Comparison of Ondansetron and Placebo for Preventing Postoperative Nausea and Emesis in Gastrointestinal Tract Surgery : A Multicenter Randomized Controlled Trial†

ORANUCH KYOKONG, M.D.*, WANNA SOMBOONVIBOON, M.D.*,
SHUSEE VISALYAPUTRA, M.D.**, SOMSRI PAUSAWADI, M.D.***,
PRAMOTE SARATAN, M.D.****, PRAMOTE VONGVISES, M.D.*****

Abstract

Background : Nausea and emesis are undesirable events that may cause discomfort and suffering in the postoperative period. This study was carried out to evaluate the efficacy and safety of ondansetron for preventing postoperative nausea and vomiting in patients undergoing gastrointestinal tract surgery.

Methods : Using a randomized double-blind study design, 408 surgical patients (163 male and 245 female) receiving general endotracheal anesthesia were studied at five medical centers in Bangkok. Ondansetron (4 mg) or placebo was administered prior to induction of anesthesia. Episodes of nausea and vomiting, adverse events and laboratory tests (complete blood count and liver function test) were evaluated during 24 hours after study drug administration.

Results : The incidence of postoperative nausea and vomiting in the placebo group (42.7 and 35.2%) were significantly higher than the ondansetron group (23.9 and 15.4%). However, no significant differences occurred in the incidence of adverse events or changes in laboratory tests in the ondansetron group compared to the placebo group.

Conclusions : Ondansetron 4 mg given intravenously before surgery is safe and effective for preventing postoperative nausea and emesis following gastrointestinal tract surgery.

Key word : Nausea and Emesis, Gastrointestinal Tract Surgery, Ondansetron, Placebo, Comparison, Multicenter Trial

* Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330,
** Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700,
*** Department of Anesthesiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400,
**** Department of Anesthesia, Rajvithi Hospital, Bangkok 10400,
***** Division of Anesthesiology, Phramongkutklao Hospital, Bangkok 10400, Thailand.

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Postoperative nausea and vomiting (PONV) are among the undesirable symptoms that may cause severe discomfort to patients and delay their discharge especially in ambulatory surgical patients. The incidence is as great as 30 to 80 per cent and has remained unchanged over the last 30 years[1]. The etiology of PONV is multifactorial[2] and a variety of antiemetics have been used to prevent or treat these symptoms. However, the effectiveness of treatment varies[1,3] and it also causes some undesirable effects such as sedation, dysphoria, hypotension and/or extrapyramidal symptoms[4-6]. Ondansetron is a relatively new antiemetic which is a carbazalone derivative that is structurally related to serotonin and possesses specific 5-hydroxytryptamine (5 HT) and subtype 3 receptor antagonism[7]. Preliminary and multicenter studies have shown that ondansetron 4 to 8 mg given intravenously is effective in the prevention and treatment of postoperative nausea and vomiting[8,9]. The objective of this multicenter trial was to evaluate the efficacy and safety of prophylactic 4 mg of intravenous ondansetron in Thai patients who underwent gastrointestinal and biliary tract surgery under general endotracheal anesthesia.

MATERIAL AND METHOD

After obtaining the institutional ethics committee approval and informed consent from patients, 408 ASA physical status I or II patients between 18 and 75 years of age were recruited. These patients were scheduled for gastrointestinal and biliary tract surgery under general endotracheal anesthesia at five medical centers in Bangkok. Patients were excluded from enrollment if they had received any other antiemetic agent within 24 hours before the study began, had vomited or retched within 24 hours, were pregnant or breastfeeding, were more than 100 kg in weight, were scheduled for inguinal hernia repair, had a recent history of drug or alcohol abuse, or had any other contraindications to ondansetron.

Patients were randomized within each center to receive either 4 mg ondansetron or placebo. Each medication was coded and contained in identical ampoules so that the patient and investigator were unaware of the nature of the drug being administered. Ampoules containing ondansetron 4 mg and placebo were labelled, pre-packed and supplied by Glaxo Group Research Limited. The study drug was administered intravenously over a 2-5 min period immediately before induction of anesthesia. Blood pressure and heart rate were monitored immediately before and after study drug administration.

Premedication was limited to any benzodiazepines except lorazepam. All patients underwent endotracheal intubation and received balanced general anesthesia including an induction agent (thiopentone or propofol), an opioid analgesic (fentanyl) and nitrous oxide-oxygen. In some instances isoflurane or halothane were administered as necessary. Neuromuscular blockade was facilitated with succinylcholine, atracurium, pancuronium or vecuronium and reversed with an anticholinesterase (neostigmine) with atropine.

Assessments of PONV were made at 1, 2, 4, 8 and 24 hours after recovery from anesthesia. An emetic episode was defined as a vomiting or retching event or any combination of these events that occurred in rapid sequence (less than 1-min between events) or any number of continuous retches and/or vomits. Continuous retching and/or vomiting was defined as two or more retches and/or vomits that occurred within one minute of each other. Nausea was defined on a categorical 11-point linear whole number scale for which 0 represented "no nausea" and 10 represented "nausea as bad as it can possibly be". Rescue therapy was allowed at any time upon patient request or if the investigator considered it appropriate. The choice of rescue antiemetic was left to the discretion of the investigator and the patient was considered a treatment failure. All adverse events and postoperative concomitant medication were also recorded. Blood samples for laboratory safety studies including complete blood counts and liver function tests were taken preoperatively and at 24 hours after study drug administration.

All statistical comparisons in this study were placebo group versus ondansetron group. Patient baseline data, incidence of nausea and emesis and adverse events were analysed by student's *t*-test, chi-square test or Fisher's exact test whenever appropriate. Number of emetic episodes and severity of nausea were analysed employing Wilcoxon rank-sum test. Multiple logistic regression was used to determine the association between several confounders including age, sex, duration and type of surgery performed. All tests were two-tailed at a significance level of 0.05.

RESULTS

Patient characteristics

A total of 408 patients (ondansetron group = 207 ; placebo group = 201) were enrolled in this study. Six of the 207 patients who received ondansetron and 2 of the 201 patients who received the placebo were not included in the analysis of efficacy because of major protocol violations that may have altered the interpretation of results. These protocol violations included receipt of other antiemetics in addition to ondansetron or surgery was cancelled after study drug administration. All 408 patients were included in the safety evaluation of ondansetron.

Table 1. Baseline data.

Variables	Ondansetron	Placebo	P-value
1. No. of patient	201	199	
2. Age (year)			
- Mean	50.36	50.07	0.84
- S.D.	14.17	15.47	
3. Sex			
- Male	81	71	0.74
- Female	120	122	
4. Weight (kg)			
- Mean	58.65	57.19	0.21
- S.D.	10.92	12.08	

The important baseline data are presented in Table1. The age, sex and weight of the patients were comparable in both groups.

Efficacy

The incidence of nausea and emesis during the first 24 hours after surgery were significantly higher in the placebo group compared to the ondensetron group (Fig. 1). The number of emetic episodes experienced during the 24-h. period after recovery from anesthesia was lower in the ondansetran group (Table 2). The severity of nausea was compared between each study group by using the highest score during the 24-h period (Table 3). The result indicated that the severity of nausea was significantly less in the ondansetron-treated group. The multiple logistic regression was performed to determine the magnitude of association between potential confounding factors (age, sex, duration and type of surgery) and the incidence of nausea and vomiting. The age, duration and type of surgery had no influence on the incidence of nausea and vomiting. Females were more likely to have nausea (1.8 times i.e ODD-RATIO = 1.8642) and have emesis (1.2 times i.e ODD-RATIO = 1,2103) compared to males (p-value = 0.0127 and 0.5439 respectively). Ondansetron was more effective than placebo in preventing nausea and emesis over the entire 24-h period. The placebo-treated group had a 2.39 and

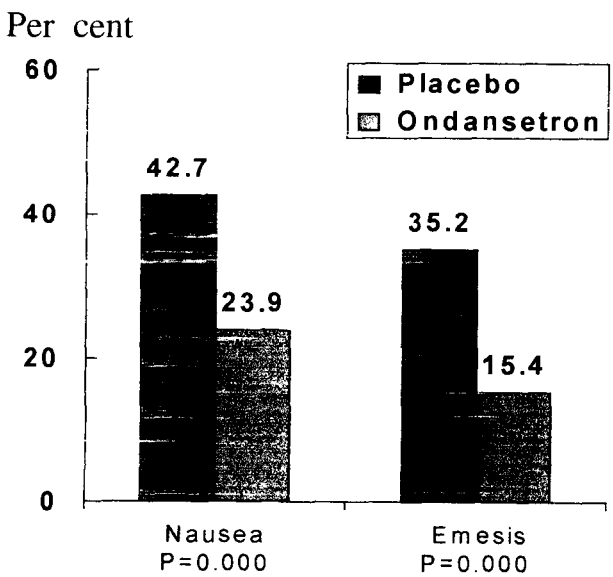

Fig. 1. The percentage of nausea and emesis in each study group.

Table 2. The number of emetic episodes during the 24-hour period.

Group	n	Mean Rank	P - Values
Ondansetron	201	180.25	0.0000
Placebo	199	220	
Total	400		

Wilcoxon Rank Sum Test

Table 3. The severity of nausea in each study group.

Group	n	Mean Rank	P - Values
Ondansetron	201	178.76	0.000
Placebo	198	221.56	

Wilcoxon Rank Sum Test

2.47 times higher rate of nausea and vomiting than the ondansetron-treated group (ODD-RATIO = 2.3974 and 2.4709 ; p-value = 0.0001 and 0.0021 respectively).

Safety

No significant difference in the incidence of adverse events between placebo and ondansetron group (4 and 4.8% respectively) was detected. The number of adverse events reported in the ondansetron group was 10 which included palpitation, hiccough (2), skin rash, premature ventricular contraction, delayed recovery, headache (3), bronchospasm, flushing, dizziness and feeling warm. In the placebo group, the reported adverse events were hypoventilation, dizziness (4), urinary retention, hiccough, urticaria, itching and constipation.

Changes in clinical laboratory test results including complete blood counts and liver function tests were generally similar in both the placebo and ondansetron groups.

DISCUSSION

The etiology of PONV is multifactorial and may include those factors related and unrelated to anesthesia. Ondansetron, which is a selective antagonist of 5-HT3 receptors, appears to be a promising antiemetic to antagonize nausea and vomiting induced by chemotherapy and radio-therapy[10] as well as PONV[8,9]. In our study, we used 4 mg of ondansetron which is the lowest effective dose according to the study by Kovac et al[11] to compare with placebo. Our results demonstrated that ondansetron continued to be effective in preventing PONV in patients undergoing gastrointestinal tract and biliary tract surgery. In those patients who had nausea and vomiting during the 24-h period of study, the severity of nausea and the number of emetic episodes were also lower in the ondansetron-treated group. These results were in agreement with other studies performed in those patients having other types of surgery[8,9,11-14]. For the factors influencing PONV, Smessaert et al[15] found the incidence of nausea and vomiting to be equal in children of both sex until 11 years of age when females began to show a tendency to vomit more frequently than males. In our study we also demonstrated that females had a higher incidence of PONV than males.

For safety evaluation, ondansetron appears to be a safe antiemetic. Several adverse effects reported in our patients who had received ondansetron were not significantly different from those seen in patients who had received placebo. Headache and dizziness which were reported to be related to ondansetron were tolerable and required no treatment. Few patients demonstrated increases in hepatic transaminase and resolved spontaneously on subsequent follow-up.

In conclusion, 4 mg of intravenous ondansetron appears to be an effective antiemetic in preventing PONV in patients undergoing gastrointestinal tract surgery. It was well tolerated and had a low incidence of side effects.

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เปรียบเทียบผลของออนแดนเซทรอน และยาหลอกในการป้องกันการคลื่นไส้อาเจียนหลังผ่าตัดทางเดินอาหาร : การศึกษาแบบสุ่มโดยใช้กลุ่มควบคุมและศึกษาสหสถาบัน

อรนุช เกี่ยวข้อง, พ.บ., วรรณา สมบูรณ์วิบูลย์, พ.บ.*,*
*ชูศรี พิศลยบุตร, พ.บ.**, สมศรี เผ่าสวัสดิ์, พ.บ.***,*
*ปราโมทย์ สระฏัน, พ.บ.****, ปราโมทย์ วงศ์วิเศษ, พ.บ.******

วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิผลและภาวะแทรกซ้อนของยาออนแดนเซทรอน ในการป้องกันการคลื่นไส้อาเจียนหลังผ่าตัดทางเดินอาหาร

รูปแบบการศึกษา : เป็นการศึกษาแบบสุ่มโดยใช้กลุ่มควบคุมในผู้ป่วยที่ผ่าตัดระบบทางเดินอาหารในโรงพยาบาล 5 แห่งของกรุงเทพมหานคร จำนวนผู้ป่วย 408 คน (ชาย 163 คน, หญิง 245 คน) ผู้ป่วยทุกคนได้รับการวางยาสลบแบบ general anesthesia แบ่งผู้ป่วยเป็น 2 กลุ่มโดยกลุ่มที่ 1 ได้รับยา ondansetron 4 มิลลิกรัมก่อนการนำสลบ กลุ่มที่ 2 ได้รับยาหลอกหลังผ่าตัดทำการประเมินอาการคลื่นไส้อาเจียนที่เวลา 1, 2, 4, 8 และ 24 ชั่วโมงหลังฟื้นจากยาสลบ นอกจากนี้ยังประเมินอาการข้างเคียงของยาออนแดนเซทรอน และตรวจ complete blood count และ liver function tests ที่ 24 ชั่วโมงหลังได้รับยา

ผลการศึกษา : การเกิดอาการคลื่นไส้และอาเจียนหลังผ่าตัดในกลุ่มยาหลอกมีจำนวน 42.7 และ 35.2 เปอร์เซ็นต์ ส่วนในกลุ่มที่ได้ออนแดนเซทรอน มีจำนวน 23.9 และ 15.4 เปอร์เซ็นต์ ซึ่งน้อยกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญ สำหรับอาการข้างเคียงของยาและผลการตรวจเลือดทางห้องปฏิบัติการไม่พบความแตกต่างที่มีนัยสำคัญทางสถิติ

สรุป : ยาออนแดนเซทรอน ในขนาด 4 มิลลิกรัมที่ให้เข้าหลอดเลือดดำก่อนการผ่าตัดให้ผลดีในการป้องกันการคลื่นไส้และอาเจียนหลังการผ่าตัดทางเดินอาการ

คำสำคัญ : คลื่นไส้อาเจียน, การผ่าตัดทางเดินอาหาร, ออนแดนเซทรอน, ยาหลอก, การศึกษาเปรียบเทียบ, สหสถาบัน

* ภาควิชาวิสัญญีวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330
** ภาควิชาวิสัญญีวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700
*** ภาควิชาวิสัญญีวิทยา, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400
**** กลุ่มงานวิสัญญี, โรงพยาบาลราชวิถี, กรุงเทพ ฯ 10400
***** กองวิสัญญีวิทยา, โรงพยาบาลพระมงกุฎเกล้า, กรุงเทพ ฯ 10400