drugs was contraindicated.

c. Sample Size: To demonstrate a 66% reduction in the incidence of dysesthesia (from 30% to 10%) in patients receiving 0.625 mg of
droperidol, the calculated sample size to obtain at least 80% power was $n = 24$. 
### Table 1: Sample size required to obtain 80% power

<table>
<thead>
<tr>
<th>δ</th>
<th>Sample size required</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>316</td>
</tr>
<tr>
<td>10%</td>
<td>86</td>
</tr>
<tr>
<td>15%</td>
<td>40</td>
</tr>
<tr>
<td>20%</td>
<td>24</td>
</tr>
</tbody>
</table>

δ: Difference between 30% incidence from literature and actual incidence seen in study.
d. Data Collection, Handling, and Analysis: The survey consisted of 10 questions with exclusively yes/no and scaled 1-10 point answer options. The data was collected from the surveys and deidentified data was inputted into a computer for storage. The results were analyzed by statistician, Dr. Yu-Hui Chang.
Results

Only 4 patients had reported past history of dysesthesia but not occurring at the time of the pre-operational survey (figure 1).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.7 ± 14.3</td>
</tr>
<tr>
<td></td>
<td>Median: 55</td>
</tr>
<tr>
<td></td>
<td>IQR: 37-61</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>0/30</td>
</tr>
<tr>
<td>History of PONV (n; %)</td>
<td>27; 90%</td>
</tr>
<tr>
<td>History of dysesthesia (n; %)</td>
<td>4; 14%</td>
</tr>
</tbody>
</table>

Table 2: Patient Demographic Information
The average age for the enrolled subjects was 50.5 years with standard deviation (SD) = 16.2. The median age was 55 with an interquartile range (IQR) spanning from 36.8 – 60.5 years.
Figure 1: Prevalence of dysesthesias. Reported by patients in pre-op.
Figure 2: Anxiety level ratings of patients pre-op and post-op
<table>
<thead>
<tr>
<th></th>
<th>Preop Anxiety</th>
<th>Postop Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>4.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Median</td>
<td>4.5</td>
<td>2</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>IQR</td>
<td>2 – 6</td>
<td>1 – 4</td>
</tr>
</tbody>
</table>

Table 3: Anxiety levels of patients during pre-operational and post-operational surveys
The incidence of dysesthesias in the 30 subjects was 0% (p<.001).

There was an average pre-op anxiety level of 4.6 on a 1-10 scale for all subjects with answers ranging from 1 to 10, SD = 3, interquartile range 2 – 6 and median 4.5. The average post-op anxiety level was 2.4 on a 1-10 scale with answers ranging from 1 to 7, SD = 2, interquartile range of 1 – 4 and median of 2 (figure 2, table 3). None of the patients in the study complained of nausea or vomiting while in the PACU.
Discussion

The data collected show a statistically significant reduction in incidence compared to historical reports. Dysesthesias in this setting may be uncommon because droperidol is used at a lower dose than in emergency departments. 2.5 mg droperidol is commonly administered in the ED whereas the dosage recommended for PONV prophylaxis in the perioperative environment is 0.625 mg. Additional drugs administered in the perioperative setting including opiates or sedatives e.g. benzodiazepines may attenuate the incidence of dysesthesia.

All patients surveyed with a preoperative anxiety level greater than 1 had reported a reduction of anxiety postoperatively. However, this reduction cannot be exclusively attributed to droperidol because of the coadministration of several other psychotropic drugs. Furthermore, patients may be more likely to feel anxious while in the preoperative holding area than the recovery unit knowing that their surgery is successfully completed. The efficacy of droperidol in preventing nausea and vomiting has been proven in previous control trials and not the
primary goal of this study. However, it is reassuring to note all of the patients in the study denied PONV.

Four patients, 14%, reported a past history of spontaneous and intermittent dysesthesias and akithisia raising concern for undiagnosed RLS. All 4 patients denied experiencing these symptoms, whether familiar or novel sensations, postoperatively.

All of the subjects in the study to date have been female. This is primarily because patients enrolled in the study were required to have moderate to high risk for PONV. Among the risk factors for PONV are non-smokers, females, and breast, GI, or gynecological procedures.
**Future Directions**

The ultimate role of droperidol in the anesthesiologist’s arsenal for prophylaxis of PONV is limited only by its reputation of adverse events such as dysesthesias and QT prolongation. We hope to prove low-dose droperidol safe with a low incidence of dysesthesia; however further investigation with EKG measurements will be needed in order for this drug to regain its value in the perioperative setting.
Conclusions

Dysesthesia from droperidol is much less common in the perioperative setting than has been reported in the outpatient setting. Based on results to date low dose droperidol is expected to prove less likely to cause dysesthesias when used in the intraoperative setting for prophylaxis of PONV than reported in emergency departments and oncology clinics.
References


Appendix I - Questionnaire

Preoperative Questions

1. Are you feeling sick to your stomach now?
   ___ Yes   ___ No
2. On a scale of 1-10, how anxious are you now? ___
3. Do you have unpleasant difficult-to-describe sensations or feelings, in your legs or arms, such as tingling, burning, cramps, or pain, or a need to move your legs?
   ___ Yes   ___ No
4. Have you ever experienced these feelings or urge to move in the past?
   ___ Yes   ___ No
5. Are the feelings or urge to move worse when you are resting?
   ___ Yes   ___ No
6. Are the feelings or urge to move better when you get up and walk around, pound on your legs, or move them?
   ___ Yes   ___ No
7. Are the feelings or urge to move worse at night or in the evening than in the morning?
   ___ Yes   ___ No

Postoperative Questions

1. Are you feeling sick to your stomach now?
   ___ Yes   ___ No

2. On a scale of 1-10 how anxious are you now? ___

3. Do you have unpleasant sensations in your legs and arms, such as tingling, burning, cramps or pain?
   ___ Yes   ___ No
Appendix II – Droperidol Administration Criteria

**Nausea and Vomiting Treatment**

Applies to post-operative and/or post-procedural patients (18 years of age and older) in the PACU, Inpatient patient care area, or hospital-based outpatient patient care area.

**EXCLUSION:**

- [ ] [ ] Allergy to Granisetron (Kytril®) and/or Droperidol (Inapnine®)?
- [ ] [ ] Patient states they are pregnant or breastfeeding?
- [ ] [ ] If Yes to any of the above questions Do Not initiate protocol. Notify service for orders.
- [ ] [ ] If No continue with protocol.

**ALERT**

It is not necessary for a patient to have had a previous ECG to receive Droperidol. However, if a patient has had an ECG within the last 12 months with the most recent ECG having a documented prolonged QTc greater than or equal to 480 msec for men and 470 msec for women do not administer Droperidol.

- [ ] [ ] If patient has a Mayo Clinic ECG within the last 12 months does the most recent ECG have a documented prolonged QTc greater than or equal to 480 msec for men and 470 msec for women?
- [ ] [ ] If Yes do not administer Droperidol (Inapnine®). Go to medication section and check the Granisetron (Kytril®) only option. If No go to medication section and check the Granisetron (Kytril®) and Droperidol (Inapnine®) option.

**MEDICATIONS:**

- Discontinue all previous antiemetic orders.

  - Granisetron (Kytril®) option
    - Granisetron (Kytril®) 0.1 mg IV once every 24 hours PRN nausea or vomiting, Reasses for nausea and vomiting 30 minutes after administration. Note: Granisetron (Kytril®) can only be given once in a 24 hour period. If unrelieved notify service for orders.

  - Granisetron (Kytril®) and Droperidol (Inapnine®) option
    - Granisetron (Kytril®) 0.1 mg IV every 24 hours PRN nausea or vomiting, Reasses for nausea and vomiting 30 minutes after administration. Note: Granisetron (Kytril®) can only be given once in a 24 hour period. If unrelieved proceed to Droperidol (Inapnine®) option.

    - Droperidol (Inapnine®) 0.625 mg IV every 30 minutes PRN nausea or vomiting. Reasses for nausea and vomiting 30 minutes after administration, if unrelieved repeat Droperidol (Inapnine®) 0.625 mg IV every 30 minutes until nausea and vomiting relieved or maximum of 3 doses have been given within a 24 hour period. If nausea or vomiting unrelieved after maximum Droperidol given notify service for orders.

    - If patient becomes nauseated or begins vomiting 24 hours after the administration of Granisetron restart protocol, administer Granisetron first.

Registered Nurse Signature: ___________________________ Nurse Pager # (if applicable): ___________________________
Registered Nurse Printed Name: _________________________ Date: mm/dd/yyyy Time: h m m

This protocol has been developed to reflect the practice patterns of the clinicians who wrote it. It sets forth recommendations as to practice, not rigid rules.
Appendix III – Consent Form

Protocol Title: The Incidence of Dysesthesia When Droperidol is used for Prophylaxis of Post Operative Nausea and Vomiting
IRB #: 11-007361
Principal Investigator: Dr. Michael Murray

You are being asked to participate in a research study about the drug droperidol. Some Emergency Department doctors have found that as many as 30% of patients who receive the drug have unpleasant sensations called dysesthesia - not feeling quite right afterwards. We use droperidol to help prevent nausea and vomiting following surgery – because it is very effective and because we find that may have FEWER side effects than other drugs we use. My colleagues and I are interested in knowing if our patients have any unpleasant sensations following the administration of droperidol.

If you agree to participate you will be asked to complete a short survey of 7 questions before surgery and 3 questions following surgery in the recovery room.

This study will not make your health better. It is for the benefit of research.

Please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty. Specifically, your current or future medical care at the Mayo Clinic will not be jeopardized if you choose not to participate.

If you have any questions about this research study you can contact me at 904-504-1454. If you have any concerns, complaints, or general questions about research or your rights as a participant, please contact the Mayo Institutional Review Board (IRB) to speak to someone independent of the research team at 507-266-4000 or toll free at 866-273-4681