A Meta-analysis of the Efficacy of Granisetron 0.1 mg for Postoperative Nausea and Vomiting (PONV)

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Citation

Abstract
This meta-analysis of published randomized clinical trials (RCTs) compared the efficacy of granisetron 0.1 mg versus ≥ 1.0 mg for prevention of postoperative nausea and vomiting (PONV). Efficacy data (proportion of patients without PONV or requiring rescue medication) were extracted and stratified by the postoperative period (i.e., early, late, and overall). Meta-analytic techniques were used to integrate findings and estimate pooled efficacy. Ten RCTs met inclusion criteria, but only 2 directly compared granisetron 0.1 mg versus 1.0 mg, which was insufficient for meta-analysis, necessitating indirect comparisons between pairwise sets of granisetron 0.1 mg and granisetron 1.0 mg with common comparators: placebo and granisetron dose levels > 1.0 mg. Granisetron 0.1 mg appears to be at least as effective as granisetron 1.0 mg during the early and overall postoperative periods. There were insufficient data for meta-analysis of any outcomes during the late postoperative period.

CONFLICT OF INTEREST DISCLOSURE
The author received in the past financial support (Independent Investigator Grant) from Roche Pharmaceuticals (maker of Kytril-granisetron).

INTRODUCTION
Postoperative nausea and vomiting (PONV), a common adverse effect of general anesthesia following surgery, may result in increased medical resource utilization (e.g., increased time in the postoperative care unit, unanticipated hospital admission). Postoperative patients find vomiting more distressing than pain [1,2]. Patients with 3 or 4 risk factors, based on surgical procedure (e.g., gynecologic, breast, craniotomy, laparotomy, laparoscopy) and/or patient history (e.g., history of PONV and/or motion sickness, female, nonsmoking), have a 40% to 80% risk of developing PONV [1,2].

An important class of antiemetic agents used to prevent and/or treat PONV are serotonin 5-hydroxytryptamine subtype 3 receptor antagonists (5-HT3, RAs), which specifically and selectively bind to serotonin 5-HT3 receptors on afferent vagal pathways in the gastrointestinal tract and at the chemoreceptor trigger zone in the brain, resulting in decreased serotonin levels [3,4]. 5-HT3 RAs currently approved by the US Food and Drug Administration for prevention of PONV are dolasetron (Anzemet, Aventis Pharmaceuticals, Inc., Kansas City, MO), granisetron (Kytril, Roche Laboratories, Inc., Nutley, NJ), and ondansetron (Zofran, GlaxoSmithKline, Philadelphia, PA). Granisetron is the only 5-HT3 RA that is not metabolized by the cytochrome (CYP)2D6 pathway. Other 5-HT3, RAs that require CYP2D6 for metabolism may adversely affect patients with certain genotype polymorphisms, resulting in 5-HT3 RA metabolism that is too rapid or poor, leading to decreased therapeutic efficacy and possible failure to prevent PONV [1,2].

Granisetron is available for injection (IV) in 1 mg/ml and 0.1 mg/ml single-use vials and orally (PO) as a 1-mg tablet and 2 mg/10 ml solution [5,6]. There is a substantial difference in the cost of injectable granisetron. In the United States, the average wholesale price for a granisetron IV 1 mg/ml vial is $195, whereas the average wholesale price for granisetron IV 0.1 mg/ml is $12.03. Use of granisetron 0.1 mg/ml potentially represents a 94% savings compared with granisetron 1.0 mg. However, concerns that granisetron 0.1 mg may not be as effective as granisetron 1.0 mg for preventing PONV have been raised.

Studies of granisetron 0.1 mg for PONV have yielded conflicting outcomes. Corman et al. [7] conducted a review of low-dose granisetron and, based on the scarcity of data, recommended against using granisetron 0.1 mg for prophylaxis in patients at risk of PONV. However, in a
recently published double-blind randomized controlled trial (RCT), Gan et al. [12] observed no significant difference in the incidence of vomiting, nausea, and rescue medication, from 0 to 6 hours and from 0 to 24 hours postoperatively following abdominal hysterectomy, in patients who received granisetron 0.1 mg with dexamethasone 8 mg or ondansetron 4 mg with dexamethasone 8 mg. D’Angelo et al. [1], in another recently published double-blind RCT of postabdominal hysterectomy patients treated with granisetron at 0.1, 0.2, or 0.3 mg doses or placebo, reported a trend of improved efficacy compared with placebo during the first 6 hours postoperatively.

Our objective was to use meta-analytic techniques to determine and compare the efficacy of granisetron 0.1 mg and 1.0 mg for PONV. A meta-analysis is a systematic, quantitative review in which the results of at least 2 primary studies are pooled to determine the effect of a treatment. Meta-analyses, which are potentially very useful when clinical trials (primarily RCTs) yield conflicting results, historically have been frequently used to assess PONV efficacy of various 5-HT3 agents [13,14,15,16,17,18,19,20,21,22,23].

**METHODS**

**SEARCH STRATEGY AND STUDY INCLUSION**

MEDLINE and the Cochrane Library were searched for all RCTs published from 1966 through February 15, 2006, that included the terms “granisetron” or “Kytril” and excluded “chemotherapy,” “chemotherapeutic,” or “cancer” in the title. RCTs were included for analysis if they (1) pertained to prophylaxis and/or treatment of PONV, (2) used an adult population, and (3) had at least one arm in which patients underwent prophylaxis or treatment of PONV with granisetron 0.1 mg or 1.0 mg (IV or PO) or a larger dose, alone or in combination with another agent (e.g., dexamethasone).

**DATA EXTRACTION**

Studies with 3 or more treatment arms were divided into pairwise comparisons (N_p) between an “intervention” group and a “control” group: patients receiving granisetron 0.1 mg or 1.0 mg (alone or in combinations with other agents) were designated as the “intervention” group, and those receiving active comparators (e.g., ondansetron, droperidol, other doses of granisetron) or placebo were designated as the “control” group. Efficacy data extracted from each treatment arm included: (1) proportion of patients without nausea, (2) proportion of patients without vomiting, and (3) proportion of patients requiring rescue medication. Efficacy data were stratified by postoperative period (defined by Habib et al. in 2004 [3]): early (0 to 6 hours postoperatively), late (> 6 to 24 hours), and overall (0 to 24 hours).

**STATISTICAL ANALYSIS**

Within-Studies Analyses. The effect size for the collected data (i.e., proportion of patients without vomiting, without nausea, or requiring rescue medication for PONV) was determined using odds ratios (ORs) with 95% confidence intervals (CIs), where OR indicates the number of events (i.e., episodes of nausea, vomiting, or use of rescue medication) divided by the number of non-events. If a CI did not cross 1.0 and the OR > 1.0, then the measured proportion was considered greater for the intervention group than for the control group in the pairwise comparison; conversely, an OR < 1.0 (CI excluding 0) meant that the measured proportion was greater for the control group. Statistical significance was determined using 2 tailed Fisher’s exact probability test with p < 0.05. However, because of possible multiple pairwise comparisons within a study, the conservative Bonferroni correction (p set at 0.05/number of pairwise comparisons in a study) was used to adjust statistical significance.

Pooled Studies: Meta-analyses. Meta-analytic techniques were employed to integrate findings and estimate overall effect sizes of granisetron 0.1 mg and 1.0 mg. Because there have been criticisms of the work of the Japanese group Fujii et al. [14,15,25,26] regarding serializations and concern that these data might affect meta-analytic outcomes, meta-analyses were conducted both including and excluding studies conducted by Fujii et al., whenever possible. ORs from pairwise comparisons were pooled (OR_p), CIs calculated, and fixed and/or random effects models employed. The Mantel-Haenszel method, which assumes that effect sizes do not significantly differ among studies, was used to calculate the fixed effects model. Its validity was tested by the heterogeneity statistic Q. When the p value for Q was significant (i.e., p < 0.05), the random effects model, which accounts for both random variations within and among studies, was employed using the method of DerSimonian and Laird [27]. Meta-analyses were performed for each efficacy outcome within each postoperative period and for safety outcomes during the overall postoperative period if and only if N_p ≥ 3 originated from ≥ 3 independent studies that reported the outcome variable.
Whenever there were insufficient data to directly compare granisetron 0.1 mg and 1.0 mg, meta-analytic techniques were used to indirectly compare them by identifying similar controls (comparators), i.e., versus placebo and versus granisetron doses > 1.0 mg. The use of indirect comparisons for meta-analyses has been established [28]. Pairwise comparisons of granisetron 0.1 mg and 1.0 mg with common comparators were pooled to determine effect sizes (OR\text{pool}). Statistical calculations were performed using MedCalc version 7.6.

RESULTS

STUDIES FOR ANALYSIS

A total of 154 RCTs were identified in the initial search. Among the 89 RCTs that pertained to PONV, 79 were excluded because they used a pediatric population or did not contain a treatment arm using granisetron 0.1 or 1.0 mg IV or PO. The remaining 10 RCTs (total of 1084 patients) included in the analysis are presented in Table 1 [12,13,31,32,33,34,35,36,37,38].

Granisetron was administered IV, except for the Fujii et al. studies [31,32,34]. Granisetron 0.1 mg–based therapy was used in 4 studies [12,13,31,32], and granisetron 1.0 mg–based therapy was used in 8 studies [29,30,31,32,33,34,35,36]. The 10 RCTs had a total of 29 randomized pairwise treatment comparisons (N\text{pair}): 9 between granisetron 0.1 mg and a comparator (N\text{pair} = 3 versus placebo, N\text{pair} = 5 versus another dose of granisetron, and N\text{pair} = 1 versus ondansetron/dexamethasone) and 20 between granisetron 1.0 mg and a comparator (N\text{pair} = 7 versus placebo, N\text{pair} = 10 versus granisetron > 1.0 mg, and N\text{pair} = 3 versus other active comparators). Because there were only 2 pairwise comparisons between granisetron 0.1 mg and granisetron 1.0

Table 1: Description of studies included in analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Surgical population</th>
<th>Administration</th>
<th>Intervention</th>
<th>Comparator/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gran et al. [12]</td>
<td>2005</td>
<td>Abdominal hysterectomy</td>
<td>EOS</td>
<td>0.3 mg + 0.1 mg</td>
<td>0.4 mg + 0.1 mg</td>
</tr>
<tr>
<td>D'Angelo et al. [13]</td>
<td>2006</td>
<td>Abdominal hysterectomy</td>
<td>15 min before ROS</td>
<td>0.1 mg</td>
<td>0.3 mg, Placebo</td>
</tr>
<tr>
<td>Dua et al. [35]</td>
<td>2004</td>
<td>Ob. radical hysterectomy</td>
<td>Before induction</td>
<td>0.1 mg</td>
<td>0.4 mg, Placebo</td>
</tr>
<tr>
<td>Hanseke et al. [36]</td>
<td>2004</td>
<td>Gynecologic surgery</td>
<td>Before EOA</td>
<td>0.1 mg</td>
<td>0.3 mg, Placebo</td>
</tr>
<tr>
<td>Fujii et al. [31]</td>
<td>2001</td>
<td>Breast surgery</td>
<td>1 hour preop</td>
<td>0.1 mg PO</td>
<td>0.4 mg PO, 0.2 mg PO, Placebo</td>
</tr>
<tr>
<td>Fujii et al. [32]</td>
<td>2001</td>
<td>Laparoscopic cholecystectomy</td>
<td>1 hour preop</td>
<td>0.1 mg PO</td>
<td>0.4 mg PO, 0.2 mg PO, Placebo</td>
</tr>
<tr>
<td>Janknegt et al. [33]</td>
<td>1999</td>
<td>Abdominal, gynecologic, breast, or otolaryngologic</td>
<td>Before induction</td>
<td>0.1 mg</td>
<td>0.3 mg + 0.5 mg, Droperidol 1.25 mg</td>
</tr>
<tr>
<td>Fujii et al. [34]</td>
<td>1995</td>
<td>Gynecologic surgery</td>
<td>1 hour preop</td>
<td>0.1 mg PO</td>
<td>0.3 mg PO, 0.2 mg PO, Placebo</td>
</tr>
<tr>
<td>Taylor et al. [35]</td>
<td>1997</td>
<td>PONV 4 hours postop</td>
<td>Post PONV</td>
<td>0.1 mg</td>
<td>0.3 mg, 0.6 mg, Placebo</td>
</tr>
<tr>
<td>Valton et al. [36]</td>
<td>1996</td>
<td>Brachytherapy</td>
<td>5 min before induction</td>
<td>0.1 mg</td>
<td>0.3 mg, 0.6 mg, Placebo</td>
</tr>
</tbody>
</table>

*Anesthetic agent doses are N unless otherwise specified.

D: dexamethasone; EOA, end of anesthesia; EOS, end of surgery; G: granisetron; IV: intravenous; N: number of patients in treatment group; O: ondansetron; PO: oral; P: placebo; PONV: postoperative nausea and vomiting.
mg [35,36], which are insufficient for meta-analytic direct comparison, indirect comparisons were performed.

**WITHIN-STUDIES ANALYSIS**

ORs for efficacy outcomes (i.e., absence of vomiting, absence of nausea, and need for rescue medication) from pairwise comparisons within each study during the early and overall postoperative periods are presented in Table 2.
Table 2: Odds ratios for absence of vomiting, absence of nausea, and need for rescue medication in early and overall postoperative periods for pairwise comparisons within each study.
EARLY POSTOPERATIVE PERIOD (0 TO 6 HOURS)

Absence of Nausea and Vomiting. During the early postoperative period, 2 studies directly compared granisetron 0.1 and 1.0 mg for absence of nausea and vomiting: Wilson et al. [33] found that the proportion of patients who did not present with nausea and vomiting was significantly greater among patients treated with granisetron 1.0 mg than in those treated with 0.1 mg. On the other hand, Taylor et al. [35] reported no significant difference between treatments. For indirect comparisons, the OR for absence of nausea and vomiting favored granisetron 0.1 mg over placebo in 1 of 3 pairwise comparisons [35] and did not significantly differ compared with granisetron 3.0 mg [33] or ondansetron [12]. The OR for the absence of nausea and vomiting with granisetron 1.0 mg was significantly greater than for placebo in 2 of 4 pairwise comparisons [35,33] but was also significantly less than placebo in one pairwise comparison [33]. No significant difference was observed when granisetron 1.0 mg was compared with granisetron doses >1.0 mg [30,31,33,34,35,36].

Requirement for Rescue Medication. Few studies reported on rescue medication use during the early postoperative period. Only one pairwise comparison from one study directly compared granisetron 0.1 mg versus granisetron 1.0 mg for rescue medication: Taylor et al. [35] found a lower incidence of rescue medication use with granisetron 0.1 mg without the Bonferroni adjustment and a near significant difference favoring granisetron 0.1 mg with the adjustment. For indirect comparisons, the OR for rescue medication significantly favored granisetron 0.1 mg over placebo in 1 of 3 pairwise comparisons [12] and was near significant in another [33]. The need for rescue medication did not significantly differ between granisetron 0.1 mg and ondansetron [12] or between granisetron 0.1 mg and granisetron 3.0 mg [33]. On the other hand, in the only study providing data on granisetron 1.0 mg for preventing the need for rescue medication during the early postoperative period [33], the OR for granisetron 1.0 mg versus placebo was not significant, but rescue medication use was significantly greater with granisetron 1.0 mg than with granisetron 3.0 mg.

LATE POSTOPERATIVE PERIOD (6 TO 24 HOURS)

None of the studies with a granisetron 0.1 mg treatment arm provided data on the absence of vomiting or nausea during the late postoperative period, nor were there any direct pairwise comparisons for rescue medication use between granisetron 0.1 mg and granisetron 1.0 mg. However, 3 studies provided data on the use of rescue medication in pairwise comparisons with granisetron 0.1 mg [33,31,35] or granisetron 1.0 mg [33] during the late postoperative period. None of the effect sizes were significant: granisetron 0.1 mg versus placebo (OR = 3.13; CI = 0.74, 13.20) or granisetron 3.0 mg (OR = 1.57; CI = 0.47, 5.18); or between granisetron 0.1 mg (with dexamethasone) and ondansetron (with dexamethasone) (OR = 0.94; CI = 0.41, 2.14); or between granisetron 1.0 mg and placebo (OR = 2.11; CI = 0.18, 25.35) or ondansetron 4.0 mg (OR = 2.11; CI = 0.18, 25.35).

OVERALL POSTOPERATIVE PERIOD (0 TO 24 HOURS)

Absence of Nausea and Vomiting. In direct pairwise comparisons between granisetron 0.1 mg and granisetron 1.0 mg for absence of nausea and vomiting during the overall postoperative period, Wilson et al. [33] observed an OR significantly favoring granisetron 1.0 mg over granisetron 0.1 mg in one comparison and was near significant in two others [33,36]. However, the OR for absence of nausea and vomiting was not significant for granisetron 0.1 mg versus ondansetron [12] or for granisetron 0.1 mg versus granisetron 3.0 mg [33,36]. The OR for the absence of nausea and vomiting was not significant for granisetron 0.1 mg versus ondansetron [12] or for granisetron 0.1 mg versus granisetron 3.0 mg [33,36]. The OR for the absence of nausea and vomiting for granisetron 1.0 mg versus placebo significantly favored granisetron 1.0 mg in at least 2 studies [30,31,33,35] but was not significant in 3 others [33,36,34]. On the other hand, the OR for absence of vomiting was not significant in 4 and 10 pairwise comparisons (for absence of nausea and vomiting, respectively) between granisetron 1.0 mg and granisetron ≥ 2.0 mg [30,31,32,33,34,35,36].

Requirement for Rescue Medication. The OR was not significant for the only direct comparison between granisetron 0.1 mg and 1.0 mg for rescue medication use during the overall postoperative period [12]. For indirect comparisons between granisetron 0.1 mg and placebo, the need for rescue medication significantly favored granisetron 0.1 mg in one pairwise comparison [33] and was not significant in another [12]. However, rescue medication use with granisetron 0.1 mg did not significantly differ from high-dose granisetron 3.0 mg [33] or versus ondansetron [12]. Granisetron 1.0 mg was superior to placebo in 2 pairwise comparisons [33,36] but did not significantly differ in 3 others.
A Meta-analysis of the Efficacy of Granisetron 0.1 mg for Postoperative Nausea and Vomiting (PONV)

The OR for rescue medication use with granisetron 1.0 mg versus granisetron > 1.0 mg was not significant in 2 pairwise comparisons [35,36], but granisetron > 1.0 mg was superior to granisetron 1.0 mg in 4 other pairwise comparisons (e.g., Fujii et al. [31]). However, the ORs for rescue medication use during the overall postoperative period for granisetron 1.0 mg versus ondansetron 4.0 mg [33] and versus droperidol [13] were not significant.

META-ANALYSIS

Early Postoperative Period. The effect sizes (OR_{meta}) for across-RCT, pairwise comparisons for data obtained during the early postoperative period are presented in Table 3.

Because there were insufficient studies for meta-analysis of direct pairwise comparisons of granisetron 0.1 mg with granisetron 1.0 mg for any outcome measure, indirect comparisons were conducted between the sets of granisetron 0.1 mg and granisetron 1.0 mg with comparators common to each set: placebo and granisetron dose levels > 1.0 mg (i.e., 2.0, 3.0, and 4.0 mg).

Indirect Comparisons With Placebo. Granisetron 0.1 mg versus placebo for absence of vomiting was homogeneous (p = 0.06) and yielded a significant effect size, whereas
granisetron 1.0 mg versus placebo was heterogeneous (p < 0.0001) and nonsignificant, whether Fujii et al. data were included or excluded (Figure 1).

**Figure 4**
Figure 1: Effect sizes, as measured by OR with 95% confidence interval (CI), of absence of vomiting favoring granisetron for the pairwise set of granisetron 0.1 mg versus placebo during the early and overall postoperative periods, granisetron 1.0 mg versus placebo during the overall postoperative period, and granisetron 0.1 or 1.0 mg versus placebo during the early and overall postoperative periods. Granisetron 0.1 mg and granisetron 1.0 mg sets are homogeneous and have overlapping CIs for both postoperative periods. *For heterogeneity statistic Q, p < 0.05.

By indirect comparison, the effect of treatment with granisetron 0.1 mg versus placebo for prevention of early postoperative vomiting had a CI that did not overlap and appeared to be superior to that of granisetron 1.0 mg versus placebo. The combined set of granisetron 0.1 mg and granisetron 1.0 mg (0.1/1.0 mg) versus placebo was heterogeneous (p < 0.0001) but yielded a significant effect size favoring granisetron 0.1/1.0 mg with or without trial data from Fujii et al.

The effect sizes (OR\textsubscript{pool}) for prevention of nausea during the early postoperative period for granisetron 0.1 mg and 1.0 mg, respectively, versus placebo were both significant and favored granisetron therapy. By indirect comparison, the effect sizes for granisetron 0.1 mg versus placebo and for granisetron 1.0 mg versus placebo had overlapping CIs (Figure 2).

**Figure 5**
Figure 2: Effect sizes, as measured by OR with 95% confidence interval (CI), of absence of nausea favoring granisetron for all pairwise sets of granisetron (0.1, 1.0, 0.1/1.0 mg) versus placebo during the early and overall postoperative periods. The 95% CIs of pairwise sets granisetron 0.1 mg and 1.0 mg, each versus placebo, overlap during both periods. Only the granisetron 1.0 mg versus placebo set is homogeneous during the early period, whereas all sets are homogeneous during the overall postoperative period. *For heterogeneity statistic Q, p < 0.05.

The combination set of granisetron 0.1/1.0 mg versus placebo had a significant effect size favoring granisetron 0.1/1.0 mg that was similar to both component sets but was heterogeneous with (p = 0.028) or without Fujii et al. study data (p = 0.015). There were insufficient data to meta-analyze pairwise comparisons of granisetron 0.1 mg and granisetron 1.0 mg versus placebo for the use of rescue medication during the early postoperative period.

**Indirect Comparisons with Granisetron >1.0 mg.** There were insufficient data to assess the effect sizes (OR\textsubscript{pool}) of granisetron 0.1 mg versus granisetron doses > 1.0 mg for prevention of vomiting during the early postoperative period. Indirect comparison with granisetron 1.0 mg versus placebo was not possible. The effect size for the combination set granisetron 0.1/1.0 mg versus granisetron > 1.0 mg was small but favored granisetron > 1.0 mg.

There were insufficient data to assess the effect sizes (OR\textsubscript{pool}) of granisetron 0.1 mg versus granisetron doses > 1.0 mg for prevention of nausea during the early postoperative period. The effect size for granisetron 1.0 mg versus granisetron > 1.0 mg was not significant. As with absence of vomiting, indirect comparison between these sets for prevention of nausea was not possible. The effect size for granisetron 0.1/1.0 mg was homogeneous (p = 0.06) but nonsignificant. There were insufficient data to determine the effect sizes of granisetron 0.1 mg and/or granisetron 1.0 mg versus
granisetron >1.0 mg for rescue medication during the early postoperative period.

Late Postoperative Period. There were insufficient data to measure effect sizes for granisetron 0.1 mg and/or 1.0 mg for absence of vomiting, absence of nausea, and need for rescue medication.

Overall Postoperative Period. The effect sizes (OR\text{pool}) for across-RCT, pairwise comparisons for data obtained during the overall postoperative period are presented in Table 4. As with the early postoperative period, there were insufficient studies to determine OR\text{pool} for direct comparison of granisetron 0.1 mg with granisetron 1.0 mg for any outcome measure. Indirect comparisons, where possible, were conducted with placebo and granisetron doses > 1.0 mg.
Table 4: Pooled effect sizes for overall postoperative period

<table>
<thead>
<tr>
<th>Overall period comparison</th>
<th>Granisetron dose</th>
<th>N</th>
<th>R_s</th>
<th>R_i</th>
<th>H_L</th>
<th>Effects model</th>
<th>OR_{0.1mg} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vomiting</td>
<td>0.1 mg [13,35,36]</td>
<td>3</td>
<td>1342891</td>
<td>955916</td>
<td>Fixed</td>
<td>1.90 (1.35, 2.74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 mg [29,30,31,32,34,35,36]</td>
<td>7</td>
<td>2944790</td>
<td>1944792</td>
<td>Fixed</td>
<td>2.77 (2.36, 3.35)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [29,30,35,36]</td>
<td>4</td>
<td>2332391</td>
<td>1365913</td>
<td>Fixed</td>
<td>3.24 (2.37, 4.43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 or 1.0 mg [13,20,32,34,35,36]</td>
<td>10</td>
<td>4287172</td>
<td>2697174</td>
<td>Random</td>
<td>2.15 (1.35, 3.41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [13,20,32,34,36]</td>
<td>7</td>
<td>3677662</td>
<td>2202662</td>
<td>Fixed</td>
<td>2.88 (2.36, 3.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G vs. &gt;1.0 mg</td>
<td>0.1 mg [29,31,32,33,34,35,36]</td>
<td>10</td>
<td>4528571</td>
<td>4518584</td>
<td>Random</td>
<td>0.67 (0.39, 1.12)</td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [29,31,35,36]</td>
<td>4</td>
<td>3369521</td>
<td>2687548</td>
<td>Random</td>
<td>1.33 (0.84, 2.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 or 1.0 mg [13,30,31,32,33,34,35,36]</td>
<td>11</td>
<td>4691801</td>
<td>5150789</td>
<td>Random</td>
<td>0.93 (0.45, 1.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [13,30,32,34,36]</td>
<td>5</td>
<td>3441501</td>
<td>3022510</td>
<td>Fixed</td>
<td>0.82 (0.43, 1.60)</td>
<td></td>
</tr>
<tr>
<td>No nausea</td>
<td>0.1 mg [13,35,36]</td>
<td>3</td>
<td>962091</td>
<td>575096</td>
<td>Fixed</td>
<td>1.77 (1.20, 2.63)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 mg [29,30,32,24,36,38]</td>
<td>6</td>
<td>1792797</td>
<td>1172271</td>
<td>Fixed</td>
<td>2.53 (1.70, 3.49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [29,38,36]</td>
<td>3</td>
<td>1608267</td>
<td>490206</td>
<td>Fixed</td>
<td>3.20 (2.02, 4.46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 or 1.0 mg [13,20,31,32,34,35,36]</td>
<td>9</td>
<td>269663</td>
<td>174667</td>
<td>Fixed</td>
<td>2.15 (1.46, 2.79)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [13,20,32,34,36]</td>
<td>6</td>
<td>1944786</td>
<td>1056832</td>
<td>Fixed</td>
<td>2.30 (1.75, 3.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G vs. &gt;1.0 mg</td>
<td>0.1 mg [29,31,32,33,34,35,36]</td>
<td>10</td>
<td>4017827</td>
<td>4007830</td>
<td>Random</td>
<td>0.76 (0.40, 1.42)</td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [33,35,36]</td>
<td>4</td>
<td>2595227</td>
<td>2595223</td>
<td>Random</td>
<td>1.26 (0.55, 2.91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 or 1.0 mg [21,32,24,36,38]</td>
<td>10</td>
<td>3208692</td>
<td>3586766</td>
<td>Fixed</td>
<td>0.71 (0.56, 0.91)</td>
<td></td>
</tr>
<tr>
<td>Resistance modification required</td>
<td>G vs. placebo</td>
<td>0.1 mg [29,30,31,34,35]</td>
<td>5</td>
<td>102591</td>
<td>1850145</td>
<td>Fixed</td>
<td>0.42 (0.30, 0.66)</td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [29,30,35]</td>
<td>3</td>
<td>705257</td>
<td>1370283</td>
<td>Fixed</td>
<td>0.35 (0.25, 0.51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 or 1.0 mg [13,30,31,32,34,35,36]</td>
<td>7</td>
<td>1053471</td>
<td>2654720</td>
<td>Fixed</td>
<td>0.46 (0.34, 0.69)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluding Full et al. [13,20,32,34,36]</td>
<td>5</td>
<td>1509416</td>
<td>2379423</td>
<td>Fixed</td>
<td>0.40 (0.30, 0.54)</td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratio calculated using fixed effects model when p < 0.05, random effects model otherwise when p = 0.05.
CI = confidence interval; OR = odds ratio; NC = not calculated (insufficient data due to n = 0 studies and/or n_i = 0); N = number of patients in each group exhibiting event; n = number of patients in control group exhibiting event; n_i = number of patients in treatment group exhibiting event; OR_{0.1mg} = pooled odds ratio.
Indirect Comparisons With Placebo. Granisetron 0.1 mg versus placebo yielded a positive, medium-sized effect size for absence of vomiting, as did granisetron 1.0 mg versus placebo, regardless of whether Fujii et al. studies were included. The CIs for both OR\(_\text{pool}\) results overlapped (Figure 1). The combined set of pairwise comparisons of granisetron 0.1/1.0 mg versus placebo favored granisetron therapy when Fujii et al. studies were included. However, granisetron 0.1/1.0 mg versus placebo favored granisetron therapy for absence of vomiting when studies by Fujii et al. were excluded.

Similar to absence of vomiting, both sets of granisetron 0.1 mg versus placebo and granisetron 1.0 mg versus placebo for absence of nausea yielded positive, medium-sized effect sizes, regardless of inclusion of Fujii et al. studies. Granisetron 0.1/1.0 mg versus placebo also yielded a positive effect size favoring granisetron, regardless of whether Fujii et al. studies were included. By indirect comparison, granisetron 0.1 mg versus placebo and granisetron 1.0 mg versus placebo had overlapping CIs, regardless of whether Fujii et al. studies were included (Figure 2).

There were insufficient data to calculate OR\(_\text{pool}\) for pairwise comparisons of granisetron 0.1 mg versus placebo for the use of rescue medication during the overall postoperative period. Granisetron 1.0 mg versus placebo favored granisetron therapy, regardless of whether Fujii et al. studies were included, as did the combined set of granisetron 0.1/1.0 mg versus placebo.

Indirect Comparisons With Granisetron > 1.0 mg. There were insufficient data to calculate OR\(_\text{pool}\) of granisetron 0.1 mg versus granisetron doses > 1.0 mg for absence of vomiting or nausea, or need for rescue medication during the overall postoperative period. The effect sizes for granisetron 1.0 mg versus granisetron > 1.0 mg for absence of vomiting and for absence of nausea in the overall period were not significant, regardless of Fujii et al. studies. The effect size for granisetron 1.0 mg versus granisetron > 1.0 mg for rescue medication, however, was large and unfavorable for granisetron 1.0 mg.

When granisetron 0.1/1.0 mg versus granisetron doses > 1.0 mg were compared for prevention of vomiting, treatment favored granisetron > 1.0 mg when Fujii et al. studies were included but was not significant when Fujii et al. studies were excluded. Granisetron 0.1/1.0 mg versus granisetron > 1.0 mg for rescue medication favored granisetron > 1.0 mg, but the set appeared to be heterogeneous (p < 0.0001).

**DISCUSSION**

Our intent was to perform a meta-analysis directly comparing granisetron 0.1 mg with granisetron 1.0 mg for prevention and/or treatment of PONV during the early, late, and overall postoperative periods and for safety. We identified 10 RCTs in which granisetron 0.1 mg or granisetron 1.0 mg was used for PONV. Our criterion for meta-analysis was that efficacy or safety data was reported in at least 3 independent studies. However, in only 2 studies \(_{35,36}\) were data available for direct comparison between RCTs comparing granisetron 0.1 mg– and granisetron 1.0 mg–based treatment for PONV.

Because it was not possible to construct meta-analyses that directly compared outcomes reported for granisetron 0.1 mg and 1.0 mg, we used indirect comparisons for meta-analyses (as established by Song et al. \(_{12}\)). Because of the dearth of data and because all but one RCT \(_{12}\) employed more than 2 treatment groups, studies with 3 or more treatment groups were separated into pairwise comparisons between granisetron 0.1 mg– and granisetron 1.0 mg–based therapy and (placebo or active) comparators. Where possible, meta-analyses were performed to indirectly compare granisetron 0.1 mg and granisetron 1.0 mg treatments (“intervention”) with common comparators (“control”), namely placebo, and granisetron doses > 1.0 mg. Our criteria for meta-analysis were amended to also include data from at least 3 pairwise comparisons (taken from at least 3 independent studies). Pairwise sets for indirect comparison that appeared to be homogeneous (p ≥ 0.05) were considered more reliable than those that appeared to be heterogeneous (p < 0.05), which might include confounding factors and/or dissimilar characteristics.

During the early postoperative period, the overall effect sizes (OR\(_\text{pool}\)) for granisetron 0.1 mg versus placebo appeared to be superior to granisetron 1.0 mg for prevention of vomiting, although the latter set was heterogeneous, implying that the granisetron 1.0 mg versus placebo set might include confounding factors. Compared with granisetron doses > 1.0 mg for prevention of vomiting, the combination set of granisetron 0.1/1.0 mg appeared superior. For prevention of nausea, the overall effect sizes (OR\(_\text{pool}\)) for the granisetron 0.1 mg and granisetron 1.0 mg sets were both superior to placebo and had overlapping CIs. However, granisetron 0.1 mg was heterogeneous, implying possible confounding factors. There were insufficient data for comparisons with
granisetron doses > 1.0 mg for prevention of nausea or need of rescue medication. Based on these findings, granisetron 0.1 mg appears to be at least as effective (and possibly more effective) than granisetron 1.0 mg during the early postoperative period. There were insufficient data for meta-analysis of any outcomes during the late postoperative period.

During the overall postoperative period, compared with placebo, the overall effect sizes (OR_{pool}) for the granisetron 0.1 mg and granisetron 1.0 mg sets, which were both homogeneous, had overlapping CIs for prevention of vomiting and for prevention of nausea. The OR_{pool} for the granisetron 0.1/1.0 mg set, which was superior to placebo for need for rescue medication, appeared to be homogeneous. Compared with granisetron doses > 1.0 mg, the OR_{pool} for granisetron 0.1/1.0 mg was inferior to granisetron > 1.0 mg for prevention of vomiting and need for rescue medication but was superior to granisetron > 1.0 mg for prevention of nausea. However, the set for rescue medication appeared to be heterogeneous, implying that granisetron 0.1 mg and granisetron 1.0 mg may be dissimilar. Based on these findings, granisetron 0.1 mg appears to be at least as effective as granisetron 1.0 mg during the overall postoperative period.

Our findings accord with a recently published retrospective cohort study of 400 patients, in which the bulk were administered granisetron 0.1 mg perioperatively for prophylaxis against PONV [37]. Most patients in the study experienced “excellent control,” including those in the highest-risk groups.

Limitations of our meta-analysis included publication bias, deficiencies in reported efficacy data, insufficient studies to perform direct meta-analyses of granisetron 0.1 mg versus granisetron 1.0 mg, and use of study aggregate data (which has significantly less power than a meta-analysis based on individual patient data). Insufficient studies necessitated the use of pairwise comparisons (i.e., direct comparison of 2 treatment arms in studies with 3 or more treatment arms). There were insufficient data to analyze heterogeneity among studies and pairwise comparisons into subsets or to perform multiple regression (multivariate) analyses to account for potential confounding factors (e.g., time of administration). Some conclusions were drawn on data from only 3 studies. Further limitations of this meta-analysis arose from the inclusion of RCTs with slightly different timing of administration of PONV medication (i.e., granisetron administered pre-, intra-, and postoperatively in response to PONV) and those in which the intervention (or control) treatment were accompanied by the use of dexamethasone for 2-drug PONV prophylaxis. These facts should be taken into consideration during critical evaluation of the results of this meta-analysis.

CONCLUSIONS
Granisetron 0.1 mg appears to be at least as effective as granisetron 1.0 mg for PONV at preventing vomiting and nausea during the early and overall postoperative periods. There are insufficient data to determine whether this comparative effect is also true for use of rescue medication. The use of granisetron 0.1 mg may be associated with a decreased incidence of headaches and hepatic enzyme increase, as well as substantial cost savings. Additional studies directly comparing granisetron 0.1 mg with granisetron 1.0 mg for PONV may provide more data, enabling a higher-powered meta-analysis to address this important issue.

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Subject: A Meta-analysis of the Efficacy of Granisetron 0.1 mg for Postoperative Nausea and Vomiting (PONV)

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