A Placebo-Controlled, Randomized Trial of Droperidol *versus* Metoclopramide for Outpatients Undergoing Gynecological Laparoscopy under Conscious Sedation

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Abstract

This study compared the prophylactic antiemetic efficacy and the adverse effects of 0.5 mg droperidol, 5.0 mg metoclopramide, and placebo for outpatients undergoing gynecological laparoscopy under conscious sedation. One hundred and fifty outpatients were randomly allocated, in a randomized double-blind manner, into three groups to receive intravenous normal saline, 0.5 mg droperidol, and 5.0 mg metoclopramide before operation. Conscious sedation using intravenous pethidine, midazolam and local infiltration were given to each patient during the operation. Emetic symptoms were graded twice by the patients, at discharge time and the 24th post-operative hour.

The difference of antiemetic effect of both study drugs failed to reach statistical significance. There was also no statistical difference of intra-operative hypoxemia, sedation score, and discharge time among the groups. Therefore, using 0.5 mg droperidol or 5.0 mg metoclopramide is not effective in providing antiemetic prophylaxis for outpatients undergoing gynecological laparoscopy under conscious sedation.

Key word : Droperidol, Metoclopramide, Laparoscopy, Gynecologic, Sedation

UERPAIROJKIT K, PAVAVES B, NALAWACHAI J
J Med Assoc Thai 2002; 85: 470-476

Conscious sedation was established as an alternative simple anesthetic technique employed for short diagnostic gynecological laparoscopy[1] and tubal sterilization[2,3] (LTR) in healthy young patients. Since the incidence of post-operative nausea and vomiting (PONV) is high, many studies have been conducted to search for an effective prophylactic antiemetic for this procedure[4,5]. The pro-

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phylactic effectiveness of low-dose droperidol at 0.6 to 1.2 mg[6-8] was reportedly good for patients under general anesthesia, however, there has not been a report in patients under conscious sedation. This study was undertaken to assess the efficacy and safety of droperidol, compared to the commonly used antiemetic, metoclopramide, and a placebo.

METHOD

After obtaining Ethics Committee approval and written informed consent, the study was carried out in 150 Thai female outpatients undergoing gynecological laparoscopy for diagnosis or tubal sterilization (LTR) from September 1999 to January 2000. The criteria for subject recruitment were: patients aged between 18-50 years who were in ASA physical status I-II, and weighed from 40-70 kg. Patients who had a history of antiemetic administration within a week, or had an underlying cardiovascular, or a respiratory disease, or coagulopathy were excluded. The patients were randomly allocated into 3 groups to receive prophylactic antiemetics as follows : normal saline in group I, 0.5 mg droperidol in group II, and 5.0 mg metoclopramide in group III. The last menstrual period (LMP), type of laparoscopy, and the patient's history of PONV and motion sickness were recorded. The study drugs were prepared and coded by a blinded investigator and then were given intravenously, followed with 75 mg pethidine and 5 mg midazolam for sedation. Supplemental oxygen of 6 l/min *via* facemask, and 5 per cent dextrose in 0.45 per cent saline 80 ml/h intravenously were given during the procedure. Local infiltration with 5 ml of 0.25 per cent bupivacaine was given at the punctured site of the trocar. Oxygen saturation was monitored by pulse oximeter. Hypoxemic events (SpO_2 < 95%) and duration of procedure were also recorded. Sedation level was scored at the end of the procedure by the blinded investigator as follows.

Score 1 completely awake, open eyes
Score 2 drowsy
Score 3 asleep, arousable by verbal or physical stimulation
Score 4 does not respond

The patients were observed in the post-anesthetic care unit and were discharged when the discharge criteria were reached[9]. The duration from sedation to discharge was recorded. Before starting the operation, each patient was told how to grade the severity of post-operative nausea and pain by a verbal numerating scale ranging from 0 (no nausea) to 10 (extreme nausea) and to record whether there was vomiting or retching at the time before discharge and during the first 24 hours after the procedure. According to Watcha and White, nausea is defined as a subjectively unpleasant feeling associated with awareness of the urge to vomit; retching is defined as the labored, spasmodic and rhythmic contraction of the respiratory muscles without the expulsion of gastric content ; vomiting is defined as the forceful expulsion of gastric contents through the mouth[10]. Acetaminophen was given as the only pain rescuer for patients after the procedure, but no rescue antiemetic was given as the former routine practice.

Statistical analyses of the data collected among the groups were performed, using an SPSS program. One-way ANOVA was used for the analysis of the differences of age, body weight, duration of the procedure and the discharge time among the groups. Kruskal-Wallis test was used for the nonparametric analysis of the verbal numerating score of pain, sedation and nausea. Finally, a Chi-square test was used for binary data (ie, the number of patients with emetic symptoms or undergoing different procedures, the intra-operative presence of hypoxemic episodes). Statistical significance was considered when $p < 0.05$.

RESULTS

According to the related patient factors of PONV, no statistical difference of body weight, history of motion sickness and LMP was found among the groups. Age was the only exceptional factor which was significantly higher in the droperidol group (34.2 yrs), compared to the control (31.9 yrs), and metoclopramide (31.2 yrs) groups, respectively.

Concerning the surgical factors of PONV, no statistical difference was found in the types of the operation and the post-operative pain. However, the duration of the procedure was significantly longer in the droperidol group (29 min) than in the control group (25.1 min) (Table 1).

The effectiveness of prophylactic antiemetics was evaluated both at the time of discharge and 24 hours after the procedure. No statistical difference was found in the severity of nausea (Table 2) and the number of patients who experienced vomiting or retching among the groups (Fig. 1). Considering the risk of undesirable effects, the high

Table 1. Patient demographic data.

	Group I (n=50)	Group II (n=50)	GroupIII (n=50)	P
Patient factors				
Age (yrs, mean ± SD)	31.9 (21-42)	34.2 (25-50)*	31.2 (21-41)	0.04
Weight (kg, mean ± SD)	51.0 (40-70)	51.4 (41-70)	52.9 (40-67)	0.34
PONV history (% of No)	6.5	12.8	10.6	0.49
Motion sickness (% of No)	24.4	29.5	34.0	0.60
LMP within7days (% of No)	22.0	18.0	24.0	0.89
Surgical factors				
Operation (No. diagnostic/LTR)	44/6	45/5	46/4	0.92
Duration (min, mean ± SD)	25.1 ± 6.7	29.0 ± 8.0*	26.4 ± 8.1	0.04
Pain (VAS 0-10)				
Discharge (median and range)	2.1 (0-7)	2.6 (0-7)	2.4 (0-8)	0.28
24th h (median and range)	3.0 (0-10)	3.5 (0-7)	3.0 (0-10)	0.11

LMP : last menstrual period; LTR : laparoscopic tubal sterilization
* statistical significant when compared with group I ($p < 0.05$)

Table 2. The grading of nausea at the time before discharge and at the 24th hour after operation.

Severity of nausea VNS 0-10	Group I (n=50)	GroupII (n=50)	Group III (n=50)	P
Before discharge	0 (0-3)	0 (0-8)	0 (0-10)	0.13
24th hour after operation	2 (0-10)	0 (0-9)	0 (0-10)	0.22

VNS : verbal numerating scale

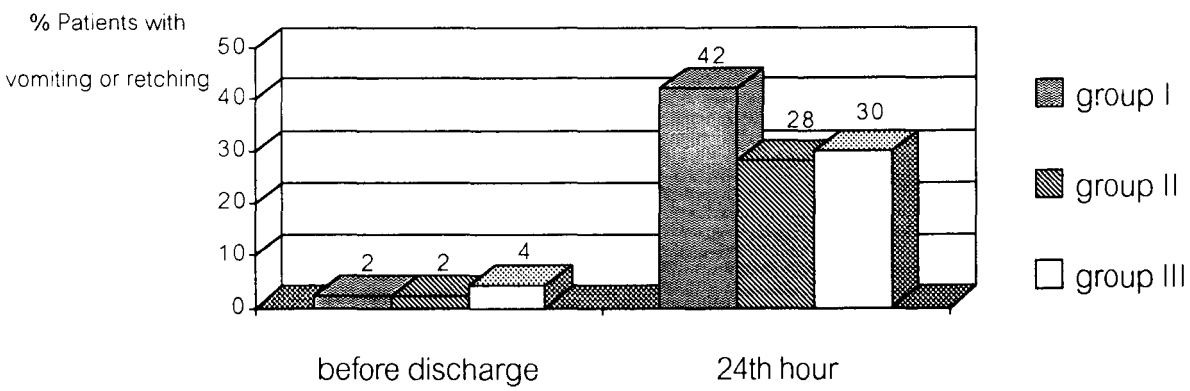

Fig. 1. Comparison of the percentages of patients establishing post-operative vomiting or retching at the time before discharge (p=0.76) and 24th hour after operation (p=0.33).

sedation score and delayed discharge time did not show any statistical difference among the groups (Table 3). In addition, hypoxemic episode did not occur in any patient in this study.

DISCUSSION

Patients undergoing gynecological laparoscopy are considered at a high risk of developing PONV. The peritoneal stretching created by carbon

Table 3. Sedation scores and discharge times.

	Group I (n=50)	Group II (n=50)	Group III (n=50)	P
Sedation score (1-4)	3 (1-4)	3 (1-4)	3(1-3)	0.63
Discharge (min, mean ± SD)	257.0 ± 45.5	267.8 ± 46.2	254.0 ± 38.7	0.25

dioxide insufflation stimulates the vagal-mediated impulse which finally triggers the vomiting center. This undesirable effect often delays the patients' discharge and causes unexpected hospital admissions. Low-dose droperidol 0.6-1.2 mg intravenously was reportedly effective as a prophylactic antiemetic for high risk surgery under general anesthesia[6-8]. However, its prophylactic efficacy and incidence of emesis have not been reported in patients under conscious sedation with narcotics and sedatives. At the authors' institute, intravenous pethidine and midazolam with supplemental oxygen was the preferred technique of sedation in a combination with local anesthetic infiltration employed in young, non-obese, and healthy patients. This technique is reported for its satisfactory ventilatory compensation with the acceptable range of arterial PO_2 and PCO_2during intraperitoneal CO_2 insufflation[1].

Intravenous droperidol at 1.0 mg has been reported to produce akathisia and discomfort which is inappropriate for its use in ambulatory anesthesia [11]. Furthermore, during the sedated situation, a narrow margin of safety is left for any additional sedation to avoid airway and respiratory problems. Therefore, only low doses of droperidol and metoclopramide are allowed to avoid over sedation and delayed discharge. Droperidol at 0.5 mg does not produce akathisia and discomfort[11] and its efficacy has not been reported for its use in conscious-sedated patients undergoing gynecological laparoscopy. Selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists may be an alternative in this situation[12]. Unfortunately, its cost, 10 times higher, has out-weighed its lack of sedative effect for routine practices[13].

Many reports illustrated that the incidence of PONV was influenced by both the patient and surgical factors[14]. These factors were LMP, age, history of motion sickness and PONV, for the patient and the type, the duration of operation, and post-operative pain for the surgical factors. According to present results, there was no statistical difference of patient factors among the groups, except for age which was significantly higher in group II. However, this significant difference of age which ranged from 18 to 50 yrs may not affect the clinical results as reported by Cohen et al[15], that the risk of PONV in patients aged over 70 yrs decreased compared to those under 50. Therefore, the variation of age range in the present study may not influence the risk of PONV. Beattie et al[16], reported a higher risk of PONV in patients undergoing operation within 7 days of LMP. According to the results, the authors also found no statistical difference in the number of PONV patients being within this risky period. Among the surgical factors, only the duration of the procedure, which was longer in group II compared to group I, was noted to be significant. However, only 3.9 minutes longer did not have any disadvantages on the clinical outcome.

As for the antiemetic efficacy in the present study, the grading of nausea was simply scored by the patient's personal estimation, using a verbal numerating scale instead of the previous method classifying the presence of symptoms of nausea which has a lower reliability. However, each patient can obviously classify herself into either group of presence or absence of vomiting or retching. Neither the nausea score nor percentages of the patient with vomiting symptoms showed any statistical difference compared to the groups at both study periods.

In the present series, neither 0.5 mg droperidol nor 5.0 mg metoclopramide has any effect on PONV prophylaxis in the sedation technique. The incidence of PONV at the 24th post-operative hour was still high up to 29 per cent and 32 per cent in the prophylactic groups compared to 43 per cent in the control group. The racial population, anesthetic techniques, and inadequate dosage of the study drugs were possible factors which should be taken into account.

Racial population has been previously reported as one of the factors correlated with PONV outcomes[14]. However, the racial factor did not

seem to have a significant influence on PONV in the series of Sirivanasandha et al[17].

During laparoscopic surgery, many factors might have some emetic-induced action on chemoreceptor trigger zone and vomiting center[10]. These are the vagal stimulation created by peritoneal stretching and surgical manipulation, and the hypercarbia stage occurs from carbon dioxide absorption during the pneumoperitoneal period which is aggravated by sedation and spontaneous ventilation. In addition, narcotics that are the commonly used analgesics in the sedation technique also have a significant emetic-induced effect on vestibular system[10,15, 18]. Furthermore, due to the use of various kinds of drugs, the sedative condition has left only a narrow margin of safety for any additional dosage of antiemetics. A higher dosage may worsen the patients' outcome such as intra-operative hypoxemia, akathisia, over sedation, and delayed discharge[19].

From an anesthetic point of view, it seems that the use of 0.5 mg droperidol or 5.0 mg metoclopramide for prophylaxis of PONV in the conscious sedation technique for outpatients undergoing laparoscopy is not effective, since it was unable to completely conquer the previously mentioned sources of strong PONV stimuli in the situation of the limitation of the use of an additional antiemetic. This supports the concept of previous studies that none of the antiemetics is perfectly effective for prophylaxis of PONV[20]. However, this technique might be appropriate for the prophylaxis of PONV in minilaparoscopy, in which the intra-operative surgical stimulation and post-operative pain has been lessened[21].

Finally, it should be emphasized that home-treatment antiemetics are still necessary for reducing patient distress and discomfort.

In summary, even though there have been many successful reports of prophylaxis efficacy of PONV, with the use of 0.5 mg droperidol or 5.0 mg metoclopramide in general anesthesia, the authors would like to suggest that its routine use in outpatients who undergo gynecological laparoscopy using the conscious sedation technique is not effective. Further consideration of antiemetic techniques and therapies is essential to achieve patient safety, rapid home-readiness and clinical pleasantness.

ACKNOWLEDGEMENTS

The authors would like to thank the nurses and paramedical staff in OBGYN operating rooms at Chulalongkorn Hospital for their great assistance in this study.

(Received for publication on November 9, 2001)

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เปรียบเทียบฤทธิ์การป้องกันอาการคลื่นไส้อาเจียนของ Droperidol ขนาดต่ำ และ Metoclopramide ในผู้ป่วยนอกที่มารับการวินิจฉัยทางนรีเวชผ่านกล้องด้วยวิธีให้ยาระงับความรู้สึกแบบ Conscious Sedation†

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ทำการศึกษาแบบ randomized double blind ในผู้ป่วยนอก 150 ราย ที่มารับการส่องกล้องทางหน้าท้องเพื่อวินิจฉัยหรือทำหมัน แบ่งเป็น 3 กลุ่ม คือ normal saline, droperidol 0.5 มก. และ metoclopramide 5.0 มก. เข้าหลอดเลือดดำตามลำดับ พร้อมกับ pethidine 75 มก. และ midazolam 5 มก. เป็นยา sedation บันทึกภาวะออกซิเจนต่ำในเลือด, ระยะเวลาของหัตถการและระยะพักในโรงพยาบาล หลังหัตถการประเมินสภาวะ sedation โดยใช้ sedation score, บันทึกอาการอาเจียนและประเมินความรุนแรงของอาการคลื่นไส้ และความเจ็บปวดโดย verbal numerating scale ที่เวลาก่อนกลับบ้านและที่ 24 ชั่วโมง หลังหัตถการ

การประเมินความรุนแรงของอาการคลื่นไส้อาเจียนโดย verbal numerating scale และจำนวนผู้ป่วยที่มีอาการอาเจียนหลังทำหัตถการ และที่ 24 ชั่วโมงหลังผ่าตัดไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ ไม่พบการเพิ่มปัญหาการขาดออกซิเจนในเลือด ไม่มีผลต่อการรู้สึกตัว และระยะเวลาอยู่โรงพยาบาลหลังทำหัตถการ เมื่อเทียบกับผู้ป่วยที่ไม่ได้รับยา

ดังนั้น Droperidol 0.5 มก. หรือ metoclopramide 5.0 มก. เข้าหลอดเลือดดำ ก่อนทำการส่องกล้องผ่านหน้าท้องทางนรีเวช เพื่อวินิจฉัยหรือทำหมันในผู้ป่วยนอกภายใต้การให้ sedation ไม่สามารถป้องกันอาการคลื่นไส้อาเจียนภายใน 24 ชั่วโมง

คำสำคัญ : Droperidol, Metoclopramide, นรีเวช, กล้อง, Sedation

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จดหมายเหตุทางแพทย์ ฯ 2545; 85: 470–476

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