Efficacy of Ondansetron and Prochlorperazine for the Prevention of Postoperative Nausea and Vomiting After Total Hip Replacement or Total Knee Replacement Procedures

A Randomized, Double-blind, Comparative Trial

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Background: Limited data are available on the efficacy of ondansetron hydrochloride compared with prochlorperazine maleate for the treatment of postoperative nausea and vomiting (PONV).

Objective: To evaluate the comparative efficacy of ondansetron and prochlorperazine for the prophylaxis of PONV in patients undergoing total hip replacement or total knee replacement procedures.

Methods: A randomized, double-blind, comparative trial was conducted at a tertiary care, university hospital. Seventy-eight patients undergoing elective total hip or total knee replacement procedures received a single dose of ondansetron hydrochloride (n = 37), 4 mg intravenously, or prochlorperazine maleate (n = 41), 10 mg intramuscularly, at the end of the surgical procedure. Rescue therapy was administered every 4 hours as needed during the initial 48 hours. Primary outcome measures were the incidences and severity of PONV. Secondary outcome measures included the number of rescue antiemetic doses required, number of physical therapy cancellations because of PONV, length of hospital stay, and cost of antiemetic agents administered.

Results: The incidence of nausea was significantly greater in the ondansetron group compared with the prochlorperazine group (81% vs 56%; odds ratio, 3.4; 95% confidence interval, 1.2-9.4) as was the severity of nausea ($P = .04$). Multivariate analysis identified administration of ondansetron, history of PONV, obesity, and female sex as risk factors for a nausea event. The incidence of vomiting tended to be greater in the ondansetron group (49% vs 32%; odds ratio, 2.0; 95% confidence interval, 0.8-5.0). The need for rescue antiemetic therapy was also greater in the ondansetron group (46% vs 27%; odds ratio, 2.3; 95% confidence interval, 0.9-6.0). The mean antiemetic drug cost per patient was significantly greater for the ondansetron group ($47.56 vs $2.47; P < .001$). However, the proportion of patients who were unable to participate in physical therapy because of PONV and the median length of hospital stay were similar in both groups.

Conclusion: Prochlorperazine is associated with superior efficacy and significant cost savings compared with ondansetron for the prevention of PONV in patients undergoing total hip and total knee replacement procedures.

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POSTOPERATIVE nausea and vomiting (PONV) is a frequent and clinically significant complication of surgery and anesthesia. Physical and psychological complications of nausea and vomiting include aspiration of vomitus, esophageal trauma (Mallory-Weiss syndrome or Boerhaave syndrome), dehydration, alkalalemia, and emotional distress. Orkin reports that for patients undergoing surgical anesthesia, the avoidance of PONV is of great concern, more so than the issues of pain, dysphoria, decreased mental acuity, and extraneous cost of postoperative care.

Total joint replacement procedures in the United States are characterized by high costs and high volume. Many orthopedic surgical centers have implemented total joint replacement clinical pathways in an attempt to reduce resource utilization and maintain quality of care. In general, total joint replacement clinical pathways encourage patients to begin physical therapy on the first day after surgery. However, persistent PONV may interfere with physical therapy activities. Incidences of PONV greater than or equal to 80% have been reported for patients after undergoing total joint replacement procedures with surgical anesthesia and no antiemetic prophylaxis. Increasingly, older patients with multiple comorbid conditions are undergoing total joint replacement procedures. This older patient population may be more prone to adverse sequelae. In addition, PONV can result in economic mor-
PATIENTS AND METHODS

Patients undergoing elective, primary, or revisionary total hip or total knee replacement procedures were eligible for participation in the study. The study protocol and informed consent forms were in accordance with the ethical standards of the Human Investigation Committee of the Rush–Presbyterian–St Luke’s Medical Center, Chicago, Ill. Patients were eligible if the following criteria were met: provision of written informed consent, age older than 17 years, and American Society of Anesthesiologists physical status I to III. Patients were excluded if antiemetic agents were administered within the 24 hours before surgery, if there was a history of hypersensitivity to ondansetron or phenothiazines, or if female patients were pregnant or breastfeeding.

The following definitions have been adopted for the purposes of this study: (1) nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit but not necessarily followed by retching or vomiting; (2) retching was defined as labored, spasmodic, rhythmic contractions of the respiratory muscles, including the diaphragm, chest wall, and abdominal wall muscles, without the expulsion of gastric contents; (3) vomiting was defined as the involuntary and forceful expulsion of gastric contents from the mouth; and (4) emetic episode was defined as retching and/or vomiting events occurring sequentially but not more than 1 minute apart.

Patients were randomized (using a random numbers table) into 2 treatment groups: the ondansetron group (n = 37) received ondansetron hydrochloride, 4 mg (in 10 mL of 0.9% isotonic sodium chloride) intravenously, concomitantly with 0.9% isotonic sodium chloride (2 mL) intramuscularly; and the prochlorperazine group (n = 41) received prochlorperazine maleate, 10 mg (2 mL) intramuscularly, concomitantly with 0.9% isotonic sodium chloride (10 mL) intravenously. The initial antiemetic dose was administered in the operating suite on completion of the surgical procedure. Because of differences in the route of administration of intravenous ondansetron and intramuscular prochlorperazine, a concomitant placebo was administered to each patient to maintain the double-blind method. Therefore, each patient received both an intravenous and an intramuscular injection. Study drug and placebo were prepared by the Department of Pharmacy.

Inhalational anesthesia consisted of a nitrous oxide and isoflurane combination. Patients undergoing regional anesthesia received either bupivacaine hydrochloride or lidocaine administered epidurally. For the induction of anesthesia, patients received intravenous fentanyl citrate and midazolam hydrochloride. For postoperative analgesia, all patients received either morphine sulfate administered intravenously (ie, patient-controlled administration device) or fentanyl administered epidurally. All epidural catheters were removed within 48 hours after surgery. Patients were allowed to receive supplemental oral or parenteral doses of analgesics at the discretion of the attending physician.

During the 48-hour postoperative period, nurses assessed for and documented the presence and severity of nausea or vomiting at 14 predefined time intervals. The number of emetic episodes occurring during each interval was recorded. The severity of nausea was rated by the patient by the use of a verbal rating scale (ie, scale of 0-4 with 0 indicating none; 1, mild; 2, moderate; 3, severe; and 4, unbearable). Rescue doses for nausea were administered if vomiting occurred or if requested by the patient. The rescue antiemetic consisted of the originally assigned study drug (along with concomitant placebo) administered every 4 hours as needed during the 48-hour postoperative period. If symptoms of nausea and vomiting were not relieved within 1 hour after the initial rescue dose, a second dose was administered. If symptoms of nausea and vomiting remained unrelieved or progressed in severity, the patient’s status was “unblinded” but he or she was not withdrawn from the evaluation of efficacy.

The χ² test and Fisher exact test were used for analyses of categorical outcomes (eg, presence of nausea or vomiting, nausea score, and number of emetic episodes). Logistic regression analysis was used to determine predictor variables for the occurrence of nausea and vomiting. Ordinary least-squares regression was used to determine predictor variables for the severity of nausea. The 2-sample t test was used for analyses of all parametric data (eg, mean antiemetic cost per patient). All reported P values are 2-tailed. The study was designed to enroll 80 patients to provide a power of 80% to detect for a 30% difference in the incidence of nausea or vomiting with an α level of .05.

The main objective of this study was to evaluate, in a double-blind and randomized manner, the comparative efficacy of ondansetron hydrochloride (4 mg) administered intravenously and prochlorperazine maleate (10 mg) administered intramuscularly for the prophylaxis of PONV in patients undergoing total hip replacement or total knee replacement procedures. Patients were assessed for 48 hours postoperatively. More specifically, we determined whether there were statistically significant differences in (1) the incidence and severity of nausea, (2) the incidence and severity of vomiting (including retching), (3) the number of rescue antiemetic doses required, (4) the proportion of patients unable to participate in physical therapy sessions because of PONV, (5) the length of hospital stay, and (6) the mean antiemetic cost per patient.
Eighty patients were enrolled in the study; however, 2 patients in the ondansetron group were excluded from data analysis on the basis of incomplete data collection. No significant adverse drug reactions were reported from either group. The baseline characteristics of the ondansetron and prochlorperazine groups are listed in Table 1. No statistically significant differences in baseline characteristics were found between the 2 groups. The age and sex characteristics of our study population were consistent for patients undergoing total hip replacement and total knee replacement procedures.

Patients in the ondansetron group were 3.4 times more likely to experience nausea (Table 2). In addition, ondansetron-treated patients rated their severity of nausea greater compared with prochlorperazine-treated patients. The incidence of vomiting was greater in the ondansetron group; however, the severity of vomiting (as measured by the number of emetic episodes) was similar in both groups. Logistic regression analysis identified predictor variables for the occurrence of a nausea event as a history of PONV, female sex, and obesity (Table 3). After controlling for these variables, the administration of ondansetron remained a significant risk factor for the occurrence of a nausea event. After controlling for risk factors in a stepwise ordinary least-squares regression model, ondansetron-treated patients rated their nausea score approximately 0.5-point greater compared with prochlorperazine-treated patients (β coefficient = .48, P = .06).

Multivariate analysis identified predictor variables for the occurrence of an emetic episode as obesity (odds ratio, 12.0; 95% confidence interval, 2.0-72.2; P = .007) and a history of PONV (odds ratio, 3.9; 95% confidence interval, 1.1-13.6; P = .03). After controlling for these variables in a multivariate logistic regression model, no statistically significant advantage was associated with either agent for emesis outcome.

Differences in the incidence of PONV based on type of joint replacement procedure, patient sex, obesity, history of PONV, method of postoperative analgesia, and method of surgical anesthesia are shown in Table 4. The characteristics of female sex, obesity, and history of PONV were associated with a greater incidence of PONV. Of interest are the sex-specific findings as summarized in...
perior control of PONV in patients undergoing total hip replacement or total knee replacement procedures.

The incidence of nausea and vomiting in this study is greater than that reported by others for this patient population. This may be accounted for by differences in patient characteristics or study methods. A significant proportion of patients in our study had 1 or more factors that have been associated with an increased risk of PONV (ie, female sex, obesity, history of PONV, nonsmoker, duration of anesthesia longer than 120 minutes). Also, the 48-hour assessment period in our study is of greater duration compared with that of other studies. Despite the high proportion of obese patients in our study, we do not believe that the lack of a weight-based dosage adjustment for antiemetics had an effect on the study outcomes. The ondansetron dosage used in our study was based on published and unpublished data that demonstrated doses greater than 4 mg administered intravenously do not confer significantly greater benefits. In addition, no information is available that would support the use of a weight-based dosage adjustment for prochlorperazine in adults.

Table 5. Women in both treatment groups experienced similar incidences of PONV. In contrast, ondansetron-treated men experienced a 3 to 4 times greater incidence of PONV compared with prochlorperazine-treated men.

A greater proportion of ondansetron-treated patients (46% [17/37]) required supplemental rescue doses compared with prochlorperazine-treated patients (27% [11/41]) (odds ratio, 2.3; 95% confidence interval, 0.9-6.0; \( P = .08 \)). Among those who received a rescue dose, the mean (SD) number of doses was 2.1 (1.6) for the ondansetron group and 1.7 (1.0) for the prochlorperazine group (\( P = .50 \)).

The proportion of patients who had cancelled at least 1 physical therapy session because of PONV was similar in both treatment groups (11% [4/37] vs 7% [3/41] for the ondansetron and prochlorperazine groups, respectively; \( P = .70 \)). The mean (SD) length of hospital stay also was similar for both groups, with a mean stay of 5.1 (1.4) days for the ondansetron group and 4.9 (1.2) days for the prochlorperazine group (\( P = .50 \)).

The cost of drug therapy per patient (prophylactic dose plus supplemental rescue doses) associated with the ondansetron group was approximately 19 times greater than that of the prochlorperazine group. The ondansetron group received a total of 72 doses for a cost per patient of $47.56 and the prochlorperazine group received a total of 60 doses for a cost per patient of $2.47 (\( P < .001 \)).

## Table 4. Incidence of Postoperative Nausea and Vomiting (PONV) in Various Subgroups of Patients

<table>
<thead>
<tr>
<th>Subgroup (n)</th>
<th>Nausea (%)</th>
<th>Vomiting (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement (40)</td>
<td>28 (70)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Total knee replacement (38)</td>
<td>25 (66)</td>
<td>17 (45)</td>
</tr>
<tr>
<td>Female (49)</td>
<td>39 (80)*</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Male (29)</td>
<td>14 (48)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Obese (60)</td>
<td>44 (73)‡</td>
<td>29 (49)§</td>
</tr>
<tr>
<td>Nonobese (18)</td>
<td>9 (50)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>History of PONV (26)</td>
<td>23 (88)</td>
<td>14 (54)</td>
</tr>
<tr>
<td>No history of PONV (52)</td>
<td>30 (58)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Patient-controlled analgesia (20)</td>
<td>16 (80)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Epidural analgesia (58)</td>
<td>37 (64)</td>
<td>20 (35)</td>
</tr>
<tr>
<td>Intraoperative anesthesia (52)</td>
<td>34 (65)</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Regional anesthesia (26)</td>
<td>18 (69)</td>
<td>12 (46)</td>
</tr>
</tbody>
</table>

*Greater incidence compared with males (\( P = .004 \)).
†Defined as greater than 120% ideal body weight.
‡Greater incidence compared with nonobese patients (\( P = .03 \)).
§Greater incidence compared with patients without a history of PONV (\( P = .006 \)).

## Table 5. Gender-Based Incidences of Nausea and Vomiting in Patients Treated With Ondansetron and Prochlorperazine

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Nausea, No. (%)</th>
<th>Vomiting, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (24)</td>
<td>20 (83)</td>
<td>.64 12 (50)</td>
</tr>
<tr>
<td>Male (13)</td>
<td>10 (77)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (25)</td>
<td>19 (76)*</td>
<td>.001 11 (44)†</td>
</tr>
<tr>
<td>Male (16)</td>
<td>4 (25)</td>
<td>2 (12)</td>
</tr>
</tbody>
</table>

*Odds ratio = 9.5 (95% confidence interval, 2.2-40.8) for prochlorperazine-treated females vs males.
†Odds ratio = 5.5 (95% confidence interval, 1.0-29.5) for prochlorperazine-treated females vs males.

Data on the comparative efficacy of ondansetron and prochlorperazine for the management of PONV have not been previously published. The results of this randomized, double-blind study demonstrate that, compared with ondansetron, prochlorperazine provides su-

## Table 5

Women in both treatment groups experienced similar incidences of PONV. In contrast, ondansetron-treated men experienced a 3 to 4 times greater incidence of PONV compared with prochlorperazine-treated men.

A greater proportion of ondansetron-treated patients (46% [17/37]) required supplemental rescue doses compared with prochlorperazine-treated patients (27% [11/41]) (odds ratio, 2.3; 95% confidence interval, 0.9-6.0; \( P = .08 \)). Among those who received a rescue dose, the mean (SD) number of doses was 2.1 (1.6) for the ondansetron group and 1.7 (1.0) for the prochlorperazine group (\( P = .50 \)).

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(Data were based on 1997 average wholesale prices and did not include drug administration fees, administration devices and supplies, or staff labor.)

## COMMENT

The incidence of nausea and vomiting in this study is greater than that reported by others for this patient population. This may be accounted for by differences in patient characteristics or study methods. A significant proportion of patients in our study had 1 or more factors that have been associated with an increased risk of PONV (ie, female sex, obesity, history of PONV, nonsmoker, duration of anesthesia longer than 120 minutes). Also, the 48-hour assessment period in our study is of greater duration compared with that of other studies. Despite the high proportion of obese patients in our study, we do not believe that the lack of a weight-based dosage adjustment for antiemetics had an effect on the study outcomes. The ondansetron dosage used in our study was based on published and unpublished data that demonstrated doses greater than 4 mg administered intravenously do not confer significantly greater benefits. In addition, no information is available that would support the use of a weight-based dosage adjustment for prochlorperazine in adults.

Of interest are the contrasting sex-specific outcomes between the ondansetron- and prochlorperazine-treated patients. The incidences of PONV associated with ondansetron seem to be independent of sex (ie, similar results between men and women). In contrast, the incidences of PONV associated with prochlorperazine seem to be dependent on sex (ie, greater in women compared with men). To our knowledge, these sex-specific antiemetic activities of prochlorperazine and ondansetron have not been described in the literature. In our study, subset analysis based on patient sex revealed that ondansetron-treated women experienced similar incidences of PONV when compared with prochlorperazine-treated women (Table 5). Had our study enrolled a predominantly female population (eg, patients undergoing gynecological surgery), differences in efficacy may not have been detected. Sex-based differences are plausible and may be due to drug-related differences in chemical structure, receptor specificity, pharmacogenetic variations, or pharmacodynamic interactions involving sex hormones. Additional studies designed to investigate sex-specific differences in the antiemetic activity of pharmacologic agents may shed more light on this issue.

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Despite the better control of PONV associated with prochlorperazine, the proportion of patients who had cancelled at least 1 physical therapy session because of PONV was similar in the ondansetron and prochlorperazine groups. In addition, the mean length of hospital stay was similar for both treatment groups (ie, 5 days).

The need for rescue therapy was significantly greater in the ondansetron group. This observation is not surprising given the greater incidence of PONV in the ondansetron group. Owing to the greater acquisition cost of ondansetron compared with prochlorperazine, it is also of no surprise that the mean antiemetic drug cost per patient was significantly greater in the ondansetron-treated group ($47.56 vs $2.47).

Although our secondary end points, which measured differences in physical therapy cancellations, length of hospital stay, and costs of antiemetic drug per patient, may significantly contribute to medical costs, we did not measure other PONV-related factors that may contribute to incurred costs (eg, direct costs associated with patient emesis, including staff time and materials expended toward assisting and cleaning the patient and other miscellaneous sanitizing costs). Indirect costs associated with PONV include lost wages due to the inability to function or work (most relevant in the outpatient setting), patients’ satisfaction with antiemetic therapy, patients’ willingness to pay to avoid a PONV experience, quality of life, and impact on family and caregivers. Additional analyses are warranted to investigate these outcomes.

In conclusion, prochlorperazine has demonstrated superior clinical efficacy compared with ondansetron in preventing PONV and is associated with less severe nausea. Despite the absence of statistically significant differences in the mean number of emetic episodes, cancellations of physical therapy sessions, or length of hospital stay, prochlorperazine can be considered a clinically superior agent. In addition, the cost of prochlorperazine is significantly less compared with ondansetron. Based on a cost-minimization model, it is appropriate to state that the use of prochlorperazine is a more cost-effective antiemetic regimen compared with ondansetron for the prevention of PONV in patients undergoing total hip and total knee replacement procedures.

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