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# Is Intravenous Ramosetron 0.3 mg Effective In The Prevention Of Postoperative Nausea And Vomiting In Women Undergoing Gynecologic Surgery?

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# Is Intravenous Ramosetron 0.3 mg Effective In The Prevention Of Postoperative Nausea And Vomiting In Women Undergoing Gynecologic Surgery?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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## ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not intravenous ramosetron 0.3 mg is effective in the prevention of postoperative nausea and vomiting (PONV) in women undergoing gynecologic surgery.

STUDY DESIGN: Review of three English language primary research articles published later than 1995.

DATA SOURCES: Randomized, double-blinded, controlled clinical trials comparing intravenous ramosetron to placebo or other control groups were identified using Ovid MEDLINE and Cochrane Library databases.

OUTCOMES MEASURED: Measured outcomes include a complete response to the intervention within the first 24-48 hours, the incidence of postoperative nausea and vomiting, need for rescue antiemetic, severity of nausea, and patient satisfaction.

RESULTS: All three RCTs analyzed found that intravenous ramosetron 0.3 mg administered during or immediately after surgery significantly decreased the incidence, compared to placebo, of patients experiencing any PONV. This effect was found to be particularly strong in the earliest postoperative period in all studies. In all three studies, ramosetron also significantly reduced the severity of nausea and increased patient satisfaction compared to placebo. Two out of the three studies showed that ramosetron reduced the need for rescue treatment of PONV in the postoperative period compared to placebo. Adverse effects were limited to drowsiness, dizziness, and headache and there were no significant difference in incidence between any groups in any of the studies.

CONCLUSION: PONV is a significant source of distress for women undergoing gynecologic surgery. The studies analyzed in this review are concordant in their finding that ramosetron, a highly selective 5-$HT_3$ antagonist, is a safe and effective option for completely preventing or reducing the severity of this troubling postoperative complication. The effectiveness of ramosetron in these studies is complemented by its availability as a less-expensive oral disintegrating tablet which may offset criticism of the high cost of currently available 5-$HT_3$ antagonists. Future studies are needed to apply these findings to additional surgical populations.



KEY WORDS: ramosetron, postoperative nausea and vomiting, gynecologic surgery

## INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common and distressing complication of general anesthesia and surgery with a particularly high incidence in gynecologic surgery.[1] The serotonin 5-$HT_3$ receptor is highly specific for nausea and vomiting, and antagonists demonstrate potent antiemetic effects in PONV as well as chemotherapy- and radiation-induced nausea and vomiting.[2-4] Ramosetron is a highly selective 5-$HT_3$ antagonist that demonstrates a greater affinity for, and slower dissociation from, the 5-$HT_3$ receptor than other drugs in this class, suggesting that it may provide longer-lasting antiemetic effects with fewer side effects.[5]

The incidence of PONV in all surgical patients is approximately 25-30%, but can rise to 75% in high-risk patients undergoing gynecologic surgery.[6,7] Hysterectomy is the second most common surgery performed in women, at 600,000 procedures per year. At a minimum incidence of 25%, PONV occurs in at least 150,000 cases per year for hysterectomy alone.[8]

While PONV may be considered an inconvenience by some clinicians, it takes on greater significance when potential impacts on complications and patient care are considered. Prolonged PONV may lead to electrolyte imbalances, dehydration, aspiration of gastric contents, Mallory-Weiss tears, esophageal rupture, wound dehiscence, and hematomas.[2,7] Prevention of these events by preventing or reducing PONV reduces costs by helping to maintain the current emphasis on surgical care in the ambulatory setting. In one study, treating PONV with a placebo resulted in costs 100X greater than treating with a generic antiemetic.[9] Approximately 0.18% of surgical patients experience intractable PONV which may lead to extended PACU stays or hospital admission.[10] Each incidence of emesis may delay PACU discharge by 20 minutes, requiring significant nursing costs,[11] and each day of hospital admission in the US costs an average of $1053.[12] PONV will also likely become a challenge for a growing number of

physician assistants as employment opportunities in the surgical specialties or as hospitalists continue to expand.[13]

PONV is difficult to predict due to its multifactorial etiology. Patient-related risk factors include younger age, female gender, obesity, history of motion sickness, anxiety, nonsmoking, and gastroparesis. Operative variables include type, site, and duration of surgery.[2,7] PONV is more commonly experienced with longer procedures and those involving laparoscopy, dilation and curettage of the uterus, knee arthroscopy, head and neck surgery, and gastrointestinal surgery.[7] Anesthesia-related risk factors include postoperative pain, use of opioids in pain management, use of nitrous oxide in anesthesia, extended preoperative fasting, and absence of nasogastric suction.[2]

Current guidelines recommend that PONV prophylaxis should be reserved for patients with a high risk. Treating low risk patients results in lack of benefit, unnecessary suffering of side effects, and increased costs.[8] Four key indicators for high PONV risk include female gender, nonsmoking, history of PONV, and opioid use.[6] If PONV risk warrants treatment, selective serotonin 5-$HT_3$ receptor antagonists given at the conclusion of surgery are the current first-line therapy despite their high cost due to their efficacy and low side-effect profile. Droperidol, an antidopaminergic agent that is as effective as ondansetron in preventing PONV, was formerly the gold standard therapy but has been supplanted by 5-HT3 antagonists due to a “black box” warning imposed by the FDA on droperidol for possible induction of QT prolongation and torsades de pointes.[8] Low-dose dexamethasone administered intravenously prior to surgery is effective at preventing PONV, but has not been studied systematically. Use of older antiemetics such as dimenhydrinate, ephedrine, prochlorperazine, promethazine and scopolamine has declined due to side effects including sedation, dizziness, and xerostomia.[8]

In summary, in patients at low risk for PONV, prophylaxis with older and less expensive antiemetics is recommended in order to prevent unnecessarily high costs. Patients with a higher risk for PONV, such as those undergoing gynecologic surgery, warrant more effective and longer lasting prophylaxis to reduce additional PACU care and hospital admission.[14] If ramosetron proves to be effective in the context of gynecologic surgery, it is also available as a less expensive oral disintegrating tablet, potentially offsetting criticism of the high cost of the intravenous formulation.[15]

**OBJECTIVE:**

The objective of this selective EBM review is to determine whether or not intravenous ramosetron 0.3 mg is effective in the prevention of PONV in women undergoing gynecologic surgery.

**METHODS:**

The three studies selected for this review were prospective, randomized, double-blind, placebo-controlled controlled trials. All study populations were composed of adult women undergoing major gynecologic surgery and interventions included intravenous ramosetron 0.3 mg administered at some point between induction of anesthesia and completion of surgery. In all studies, placebo infusion was used as a control and outcomes included complete response (i.e. no PONV) within the first 24-48 hours, incidence of PONV, need for rescue, severity of nausea, and patient satisfaction. All outcomes were patient-oriented evidence that matters (POEMS).

A literature search was performed using Ovid Medline and the Cochrane Database of Systematic Reviews to identify randomized controlled trials (RCTs) using the keywords “ramosetron”, “nausea”, “vomiting”, and “postoperative.” Included search results were RCTs that were published after December 31, 1995 with study design and POEM outcomes that

answered the proposed question. Excluded studies were those published on or before December 31, 1995, that were not RCTs, that studied women younger than 18 years old, or that studied non-gynecologic surgeries. Articles selected for analysis were published after 1999 in English language, peer-reviewed journals. Studies were selected based on their study design, relevance to the question asked, and importance of outcomes to patients. Statistical analysis in the selected articles was limited to calculation of *P*-values. Table 1 lists the demographics and characteristics of patients in the included studies.

In all selected studies, trained nurses were blinded to study groups and assessed patients at regular intervals to record all episodes of PONV in the PACU or general ward for the first 24 to 48 hours. This data was used to derive the measured outcomes of complete response, incidence of nausea and vomiting, and the need for rescue. Fujii et al divided the observation period into three time intervals: 0-1 hours, 1-24 hours, and 24-48 hours post-procedure. Lee et al used two intervals of 0-1 hours and 1-24 hours post-procedure. Kim et al used two intervals of 0-6 hours and 6-24 hours post-procedure.

Severity of nausea was rated by patients at each assessment using numeric visual analogue scales that ranged from from 0 (no nausea) to 10 or 100 (most severe nausea) or by modified Rhodes index questionnaire for nausea, retching and vomiting.[16-18] Patient satisfaction was rated at the end of the studies using a linear scale ranging from 0 (complete dissatisfaction) to 10 (complete satisfaction)[16,17] or three-point scale (satisfied, neutral, or dissatisfied).[18]

**RESULTS:**

Although patient characteristics and inclusion/exclusion criteria of the selected studies were not identical, Table 1 demonstrates that the patient populations were similar overall.

Table 1: Demographics and characteristics of patients in selected studies

| Study | Type | # pts | Age | Inclusion criteria | Exclusion criteria | W/D | Interventions |
|---|---|---|---|---|---|---|---|
| Fujii[16], 2000 | RCT | 120 | 21-63 | Healthy 21-63 year old females;<br>Undergoing major gynecologic surgery;<br>ASA physical status I/II | GI disease;<br>Hx of motion sickness and/or PONV;<br>Antiemetic within 24 hrs prior to surgery | 0 | IV ramosetron at 0.15 mg, 0.3 mg, and 0.6 mg at completion of surgery |
| Kim[18], 2009 | RCT | 162 | 21-71 | Healthy 21-70 year old female undergoing elective gynecologic surgery under general anesthesia | Pregnancy;<br>Weight > 30% above ideal body weight;<br>Vomiting or retching within 24 hrs before surgery;<br>Antiemetic, steroids, or psychoactive meds within 24 hours before surgery;<br>Respiratory, CV, renal, hepatic, endocrine, GI, or neuro disease | 0 | IV ramosetron 0.3 mg or ondansetron 8 mg 30 min prior to completion of surgery |
| Lee[17], 2009 | RCT | 120 | 18-60 | Healthy 18-60 year old females undergoing major gynecologic surgery<br>ASA physical status I/II | GI disease;<br>Hx of motion sickness or previous PONV;<br>Currently menstruating;<br>Antiemetic within 24 hrs before surgery | 0 | IV ramosetron 0.3 mg immediately after anesthesia induction;<br>Oral ramosetron 0.1 mg administered 1 hr prior to surgery |

Table 2 shows the primary outcomes and resulting statistical analysis from the selected studies. In Fujii et al, a complete response was achieved with ramosetron in the 0-3 hour interval in 87% of patients compared to 40% with placebo. The relative benefit increase (RBI) and absolute benefit increase (ABI) were calculated to be 118% and 47%, respectively. The number needed to treat (NNT) was calculated to be 2. In the 3-24 hour interval, complete response was achieved in 87% compared to 43% with placebo. This effect was calculated to have an RBI of

102%, an ABI of 42%, and an NNT of 2. In the 24-48 hour interval, complete response was achieved in 90% of patients with ramosetron compared to 50% for placebo. This effect was calculated to have an RBI of 80%, ABI of 40%, and an NNT of 3. For all of the above comparisons, $P = 0.001$

Table 2 Primary outcome data from selected studies. Data reported as number of patients (%) Complete response = No PONV; Interval = hours observed after anesthesia ; RBI= relative benefit increase; RRR= relative risk reduction ; ABI=absolute benefit increase; ARR= absolute risk reduction; NNT= number needed to treat

| | Primary Outcome | Interval | Placebo | Ramosetron | $P^*$ | RBI/ RRR | ABI/ ARR | NNT |
|---|---|---|---|---|---|---|---|---|
| Fujii et al (2000) | Complete response (No PONV) | 0-3 | 12 (40%) | 26 (87%) | 0.001 | 118% | 47% | 2 |
| | | 3-24 | 13 (43%) | 26 (87%) | 0.001 | 102% | 44% | 2 |
| | | 24-48 | 15 (50%) | 27 (90%) | 0.001 | 80% | 40% | 3 |
| Lee et al (2009) | Complete response (No PONV) | 0-1 | 26 (65%) | 36 (90%) | 0.014 | 38% | 25% | 4 |
| | | 1-24 | 27 (67.5%) | 35 (87.5%) | 0.059 | 30% | 20% | 5 |
| Kim et al (2009) | Incidence of any PONV | 0-24 | 37 (69%) | 27 (50%) | <0.05 | 28%† | 19%‡ | 4 |

*$P$ value < 0.05 is statistically significant
† Reported as relative risk reduction
‡ Reported as absolute risk reduction

In Lee et al, a complete response in the 0-1 hour interval was achieved in 90% of patients compared to 65% with placebo. The RBI was calculated to be 38%, ABI was calculated to be 25%, and NNT was calculated to be 4, with a $P$ value of 0.014. In the 1-24 hour interval, complete response was achieved in 87.5% compared to 67.5% with placebo with an RBI of 30%

and ABI of 20%. For this less impressive effect, NNT was calculated to be 5. These findings were deemed not statistically significant with a calculated *P* value of 0.059.

In Kim et al, the incidence of nausea and/or vomiting was 50% in the ramosetron arm compared to 69% in the placebo arm in the combined 0-6 hour and 6-24 hour periods. Since the primary outcome was incidence of an undesirable effect instead of the incidence of a desirable effect, relative risk reduction (RRR) was calculated instead of benefit increase. For this effect, RRR was 28%, ARR was 19%, and NNT was 4. The comparison was found to be statistically significant with a calculated *P* value $< 0.05$.

Table 3 shows the secondary outcomes and resulting statistical analysis from the selected studies. Secondary outcomes in Fujii et al included incidence of nausea and vomiting, need for rescue, severity of nausea, and patient satisfaction. While the incidence of both nausea and vomiting was reduced in the ramosetron arm in all three time intervals of Fujii et al, this effect reached statistical significance only for the incidence of nausea during the initial 0-3 hour interval ($P = 0.041$). While rescue was required in 40%, 33%, and 27% of patients given placebo in the 0-3, 3-24, and 24-48 hour intervals, respectively, no patients given ramosetron required rescue at any time during the study ($P = 0.001 – 0.004$). Again, this effect was most pronounced in the 0-3 hour interval with a calculated RRR of 67%, ARR of 40%, and NNT of 3.

Values for severity of nausea and patient satisfaction were reported as ordinal data and not dichotomized for analysis in this review, but improvements in these outcomes in the ramosetron arm were noted in all time intervals and deemed to be statistically significant with *P* values ranging from 0.002 to 0.03.

Table 3 Secondary outcomes data from selected studies. Interval = hours observed after anesthesia; Rescue = need for rescue antiemetic medication
Data reported as number of patients (%) and mean

| | Interval | Outcome | Placebo | Ramosetron | $P^*$ | RRR | ARR | NNT |
|---|---|---|---|---|---|---|---|---|
| Fujii et al (2000) | 0-3 | Nausea | 9 (30%) | 2 (7%) | 0.041 | 33% | 23% | 4 |
| | | Vomiting | 8 (27%) | 2 (7%) | 0.079 | 27% | 20% | 5 |
| | | Rescue | 12 (40%) | 0 (0%) | 0.001 | 67% | 40% | 3 |
| | | Severity† | 0 | 0 | 0.002 | -- | -- | -- |
| | | Satisfaction | 2.5 | 8.5 | 0.005 | -- | -- | -- |
| | 3-24 | Nausea | 8 (27%) | 3 (10%) | 0.181 | 23% | 17% | 6 |
| | | Vomiting | 8 (27%) | 2 (7%) | 0.079 | 27% | 20% | 5 |
| | | Rescue | 10 (33%) | 0 (0%) | 0.001 | 49% | 33% | 3 |
| | | Severity† | 0 | 0 | 0.03 | -- | -- | -- |
| | | Satisfaction | 2.5 | 8.5 | 0.006 | -- | -- | -- |
| | 24-48 | Nausea | 7 (23%) | 2 (7%) | 0.145 | 21% | 16% | 6 |
| | | Vomiting | 7 (23%) | 1 (3%) | 0.052 | 26% | 20% | 5 |
| | | Rescue | 8 (27%) | 0 (0%) | 0.004 | 37% | 27% | 4 |
| | | Severity† | 0 | 0 | 0.022 | -- | -- | -- |
| | | Satisfaction | 3.5 | 8.5 | 0.009 | -- | -- | -- |
| Lee et al (2009) | 0-1 | Nausea | 13 (32.5%) | 4 (10%) | 0.027 | 33% | 22.5% | 4 |
| | | Vomiting | 2 (5%) | 1 (2.5%) | 1.00 | 3% | 2.5% | 40 |
| | | Rescue | 3 (7.5%) | 1 (2.5%) | 0.615 | 5% | 5% | 20 |
| | | Severity‡ | 3.0 | 0.7 | 0.013 | -- | -- | -- |
| | 1-24 | Nausea | 12 (30%) | 5 (12.5%) | 0.099 | 25% | 17.5% | 6 |
| | | Vomiting | 3 (7.5%) | 1 (2.5%) | 0.615 | 5% | 5% | 20 |
| | | Rescue | 4 (10%) | 1 (2.5%) | 1.00 | 8% | 7.5% | 13 |
| | | Severity‡ | 3.6 | 1.1 | 0.041 | -- | -- | -- |
| Kim et al (2009) | 0-24 | Rescue | 22 (41%) | 8 (15%) | <0.05 | 44% | 26% | 4 |
| | | Severity§ | 48 | 28 | <0.05 | -- | -- | -- |

$P < 0.05$ is statistically significant † Severity based on a 0-10 VAS ‡ Severity based on score of Modified Rhodes index of nausea, vomiting, and retching
§ Severity based on a 0-100 VAS

In Lee et al, the incidences of nausea, vomiting, and rescue were reduced in the patients given ramosetron in both the 0-1 and 1-24 hour intervals, but a pronounced treatment effect was only seen for the incidence of nausea in the 0-1 hour interval, with a calculated *P* value of 0.027, RRR of 33%, ARR of 22.5%, and NNT of 4. All other comparisons regarding incidence of nausea, vomiting or rescue were not found to be statistically significant. Severity of nausea measured by Modified Rhodes index score was significantly reduced in both the 0-1 hour and 1-

24 hour intervals by a mean 2.2 ($P = 0.013$) and 2.5 points ($P = 0.041$), respectively. Patient satisfaction was also increased by a mean of 1.5 on a linear numerical scale from 1-10 in the ramosetron arm ($P < 0.001$)

In Kim et al, the incidence of rescue was 22% in the ramosetron arm versus 41% in the placebo arm. This statistically significant ($P < 0.05$) treatment effect had a RRR of 44%, ARR of 26%, with an NNT of 4. Patient satisfaction was reported as the number of patients in each study arm that were satisfied with the anesthetic experience, and was significantly higher with ramosetron, at 85%, versus those receiving placebo, at 69%. This effect had a calculated RBI of 23%, ABI of 16%, an NNT of 6, and was deemed statistically significant with a $P$ value $< 0.05$. As in the other studies, severity of nausea was reported as ordinal data and not dichotomized for further analysis. However, ramosetron produced a mean 20 point reduction on a 100-point visual analogue scale, an effect that was found to be statistically significant with a $P$ value of $< 0.05$.

Headache, dizziness, and drowsiness were the most common adverse events recorded in the studies. Since there were no significant differences in the incidences of any adverse events among treatment groups in any study, no relative risk increase (RRI), absolute risk increase (ARI), or number needed to harm (NNH) analysis was performed.

**DISCUSSION:**

The RCTs included in this review show notable concordance in both study design and results. A considerable limitation in studies of this type, however, lies in quantifying a response as multifactorial and subjective as PONV. Although inclusion criteria for all of the studies were similar, Kim et al used additional exclusion criteria that could be considered risk factors for PONV. Fujii et al and Lee et al may have included patients with these additional factors, leading to higher PONV risk in their study patients. In terms of study methods, Fujii et al administered

ramosetron at the completion of surgery, Kim et al administered the drug during surgery, and Lee et al administered the drug immediately after anesthesia induction. These differences may have skewed efficacy results, particularly in the early time intervals of the studies. All three studies also used different medication regimens to manage postoperative pain. These discrepancies could certainly impact the outcomes assessed in the studies.

While the primary outcomes such as complete response and incidence of nausea/vomiting as measured by trained nurses may be considered very reliable, patient-derived data on need for rescue, overall satisfaction, and severity of nausea and vomiting may be skewed by several factors. Recovery from general anesthesia is a variable process that may render patients confused and unable to reliably quantify or qualify their level of discomfort.[1,2] The need for rescue is also a subjective decision point that is ultimately based on patients' individual threshold for discomfort. Since all studies were performed in Japan, the possibility of an ethnic or cultural bias in reporting the incidence and severity of nausea and vomiting cannot be ruled out.

Interestingly, the mean values for severity of nausea in Fujii et al in all time intervals and treatment groups are 0, even though *P* values between ramosetron and placebo were calculated to be statistically significant (Table 3). This apparent discrepancy is not explained in the article and may represent a publication error.

The studies analyzed in this review did not emphasize adverse events and found no statistically significant occurrences in any study groups. Although ramosetron is a member of a well-studied drug class with an established safety record, it is only available in Japan and Southeast Asia as a treatment for diarrhea-predominant irritable bowel syndrome. Since most studies on ramosetron have been performed in Asian patients, one must consider the possibility of increased safety in these populations due to pharmacogenetic variables.

**CONCLUSION :**

Ramosetron administered intravenously at a dosage of 0.3 mg either during or immediately following gynecologic surgery was shown to be effective in the prevention of PONV. This analysis suggests that ramosetron significantly increases the likelihood of eliminating any PONV when compared to placebo treatment in the first 48 hours after surgery, but that the treatment effects are more prominent in the early postoperative phase. For patients in whom ramosetron did not completely prevent PONV, the need for rescue therapy was significantly reduced compared to those who received placebo. The inherent difficulty of measuring a subjective and multifactorial event such as PONV warrants further study on this topic. While pain management is required in any perioperative study, future investigations should minimize the use of opioids in pain control due to emesis-related side effects. Studies should also include more ethnically heterogenous patients to minimize potential pharmacogenetic effects and cultural bias in reporting the incidence and severity of nausea.

The prospect of PONV weighs heavily on the minds of patients prior to surgery. As an increasing number of physician assistants assume work in surgical specialties, perioperative patient management will become an ever-increasing responsibility. Studies on prophylaxis of PONV with ramosetron should be expanded to other nations, patient populations, and surgical procedures to demonstrate whether or not ramosetron represents yet another effective option for physician assistants to dramatically improve the well-being of patients in the postoperative period.

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