Ondansetron vs. Metoclopramide for the Prevention of Nausea and Vomiting after Gynecologic Surgery

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Background: *Postoperative nausea and vomiting (PONV) remains a very troublesome concomitant phenomenon after general anesthesia. The present study was designed to compare the efficacy and safety of ondansetron with metoclopramide for prophylaxis of PONV in patients undergoing major gynecological surgery.*
Material and Method: *A prospective, randomized, double-blind, 382 female patients received either ondansetron 4 mg or metoclopramide 10 mg intravenous administration immediately before the induction of anesthesia. A standard general anesthetic technique was employed throughout. Nausea, vomiting, and safety assessments were performed continuously during the 24 h postoperative period.*
Results: *Of the 380 patients evaluated, significantly fewer ondansetron 4 mg treated patients (89/189;47%) experienced postoperative nausea and/or vomiting compared with metoclopramide treated patients (115/191; 60%) during the study period (p = 0.007, 95% CI: 1.07, 1.66). Postoperative adverse events were not significantly different between the groups.*
Conclusion: *Prophylactic use of ondansetron is more effective than metoclopramide for preventing PONV in patients undergoing major gynecological surgery.*

Keywords: *Gynecology, Nausea, Vomiting, Antiemetics, Ondansetron, Metoclopramide*

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Postoperative nausea and vomiting (PONV) is a distressing, unpleasant experience and a frequent unfavorable event after surgery performed under general anesthesia. Female patients are particularly susceptible[1]. The incidence of (PONV) range from 20 to 30% during the first 24 hours after surgery[1,2]. PONV occurs frequently after gynecological surgery, with an incidence as high as 88%[1,3]. In fact, with the ever-increasing safety of anesthesia, PONV is now one of the greatest concerns that patients express regarding anesthesia and surgery. When surveyed preoperatively, 72% of patients stated that prevention of PONV should be given the highest priority[4]. In addition to being an important patient concern, PONV remains one of the primary reasons for delayed discharge from the post-anesthetic care unit (PACU), and for unscheduled admission after outpatient procedures[5-7]. Moreover, persistent nausea and vomiting may result in electrolyte imbalance (hypokalaemia, hypochloraemia, and hyponatremic metabolic acidosis) and dehydration[8,9]. Persistent retching or vomiting can cause tension in suture lines, venous hypertension, and increased bleeding under skin flaps. It can also expose the subject to an increased risk of pulmonary aspiration of vomitus if airway reflexes are depressed from the residual effects of the anesthetic and analgesic drugs[8].

Because antiemetics are not always effective, the routine prophylactic antiemetic cannot be recommended[10,11]. Ondansetron is available and recommended for the prevention of nausea and vomiting induced by cancer chemotherapy. It is also effective in reducing the nausea and vomiting that occur after anesthesia. The present study evaluated the efficacy and safety of administering 4 mg of ondansetron for prophylaxis of (PONV) in patients undergoing major gynecological surgery under general anesthesia. The results for

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ondansetron (4 mg) were compared with those for metoclopramide (10 mg), a commonly used drug in Chaiyaphum Hospital. The choice of the 4 mg ondansetron dose was based on pooled data from studies that have suggested this is the optimal dose for the prophylaxis of PONV[12,13].

Material and Method

The present study is not supported by any funds of drug commercials. After obtaining approval from the Ethical Committee and patients informed consent, the authors studied 382 ASA I-II females scheduled to undergo elective major gynecological surgery under general anesthesia. Female patients between the ages of 20 and 65 yr were eligible. The exclusion criteria were laboratory or clinical evidence of cardiovascular, hematologic, pulmonary, renal, hepatic, neurological or endocrine abnormalities, gastrointestinal disease, pregnancy, morbid obesity, history of substance abuse, anti-emetic, and antipsychoactive medication within 24 hours before surgery, and the need for a nasogastric tube postoperatively. To identify patients with a predisposition to PONV, patients were asked about previous anesthetic experiences and motion sickness.

Patients were randomly allocated to receive one of two intravenous treatment regimens 4 mg ondansetron (Onsia®; Siam Bheasach, Thailand) or 10 mg metoclopramide (Vomitin®; Nida Pharma, Thailand). These drugs were prepared in identical syringes (also, the colors of the two drugs were identical) and were administered immediately prior to induction of general anesthesia. A randomization list and sealed envelopes were prepared before anesthesia according to a list of randomized numbers generated by the method of block randomization, with block size varying from 2 to 6. According to this list, identical syringes containing each antiemetic were prepared by a nurse anesthetist not involved in the study. In this way, the anesthesiologist, anesthetist, patients, and PACU nurses were all blinded to the identity of the prophylactic treatment.

For pre-medication, all patients received a standard anesthetic treatment consisting of a 0.3-0.5 mg/kg midazolam IV and a 1-2 mcg/kg fentanyl IV 3-5 min before induction of anesthesia. Anesthesia was induced using a 5 mg/kg thiopentone IV, and a 1-2 mg/kg succinylcholine IV was used to facilitate tracheal intubation. After tracheal intubation, anesthesia was maintained with nitrous oxide 66%, sevoflurane 0.5%-2% in oxygen, and atracurium. Ventilation was controlled mechanically. At the cessation of the surgical procedure, 0.02 mg/kg atropine and 0.04 mg/kg neostigmine were administered by IV to reverse muscle relaxation, and the trachea was extubated.

Nausea and vomiting were assessed immediately after surgery and at 1h in the PACU. In addition, nausea and vomiting were assessed at 1-6 h and 6-24 h in the gynecological ward. Two symptoms were assessed separately: nausea was recorded as none, mild (rescue medication not required) or severe (rescue medication required), and vomiting was recorded as either present or absent. Sedation levels were also recorded at the PACU. Sedation level was graded as 0 = comatose, 1 = sleeping, difficult to wake, 2 = sleeping, easy to wake, 3 = drowsy, uncooperative, 4 = drowsy, cooperative, and 5 = awake. The details of any other adverse effects were recorded by a nurse anesthetist, not apprised of which drug had been administered.

Rescue medication for nausea and/or vomiting was allowed at any time upon physician determination, patient request, more than three emetic episodes, or nausea lasting at least 15 min. The choice of rescue antiemetic was Dimenhydrinate 50 mg IV. The number of doses of "rescue antiemetics" was recorded along with the reason for antiemetic therapy.

The sample size of 191 patients per treatment group was estimated to ensure the study appropriate for the investigation. Based on the assumptions that (a)the incidence of PONV in a patient receiving metoclopramide would be 40%,(b) the range of equivalence is set at 15% reduction in PONV that would be clinically distinguishable, and (c) alpha = 0.05 with a power of 0.8.

Analysis of variance was used for comparison of all continuous variables between the groups. Chi-square test was used for analysis of categorical demographic data. The difference in the incidence of PONV (the number of patients suffering neither nausea nor vomiting and the number of patients experiencing one or both of the symptoms) between the two groups was determined, and 95% confidence intervals were calculated for these differences. The significance of any differences was assessed using chi-square tests, or Fisher's exact test where numbers were small. All hypothesis tests were two-tailed at the significant level of 0.05. The statistical package used for all the analysis was STATA (Stata Corp, College Station, TX).

Results

Three hundred eighty two patients were enrolled in the present study. Two patients in the ondansetron group were excluded from the trial due to complications in surgery (final operations were bowel

surgery). There were no significant differences between the two groups with regard to the demographics variables (Table 1).

The efficacy of ondansetran 4 mg as a prophylactic antiemetic compared with metoclopramide 10 mg is summarized in Table 2. The authors used the total incidence of nausea and/or vomiting to represent PONV. The incidence of PONV during the period 0-1 h after anesthesia was 14% with ondansetron and 14% with metoclopramide; corresponding incidences during the period 1-6 h after anesthesia were 20% and 32%; corresponding incidences during the period 6-24 h after anesthesia were 39% and 47%. The overall incidence of PONV during the whole 24 h period was 47% in the ondansetron group, compared with 60% in the metoclopramide group. Thus, the incidence of PONV from 1-6 h after anesthesia in patients who had received ondansetron was lower than in those who had received metoclopramide ($p = 0.01$). The risk estimate (95% CI) of the treatment groups was 1.15 (1.04, 1.32). A similar relationship was also observed during the 0-24 h postoperative periods ($p = 0.007$), with risk estimates (95% CI) of 1.33 (1.07, 1.66). There were no significant differences between the treatment groups in the incidence of PONV during the period 0-1 h and 6-24 h after anesthesia (Table 2).

When nausea and vomiting data were separated, the results found that the incidence of mild nausea during the period 6-24 h after anesthesia was lower in the ondansetron group ($p = 0.03$).

The proportions of patients in each of the sedation categories, discharge times from the PACU and amounts of postoperative analgesia medication were not significantly different ($p > 0.05$ for each category) between the groups.

For all observation periods there were no significant differences in the incidence of adverse events between the treatment groups (Table 3). One patient in the metoclopramide group had extrapyramidal symptoms (mild sensation of tightness in neck and tongue) 6 h after anesthesia.

Discussion

Postoperative nausea and vomiting are among the most common complications after anesthesia and surgery. Women undergoing gynecological surgery performed under general anesthesia are particularly at risk in experiencing these problems[1]. The etiology of PONV after major gynecological operations is complex and is dependent on a variety of factors, including patient demographic characteristics, type of operations anesthetic technique, and postoperative care[1]. Patient-related factors are age, sex, and obesity, history of motion sickness or previous PONV, and stage of menstrual cycle. However, in the present study, care was taken to ensure that the treatment groups were comparable in terms of type of patient, demographics, surgical procedures, anesthetics administered, and analgesics used after the operation (other than the study medication). Therefore, the difference in the incidence of PONV between the study groups can be attributed to the differences between the agents tested.

The results of the present study show that prophylactic administration of 4 mg of intravenous

Table 1. Patient characteristics, type of surgery, and anaesthetic data

	Ondansetron n = 189	Metoclopramide n = 191
Age (yr)	43 ± 10	44 ± 9
Weight (kg)	58 ± 10	58 ± 9
Height (cm)	153 ± 11	154 ± 5
History of PONV: n(%)	59 (31)	64 (34)
History of motion sickness n(%)	23 (12)	37 (19)
Type of surgery		
TAH ± BSO: n (%)	151 (80)	145 (76)
Adnexal surgery: n (%)	23 (12)	32 (17)
Vaginal hysterectomy: n (%)	15 (8)	14 (7)
Duration of anesthesia (min)	66 ± 20	66 ± 23
Duration of surgery (min)	52 ± 20	53 ± 22
Intraoperative IV fluid (ml)	617 ± 317	641 ± 333
Intraoperative analgesics used Fentanyl (mcg)	68 ± 20	61 ± 18

Data presented as mean ± SD or number (%)

Table 2. Incidence of PONV

Outcome	Ondansetron n = 189	Metoclopramide n = 191	Risk estimate (95% CI)
0-1 hr after anesthesia			
Nausea			
- mild	25 (13)	26 (14)	0.97 (0.58-1.62)
- severe	-	-	-
Vomiting	2 (1)	5 (3)	0.40 (0.08-2.06)
Total PONV	26 (14)	26 (14)	1.01 (0.61-1.7)
1-6 hr after anesthesia			
Nausea			
- mild	34 (18)	52 (27)	1.13 (1.01-1.26)*
- severe	4 (2)	8 (4)	0.51 (0.12-1.65)
Vomiting	5 (3)	16 (8)	1.06 (1.01-1.12)*
Total PONV	38 (20)	61 (32)	1.15 (1.04-1.32)*
6-24 hr after anesthesia			
Nausea			
- mild	65 (34)	84 (44)	1.17 (1.00-1.38)*
- severe	8 (4)	6 (3)	0.99 (0.95-1.03)
Vomiting	37 (20)	50 (26)	1.09 (0.98-1.22)
Total PONV	73 (39)	90 (47)	1.16 (0.97-1.38)
0-24 hr after anesthesia			
Nausea			
- mild	80 (42)	108 (57)	1.32 (1.08-1.62)*
- severe	22 (12)	23 (12)	1.01 (0.93-1.08)
Vomiting	38 (20)	54 (28)	1.11 (1.00-1.25)*
Total PONV	89 (47)	115 (60)	1.33 (1.07-1.66)*

Values are expressed as number (%)
* $p < 0.05$

Table 3. Incidence of adverse events

	0-1 hr after anesthesia		1-6 hr after anesthesia		6-24 hr after anesthesia	
Side effect	Ondan. n = 189	Metoclo. n = 191	Ondan. n = 189	Metoclo. n = 191	Ondan. n = 189	Metoclo. n = 191
Headache	1 (1%)	1 (1%)	3 (2%)	4 (2%)	2 (1%)	4 (2%)
Dizziness	38 (20%)	32 (18%)	77 (41%)	75 (39%)	113 (60%)	106 (55%)
Bowel ileus	0	0	1 (1%)	2 (1%)	33 (18%)	38 (20%)
Abdominal cramps	0	0	0	0	4 (2%)	4 (2%)
Visual disturbance	18 (10%)	20 (11%)	17 (9%)	13 (7%)	1 (1%)	3 (2%)
EPS	0	0	0	0	0	1 (1%)
Total	57 (30%)	53 (19%)	98 (52%)	94 (49%)	153 (81%)	155 (81%)

Ondan. = Ondansetron
Metoclo. = Metoclopramide
EPS = extrapyramidal symptom
Values are expressed as number (%)

ondansetron given immediately prior to induction of anesthesia reduces the incidence of PONV during the first 24 h postoperatively, with no increase in adverse side effects or delay in PACU discharge, when compared with the intravenous metoclopramide 10 mg.

Other published studies that evaluated the efficacy of ondansetron administered intravenously have shown similar reductions in the incidence of PONV during the 24 h post recovery period[13,14-20] and, as with the present study, the reduction was pronounced during the 1-6 h and 0-24 h observation periods. It is also important to stress that they support the low incidence of side-effects observed with ondansetron, which the authors have noted.

In the present study, the authors found that one patient in the metoclopramide group complained of a mild sensation of tightness in the neck and tongue 6 h after anesthesia. She was not given any special medication and symptoms had resolved by the next period of assessment. The authors considered it to be an extrapyramidal symptom.

The purpose of the present study was to determine the efficacy of ondansetron vs. metoclopramide for the prevention of PONV. Ondansetron had been shown previously to be superior to placebo[16,17] so, on ethical grounds, a placebo group was not included in the present study. In conclusion, intravenous ondansetron differs from metoclopramide in its prevention of PONV after major gynecological surgery. Immediate recovery and postoperative adverse events were not significantly different between the treatment groups.

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ประสิทธิผลของ ondansetron และ metoclopramide ในการป้องกันอาการคลื่นไส้อาเจียนหลังผ่าตัดทางนรีเวช

บรรจง ครอบบัวบาน, สำรอง พิทักษ์พล, ศิริวรรณ ดิเรกโภค

ภูมิหลัง: *อาการคลื่นไส้และอาเจียนหลังผ่าตัดเป็นอาการที่ผู้ป่วยรู้สึกไม่สบายและพบบ่อยหลังการผ่าตัด และให้ยาระงับความรู้สึกแบบทั่วไป โดยเฉพาะผู้ป่วยที่มารับการผ่าตัดทางนรีเวช*

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบประสิทธิผลและความปลอดภัยของยา ondansetron ขนาด 4 มิลลิกรัม และ metoclopramide ขนาด 10 มิลลิกรัม ในการป้องกันอาการคลื่นไส้อาเจียนหลังผ่าตัดในผู้ป่วยที่มารับการผ่าตัดใหญ่ทางนรีเวช ภายใต้การให้ยาระงับความรู้สึกแบบทั่วไป*

วิธีการศึกษา: *เป็นการศึกษาแบบ randomized, double-blind, controlled trial ชนิด equivalence trial ในผู้ป่วยจำนวน 382 ราย เพื่อได้รับยา ondansetron ขนาด 4 มิลลิกรัม หรือ metoclopramide 10 มิลลิกรัม ทางหลอดเลือดดำทันที ก่อนการนำสลบ ประเมินอาการคลื่นไส้ อาเจียนและผลข้างเคียงของยาที่ช่วงเวลา 0-1 ชั่วโมง, 1-6 ชั่วโมง และ 6-24 ชั่วโมงหลังผ่าตัด*

ผลการศึกษา: *พบว่าอุบัติการณ์การเกิดอาการคลื่นไส้ และ/หรืออาเจียนในกลุ่มที่ได้รับยา ondansetron และในกลุ่มที่ได้รับยา metoclopramide ในช่วง 0-24 ชั่วโมงแรกหลังผ่าตัดในกลุ่มที่ได้รับยา ondansetron มีร้อยละ 47 และในกลุ่มที่ได้รับยา metoclopramide ร้อยละ 60 (p = 0.007, 95% CI: 1.07, 1.66) ส่วนผลข้างเคียง ของยาในผู้ป่วยทั้งสองกลุ่มพบว่ามีความแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ*

สรุป: *การให้ยา ondansetron ขนาด 4 มิลลิกรัม ก่อนการนำสลบ มีผลการป้องกันอาการคลื่นไส้อาเจียนหลังการผ่าตัดทางนรีเวชได้ดีกว่าการให้ยา metoclopramide ขนาด 10 มิลลิกรัม*