Efficacy of Ephedrine in the Prevention of Postoperative Nausea and Vomiting

David M. Rothenberg, MD, Samuel M. Parnass, MD, Kim Litwack, PhD, RN, Robert J. McCarthy, PharmD, and L. Michael Newman, MD, PhD

Although reported in the aerospace literature and anecdotally by anesthesiologists, the putative antiemetic effect of ephedrine remains unquantitated. We therefore prospectively studied ephedrine as an antiemetic agent in the perioperative setting in 97 patients undergoing general anesthesia for outpatient gynecologic laparoscopy. Patients were assigned in a double-blind randomized fashion to receive a standardized general anesthetic followed by an intramuscular dose of either ephedrine (0.5 mg/kg), droperidol (0.04 mg/kg), or saline before the conclusion of surgery. Nausea, retching, or vomiting, as well as the degree of sedation and discharge times, were assessed in the recovery room and for 24 h postoperatively. Ephedrine was found to have a significantly antiemetic effect (P < 0.05) when compared with placebo and an antiemetic effect similar to that of droperidol. Sedation scores were also significantly less in the ephedrine group than in both placebo and droperidol groups. Finally, variations in mean arterial blood pressure among the three groups were not statistically significant. We conclude that ephedrine is an effective antiemetic agent with minimal sedative side effects in patients undergoing outpatient laparoscopy.

Key Words: VOMITING, POSTOPERATIVE—ephedrine. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—ephedrine, antiemetic effects.

The incidence of postoperative nausea and vomiting in ambulatory surgery has been reported to be as high as 50% (1,2). Surgical procedures such as laparoscopy, therapeutic abortions, orchiopectomy, varicocelectomy, or strabismus surgery are associated with an especially high incidence of nausea and vomiting (1,3–6). In an ambulatory surgery population this may prove to be an especially difficult problem, with early discharge from the ambulatory unit often being precluded by postoperative nausea and vomiting, or by the sedative side effects of currently used antiemetic agents. The prophylactic use of ephedrine as an antiemetic agent has been described for the prevention of motion sickness (7,8). Although ephedrine has been utilized in treating nausea and vomiting in the postanesthesia recovery rooms, especially in patients whose symptoms are related to their assuming an upright position (B. V. Wetchler, personal communication), there are at present no controlled studies assessing the effect of ephedrine in preventing nausea and vomiting after general anesthesia. This study was therefore designed to determine the antiemetic effect of ephedrine in a prospective, randomized, and double-blinded fashion in patients undergoing outpatient gynecologic laparoscopy.

Methods
After approval of our institution's Human Investigation Committee, informed consent was obtained from 100 ASA physical status I or II patients undergoing outpatient gynecologic laparoscopy. Exclusion criteria included patients with a history of hypertension or organic heart disease, and patients being treated preoperatively with medications with potential antiemetic effects (e.g., benzodiazepines, steroids, droperidol, scopolamine, antihistamines, or metoclopramide).

After preoxygenation and defasciculation with 3 mg intravenous (IV) d-tubocurare, induction of anesthesia was achieved with 5 mg/kg IV thiopental.
followed by endotracheal intubation facilitated with 1.5 mg/kg IV sucumicholine. Positive pressure ventilation by mask was avoided before intubation so as to minimize gastric distention. All patients received 2 μg/kg IV fentanyl as part of a balanced anesthetic technique and to provide postoperative analgesia. Anesthesia was maintained with hemodynamically adjusted levels of isoflurane in nitrous oxide (70%) and oxygen (30%). Muscle relaxation in accordance with surgical needs was achieved with intermittent doses of vecuronium. No other anesthetic agents or intraoperative medications were used. All patients received IV infusions of lactated Ringer’s solution in quantities determined to be appropriate by the anesthesiologist.

Before reversal of neuromuscular blockade with 0.07 mg/kg IV neostigmine and 0.01–0.02 mg/kg IV glycopyrrolate, a blinded dose of either placebo (0.9% saline intramuscular [IM]), 0.04 mg/kg IM droperidol, or 0.5 mg/kg IM ephedrine was administered. All doses were prepared in equal volumes, and all IM injections were made into the deltoid muscle using a 22-gauge needle.

In the recovery room the patients were evaluated every 5–10 min for nausea, retching, or vomiting by a nurse not directly involved in the study. If a patient experienced some or all of these signs or symptoms, she was categorized by the most severe sign or symptom (i.e., if the patient had nausea and vomiting, she was classified as vomiting). Nausea was assessed by the recovery room nurse asking “Do you have any complaints?” Sedation was assessed using a three-point scale: 0, unarousable; 1, lethargic; 2, alert. Nausea, retching, vomiting, or pain were treated at the discretion of the patient’s anesthesiologist. The type and dosage of antiemetic or analgesic administered were documented. Time between arrival in the recovery room and the ability to ambulate without symptoms, as well as the time to discharge, were recorded, as were total IV fluids. Mean arterial pressure and heart rate were recorded every 5–10 min.

Within 24 h a telephone call was made to each patient to inquire about the above or additional postoperative symptoms.

Ordinal data were analyzed by χ² and interval data by analysis of variance. Significance was accepted at P < 0.05.

### Results

Of the 100 patients studied, three patients required laparotomy and were therefore excluded from the study. Of the remaining 97 patients, 33 were assigned to the placebo group, 32 to the droperidol group, and 32 to the ephedrine group. There were no differences in regard to age, weight, amount of IV fluids administered, or duration of anesthesia between the three groups (Table 1).

The incidence of nausea, retching, and vomiting in both the recovery room and at home appears in Table 2. Ephedrine was as effective as droperidol, and both were significantly more effective than placebo in minimizing nausea and vomiting. Patients in both the droperidol and ephedrine groups required significantly less antiemetic therapy in the immediate postoperative period. Also, patients who received ephedrine had significantly lower sedation scores than patients given either droperidol or saline (P < 0.01) (Table 2). A trend toward shorter discharge time was noted in the ephedrine group (P = 0.08); however, statistical significance was not achieved. Finally, there were no significant differences among the three groups with regard to mean arterial pressure. Follow-up evaluation of the patients at home showed no significant differences in the incidence of vomiting, nor were any other untoward events noted (e.g.,

<table>
<thead>
<tr>
<th>Group</th>
<th>Saline</th>
<th>Droperidol</th>
<th>Ephedrine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>33</td>
<td>32</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32 ± 6</td>
<td>31 ± 6</td>
<td>30 ± 6</td>
<td>0.32</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 ± 15</td>
<td>62 ± 13</td>
<td>66 ± 9</td>
<td>0.30</td>
</tr>
<tr>
<td>Length of anesthesia (min)</td>
<td>64 ± 34</td>
<td>59 ± 23</td>
<td>68 ± 23</td>
<td>0.41</td>
</tr>
<tr>
<td>Fluids in operating room (mL)</td>
<td>1059 ± 476</td>
<td>960 ± 262</td>
<td>1132 ± 446</td>
<td>0.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Saline</th>
<th>Droperidol</th>
<th>Ephedrine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total nausea/retch/vomit</td>
<td>66.7</td>
<td>37.5a</td>
<td>34.4b</td>
<td>0.01</td>
</tr>
<tr>
<td>Antiemetic treatment (%)</td>
<td>51.5</td>
<td>18.8a</td>
<td>21.9b</td>
<td>0.01</td>
</tr>
<tr>
<td>Sedation (%)</td>
<td>36.4c</td>
<td>65.6</td>
<td>6.3nd</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Discharge time (min)</td>
<td>91 ± 39</td>
<td>97 ± 51</td>
<td>76 ± 39</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Time 0</td>
<td>102 ± 13</td>
<td>94 ± 19</td>
<td>99 ± 10</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>99 ± 10</td>
<td>92 ± 12</td>
<td>92 ± 9</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>92 ± 11</td>
<td>88 ± 14</td>
<td>86 ± 11</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up

| Vomit at home (%) | 9.1 | 6.3 | 6.3 | 0.88 |

*P < 0.05 compared with saline data.

*P < 0.05 compared with droperidol data.

*P < 0.05 compared with droperidol data.
severe nausea, prolonged sedation, dystonic reactions, or palpitations).

Discussion
The prevention and treatment of nausea and vomiting after general anesthesia for outpatient surgery continues to pose significant problems for both patients and ambulatory surgery units. Nausea and vomiting are among the most common complications of outpatient surgery and the number one nonsurgical reason for unexpected admission to the hospital (9). Previous studies have reported varying success rates with different antiemetic therapies (10–12). Sedation due to large dosages of antiemetics may delay discharge from a recovery room, and late side effects with droperidol, such as anxiety and restlessness, have been reported in ambulatory surgery patients (13). In our study we attempted to evaluate the efficacy of ephedrine as a nonsedating antiemetic agent for preventing nausea and vomiting after outpatient gynecologic laparoscopy.

Ephedrine, a sympathomimetic drug, was found by Wood and Graybiel as early as 1968 to be effective in preventing motion sickness (7). Studying the effects of scopolamine on motion sickness in healthy naval volunteers, they gave ephedrine with scopolamine in an attempt to counteract the sedative side effects of scopolamine. They found that not only was the combination effective in minimizing motion sickness, but that ephedrine alone (administered in a control group) also had a significant antiemetic effect. Other sympathomimetic drugs have been reported in the early literature to be effective in treating motion sickness (7). The beneficial effects of these agents are bolstered by the fact that phenoxybenzamine, a sympatholytic drug, causes symptoms that mimic true motion sickness. Motion sickness is believed to be caused by a disequilibrium in the vestibular apparatus that, in turn, sends afferent impulses to the chemoreceptor trigger zone via cholinergic and histaminic fibers and thence to the vomiting center (8).

Whether this pathway is ultimately responsible for the nausea and vomiting seen after surgery and anesthesia is only speculative. A high degree of vagal tone in the perioperative period may also add to the incidence of postoperative nausea and vomiting, and ephedrine may minimize these symptoms by increasing sympathetic tone. This is presumed to be the mechanism by which the parasympatholytic agent scopolamine acts to prevent nausea and vomiting (14).

Finally, hypotension during spinal or epidural anesthesia, is often heralded by nausea and vomiting. This has been ascribed in part to a reduction in medullary blood flow to the chemoreceptor trigger zone (15), and therefore ephedrine is commonly employed to increase mean arterial pressure and presumably improve medullary blood flow, thus minimizing these symptoms. An increase in gastric peristalsis due to preganglionic sympathetic denervation of the stomach may also provoke nausea and vomiting during spinal anesthesia (16), but whether ephedrine could mitigate this mechanism remains unknown. Ephedrine may also have beneficial effects in minimizing the nausea and vomiting associated with postural hypotension after outpatient surgery. These signs and symptoms may occur after general anesthesia, especially with ambulation, due either to intravascular volume depletion or to residual vasodilation from potent inhalation anesthetics, or both.

Concerns about the prophylactic use of ephedrine in patients with hypertension or organic heart disease are valid; therefore, we avoided its use in such patients so as to minimize the risk of potential myocardial or cerebrovascular damage. In otherwise healthy patients the risks of prophylactic ephedrine appear to be minimal. Phenylpropanolamine, a racemic form of norephedrine, has been anecdotally reported to cause transient elevations in blood pressure (17) and cerebrovascular complications after higher doses in susceptible patients (18,19). Most of these studies, however, were done with small numbers of patients, without controls, and with large doses of phenylpropanolamine. A more recent multicenter, double-blind study failed to show any significant hemodynamic response with a 75-mg dose of phenylpropanolamine when administered on a short-term basis (20).

This study demonstrates that ephedrine is an effective prophylactic antiemetic agent in patients having general anesthesia for outpatient laparoscopy. It may be particularly indicated as prophylaxis in patients prone to motion sickness or for those in whom dizziness, nausea, and/or vomiting occur upon ambulation postoperatively. Its mechanism of action as an antiemetic is uncertain, but when compared with a relatively high dose of droperidol it is equally effective and minimizes sedation.

References
2. Rising S, Dodgson MS, Steen PA. Isoflurane v. fentanyl for


