A Randomized Placebo-Controlled Trial of Oral Ramosetron for Prevention of Post Operative Nausea and Vomiting after Intrathecal Morphine in Patients Undergoing Gynecological Surgery

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Background: *The incidence of postoperative nausea and vomiting (PONV) after intrathecal morphine is high. Ramosetron is a 5-HT_3 antagonist that has been shown to reduce PONV in general anesthesia. The objective of this study was to evaluate the efficacy of Ramosetron in preventing PONV.*

Material and Method: *165 patients undergoing elective gynecological surgery under spinal anesthesia were randomly allocated to two groups: the Ramosetron group (0.1 mg orally, n = 82), and the placebo group (oral corn starch, n = 83). The incidence of PONV, severity of nausea and use of rescue antiemetic during the first 24 hour after surgery were evaluated.*

Results: *The incidence of PONV was significantly lower in the Ramosetron group compared with the placebo group (24.4% vs. 44.6%, number needed to treat (NNT) = 5.0). The severity of nausea was significantly lower in the Ramosetron group compared with the placebo group (20.7% vs. 39.8%, NNT = 6.0) in the 24 hour period.*

Conclusion: *Oral Ramosetron 0.1 mg was more effective than placebo in PONV prevention and reduced the incidence of moderate to severe nausea after intrathecal morphine in the first 24 hour after gynecological surgery.*

Keywords: *Ramosetron, Intrathecal morphine, Postoperative nausea and vomiting, Gynecological surgery*

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Spinal anesthesia with intrathecal morphine is highly effective in management of intraoperative and postoperative pain after gynecological surgery. Spinal anesthesia also permits early ambulation and reduces the risk of complications. However, the high incidence of postoperative nausea and vomiting (PONV), estimated to be 30-70%[1], could lead to patients' dissatisfaction with this anesthesia.

Selective serotonin 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are first-line drugs for the prevention of PONV because they have fewer side effects and better efficacy compared with other drugs. Most studies have examined the efficacy of ondansetron in the prevention of PONV and chemotherapy-induced nausea and vomiting[2,3].

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Ramosetron is a 5-HT_3 antagonist that was found to be more potent and lasted longer than previously-developed agents in this class[4]. Choi et al reported that intravenous (IV) ramosetron was more effective than IV ondansetron in reducing PONV severity in patients undergoing spinal surgery[5]. Hahm et al reported that ramosetron 0.3 mg IV resulted in a lower incidence of PONV compared with ondansetron 4 mg IV 24-48-h postoperatively after receiving epidural hydromorphone during knee surgery[6]. The efficacy of 0.1 mg oral ramosetron is equivalent to 0.3 mg IV ramosetron in reducing the incidence of PONV in patients undergoing gynecological surgery with total intravenous anesthesia[7]. Evidence shows that ramosetron could prevent chemotherapy-induced nausea and vomiting, and PONV[3,8]. To our knowledge, there are no previous studies evaluating the efficacy of oral ramosetron for PONV prevention after intrathecal morphine.

We conducted a prospective, randomized, double-blind, placebo-controlled study to evaluate the

efficacy of ramosetron in the prevention of PONV after intrathecal morphine in gynecological surgery patients during the first 24 hour after surgery.

Material and Method

The local IRB (Siriraj Hospital Institutional Review Board, Bangkok, Thailand) approved the study (744/2555(EC2)). We enrolled 165 patients with American Society of Anesthesiologists physical status I or II who were more than 18 years of age, undergoing elective gynecological surgery (hysterectomy, ovarian cystectomy, or salpingo-oophorectomy), and who gave informed consent from March 2013 to May 2014. Patients' medical history and characteristics including age, weight, history of PONV and motion sickness were identified and recorded. The exclusion criteria were pregnancy; BMI >30 kg/m^2; current smoker; administration of antiemetics, systemic steroids, or psychoactive medications within 24 hour prior to the operation; and vomiting or retching 24 hour prior the operation.

Patients were randomly allocated to receive one of the two study medications using computer-generated randomized numbers: oral ramosetron 0.1 mg (ramosetron group) or corn starch (placebo group). The medications were given to patients 1 hour before the operation by a ward nurse not involved in the study. Patients, investigators who collected the intraoperative and postoperative data, and nurses involved in postoperative patient care were blinded to the treatment. The medication code was not disclosed until the analysis of the results was complete.

All patients received a balanced salt solution at an intravenous infusion rate of 80-100 ml/h, or more than 500 ml, before spinal anesthesia. Spinal anesthesia was performed at the L3-4 interspace with a 25-27 gauge Quincke or Whitacre needle and 3.0-3.5 ml of 0.5% heavy bupivacaine with 0.2 mg morphine. After bilateral T6 sensory block to pin prick was achieved, surgery was initiated. Standard intraoperative monitoring and data recording consisted of continuous electrocardiogram, pulse oximetry, and non-invasive blood pressure. Patients received IV fluids or a vasopressor when hypotension occurred. Patients were given pethidine 20 mg IV prn every 2 h when visual analog scale (VAS) pain score was >5 or on patient request in both groups, for postoperative pain control. Patients were observed postoperatively in the post anesthesia care unit until they were stable 1 to 2 hours.

At 0-2 hour, 2-6 hour and 6-24 hour post operatively, the number of patients who had PONV, the severity of nausea, and the need for rescue antiemetics were evaluated. We assessed the nausea severity using the following VAS scale: 0 = none, 100 = maximum, and moderate to severe nausea was defined as VAS >50 or as the presence of vomiting. Patients were given rescue antiemetics if vomiting occurred. Rescue medication for PONV (ondansetron 8 mg IV prn every 8 hour as the initial rescue drug, and metoclopramide 10 mg IV prn every 4 hour as a second-line rescue drug and dimenhydrinate 50 mg IV as a third line drug was given when patients requested or if there was a complaint of moderate to severe nausea (VAS >50) or vomiting. Vomiting was defined as expulsion of stomach contents, and retching was defined as an involuntary attempt to vomit that did not produce stomach contents. The degree of pruritus was evaluated using direct questioning about its presence and whether treatment was desired. The intensity of pruritus was classified on a four-point scale (0 = none, 1 = mild pruritus but only in a small area of the body, 2 = moderate pruritus requiring treatment, 3 = severe pruritus). Antipruritic drugs were administered upon patient request with chlorpheniramine 10 mg IV prn every 6 hour as the first-line drug and naloxone 0.02 mg IV as the second-line drug. A three-point scale (satisfied, neutral, dissatisfied) was used to evaluate patient satisfaction at 24 hour after surgery. Other side effects (headache, dizziness, constipation, diarrhea, hot flashes) were evaluated and recorded by the investigator throughout the study period.

The incidence of nausea and vomiting during the 24-h postoperative period were the primary outcomes in this study and the incidence of pruritus during the same period and patient satisfaction were secondary outcomes.

Sample size was predetermined using a power analysis to achieve an 80% chance of detecting a 50% reduction in PONV from the basal incidence of 40% with assumed significance level of $\alpha = 0.05$. The calculated minimum sample size was 82 patients in each group. An additional 10% of patients were included in each group to allow for possible incomplete data collection or patient dropout. Statistical analysis was performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical data are reported as numbers and percentages, and continuous data are reported as mean $\pm$ standard deviation in normal distributions and median (min, max) in non-normal distributions. Chi-square test or Fisher's exact test were used to compare the incidence of PONV between the groups. The independent t-test or

the Mann-Whitney U-test was used to compare continuous data. A difference was regarded as significant with $p<0.05$.

Results

200 patients were enrolled in this study. Thirty-five patients were not eligible (17.5%), primarily (n = 31) because of conversion from spinal anesthesia to general anesthesia. Eligible patients (n = 165) were randomly assigned to receive either placebo or ramosetron.

Patient characteristics

165 patients were analyzed; 82 patients in the ramosetron group and 83 patients in the placebo group. The characteristics of the study groups are presented in Table 1. No significant differences in age, body weight, height, and BMI existed between the two groups. Most patients were American Society of Anesthesiologists I status (placebo vs. ramosetron: 61.4% vs. 62.2%). A history of PONV was presented in 1.2% of patients in the placebo group and 2.3% in the ramosetron group. More than 70% of patients had no history of motion sickness. There were no significant differences in needle type and size, or type of surgery between the two groups. The mean duration of anesthesia was approximately 96 minute. The incidences of intraoperative hypotension, nausea and vomiting, pruritus and postoperative Pethidine were also not different between the two groups.

The incidence of nausea and vomiting, and use of antiemetic agents are shown in Table 2. The incidence of nausea in patients who underwent gynecological surgery in the 0-2, 2-6, 6-24, and 0-24-h periods after the operation were 31.3%, 51.8%, 48.2%, and 62.7%, respectively. We found that the incidence of postoperative nausea and vomiting in the ramosetron group was significantly lower than that in the placebo group in the 0-24-h postoperative periods (p = 0.006) and also the incidence of nausea was significantly lower in the ramosetron group than in the placebo group at 0-2 hour, 2-6 hour, 6-24 and 0-24 hour (p = 0.049, 0.005, and 0.024, respectively). The

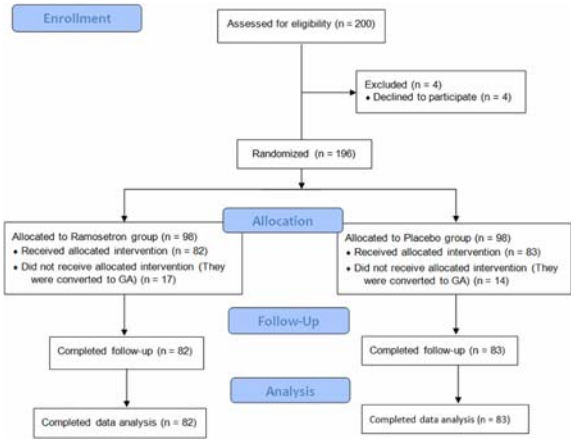

Fig. 1 Flow diagram.

Table 1. Patient characteristics and operative data

	Ramosetron (n = 82)	Placebo (n = 83)	*p*-value
Age (years)	43.98±8.47	45.77±10.08	0.221
Body weight (kg)	58.38±9.36	58.87±8.59	0.725
Height (cm)	158.25±4.99	158.28±5.23	0.967
BMI (kg/m^2)	23.28±3.39	23.50±3.27	0.677
ASA			
I (n, %)	51 (62.2)	51 (61.4)	0.921
II (n, %)	31 (37.8)	32 (38.6)	
History of PONV	3 (3.7%)	1 (1.2%)	0.367
History of motion sickness	10 (12.2%)	7 (8.4%)	0.427
Duration of Surgery (min)	97.5 (50,235)	95 (35,200)	0.681
Intraoperative hypotension	62 (75.6%)	60 (72.3%)	0.627
Intraoperative nausea and vomiting	18 (22%)	21 (25.3%)	0.613
Postoperative pethidine IV	23 (28.1%)	24 (28.9%)	0.902

Data are mean ± standard deviation, median (min, max), or number of patients (%).
BMI = body mass index; ASA = American society of anesthesiologists; PONV = postoperative nausea and vomiting; IV = intravenous

Table 2. Incid ence of nausea, severity of nausea, incidence of vomiting, and the use of rescue antiemetics

	Ramosetron n (82), (%)	Placebo n (83), (%)	*p*-value	ARR	NNT
0-2 hours post-op					
Nausea	18 (22)	26 (31.3)	0.173	9.3	11
Nausea VAS >50	4 (4.9)	13 (15.7)	0.023*	10.7	10
Vomiting	9 (11)	16 (19.3)	0.137	8.3	12
Rescue drug	2 (2.4)	11 (13.3)	0.010*	10.8	10
2-6 hours post-op					
Nausea	30 (36.6)	43 (51.6)	0.049*	15	7
Nausea VAS >50	7 (8.5)	24 (28.9)	0.001*	20.3	5
Vomiting	11 (13.4)	31 (37.3)	<0.001*	23	5
Rescue drug	11 (13.4)	17 (20.5)	0.227	7	15
6-24 hour post-op					
Nausea	22 (26)	40 (48.0)	0.005*	21	5
Nausea VAS >50	10 (12.2)	11 (13.3)	0.838	1	95
Vomiting	9 (11)	9 (10.8)	0.978		
Rescue drug	12 (14.6)	7 (8.4)	0.212		
0-24 hour post-op					
Nausea	37 (45.1)	52 (62.7)	0.024*	17.5	6
Nausea VAS >50	17 (20.7)	33 (39.8)	0.008*	19	6
Vomiting	20 (24.4)	38 (45.8)	0.004*	21	5
Nausea & vomiting	20 (24.4)	37 (44.6)	0.006*	20	5
Rescue drug	21 (25.6)	30 (36.1)	0.143	10.5	10

Data are n (%).
ARR = absolute risk reduction; NNT = number needed to treat; *VAS = visual analogue scale score 0-100 (0 = none, 100 = maximum)

severity of nausea (VAS >50) was significantly lower in the ramosetron group compared with the placebo group at 0-2 hour, 2-6 hour, and 0-24 hour (p = 0.023, 0.001, and 0.004, respectively). The incidence of vomiting was also noted to be significantly lower in ramosetron group than in the placebo group at 2-6 hour and 0-24 hour (p<0.001 and p = 0.004, respectively). There were no significant differences in the quantity of rescue antiemetic drug usage between the two groups. The number needed to treat (NNT) for oral ramosetron to prevent postoperative nausea and vomiting (NNT = 5) and reduce the severity of nausea (NNT = 5.0) in the 0-24 hour period after surgery.

There were no differences in the overall pruritus score and pain score between the groups. The mean pain score (VAS approximately 30) was also similar among the two study groups. There were no significant differences regarding patient satisfaction rating between the ramosetron and placebo groups and there were no statistically significant difference in the incidence of adverse events between the two groups (Table 3). Dizziness and hot flashes were the most frequently reported adverse events in the study. Interestingly, diarrhea was found only in ramosetron group but there was no statistical significant.

Table 3. Adverse events

	Ramosetron (n = 82) (%)	Placebo (n = 83) (%)	*p*-value
Adverse event			
PDPH	0	2 (2.4)	0.497
Headache	5 (6.1)	5 (6.0)	1.000
Dizziness	28 (34.1)	37 (44.6)	0.170
Constipation	9 (11)	4 (4.8)	0.142
Diarrhea	4 (4.9)	0	0.059
Hot flash	9 (11)	7 (8.4)	0.581

Data are n (%)
PDPH = postdural puncture headache

Discussion

The aim of this study was to compare oral ramosetron with placebo for the prevention of PONV

and pruritus after intrathecal morphine in patients undergoing gynecological surgery. The findings of this study indicated that oral ramosetron at 0.1 mg could prevent PONV between 0 and 24 hour, and could reduce nausea severity in the 0-24-h period after gynecological surgery.

Intrathecal morphine is used for relief of post-operative pain; however, it is followed by complications such as nausea, vomiting, urinary retention, pruritus, and delayed respiratory depression. There are three factors contributed to PONV risk. First, patient factors such as age, sex, obesity, prior history of motion sickness or PONV, and non-smoker status are associated with an increased incidence of PONV. Second, spinal anesthesia, including the use of opioids intraoperatively and postoperatively increases the risk of PONV. Third, the surgical procedure and duration also influence PONV[1,9]. Patient characteristics and risk factors in this study were similar between the two groups; therefore, the observed differences between the groups were related to the treatments provided.

The mechanism of ramosetron in the prevention of PONV is not currently known, but it has been suggested that ramosetron is a highly potent 5-HT_3 receptor antagonist with high bioavailability. When comparing ramosetron with older drugs in this class, the binding affinity of $5HT_3$ receptors for ramosetron is significantly greater and the dissociation rate from the receptors is slower[4]. Also, because of the longer elimination half-life of ramosetron (9 hour) compared with ondansetron (3.5 hour), ramosetron is more potent and has a longer duration than older $5HT_3$ antagonists[10].

Kim et al reported that IV ramosetron is effective in reducing the incidence of PONV and severity of nausea in high-risk female patients during the first 24 hours after surgery[11]. Lee et al reported that 0.1 mg oral ramosetron premedication effectively reduces the incidence of PONV in breast cancer patients[12]. We used the oral form of ramosetron at 0.1 mg as recommended by the manufacturer. Our results demonstrated that 0.1 mg oral ramosetron was effective in significantly reducing the incidence of PONV after intrathecal morphine in gynecological surgery in the 0-24-h postoperative period and it also reduced the incidence of moderate to severe nausea in the 0-24-h postoperative period.

The most common adverse effects of ramosetron were dizziness and hot flashes in our study, and were similar between the groups. Interestingly, diarrhea was found only in ramosetron group but it was not significantly different.

The efficacy of ramosetron in preventing pruritus was not demonstrated in this study. A further study to evaluate its efficacy in pruritus prophylaxis after intrathecal morphine is needed with an increase in the drug dose and study sample size.

A limitation of this study was that we did not evaluate oral ramosetron with gold standard medications such as ondansetron and metoclopramide. In addition, we assessed PONV subjectively, only, based on VAS score and did not measure objective data such as C-reactive protein, urea, and ketones that are biochemical parameters of nausea and vomiting.

Although ramosetron is highly effective in preventing PONV after intrathecal morphine in gynecological surgery, the cost of ramosetron is higher than other conventional drugs and the NNT for oral ramosetron to prevent postoperative nausea and vomiting (NNT = 5.0) and reduce the severity of nausea (NNT = 6.0) in the 0-24 h period after surgery; therefore, the cost-effectiveness needs to be considered in its clinical use.

Conclusion

We conclude that oral ramosetron is an effective antiemetic in the prevention of PONV. Pre-operative prophylactic administration of a single dose of oral ramosetron at 0.1 mg is better than placebo in reducing the incidence of PONV and severity of PONV in the 0-24 h postoperative period in patients undergoing gynecological surgery under regional anesthesia. However, ramosetron did not prevent pruritus after intrathecal morphine and overall patient satisfaction was not improved. A future study is needed to compare oral ramosetron with other drugs.

What is already known on this topic?

Ramosetron is $5HT_3$ receptor antagonists that has been shown to reduce PONV in general anesthesia due to it has more potent and longer acting than other drugs in this class. Moreover, most of research focused on intravenous ramosetron in general anesthesia, but there were no previous studies to evaluate oral ramosetron 0.1 mg for preventing PONV after intrathecal morphine.

What this study adds?

This study has shown the efficacy of oral ramosetron for preventing PONV and severity of nausea after intrathecal morphine in gynecological surgery.

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Potential conflicts of interest

None.

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การเปรียบเทียบระหว่างยากิน ramosetron กับยาหลอกเพื่อป้องกันอาการคลื่นไส้อาเจียนหลังจากได้รับยา morphine ทางน้ำไขสันหลังในผู้ป่วยที่มารับการผ่าตัดทางนรีเวช

สุรัสวดี วังน้ำทิพย์, ฐิติมา ชินะโชติ, สมชาย อมรโยธิน, กรุณา วงศ์ตั้งมั่น, น้ำผึ้ง สุคันธรัต, พาพิรุณ น้อยตาแสง

ภูมิหลัง: อัตราการเกิดอาการคลื่นไส้อาเจียนหลังได้รับยา morphine ทางช่องไขสันหลังค่อนข้างสูง ซึ่งยา ramosetron เป็นยากลุ่ม $5HT_3$ receptor antagonists ได้แสดงให้เห็นว่าสามารถลดอาการคลื่นไส้-อาเจียน ในผู้ป่วยที่ได้รับการระงับรู้สึกแบบทั่วร่างกาย ดังนั้นจุดประสงค์ในการทำวิจัยนี้เพื่อประเมินประสิทธิภาพของยากิน ramosetron 0.1 มก. ในการป้องกันอาการคลื่นไส้-อาเจียน หลังได้รับยา morphine ทางช่องไขสันหลังในผู้ป่วยที่มารับการผ่าตัดนรีเวช

วัสดุและวิธีการ: ผู้ป่วยจำนวน 165 คน ที่มารับการผ่าตัดทางนรีเวชภายใต้การระงับความรู้สึกทางช่องไขสันหลังถูกสุ่มออกเป็นสองกลุ่ม ได้แก่ ยากิน ramosetron 0.1 มก. (n = 82) และยาหลอก (n = 83) โดยจะประเมินอัตราการเกิดอาการความรุนแรงและจำนวนการใช้ยาเพื่อรักษาอาการคลื่นไส้และอาเจียนหลังผ่าตัดภายใน 24 ชั่วโมง

ผลการศึกษา: อัตราการเกิดอาการคลื่นไส้และอาเจียนหลังผ่าตัดในกลุ่มที่ได้รับยากิน ramosetron ต่ำกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญ (24.4% vs. 44.6%, NNT = 5) และความรุนแรงของอาการคลื่นไส้ในกลุ่มยากิน ramosetron น้อยกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญ (20.7% vs. 39.8%, NNT = 6.0) หลังผ่าตัด 24 ชั่วโมง

สรุป: ยากิน ramosetron 0.1 มก. มีประสิทธิภาพในการป้องกันการเกิดอาการคลื่นไส้-อาเจียน และลดความรุนแรงในการเกิดอาการหลังได้รับยา morphine ทางช่องไขสันหลังหลังการผ่าตัดทางนรีเวช 24 ชั่วโมง เมื่อเทียบกับยาหลอก