A Comparison of Commonly Used Anti-Emetics for the Prevention of Emetic Sequelae after a Major Gynaecological Surgery

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ABSTRACT

Study design: Prospective, randomized, double-blind, placebo-controlled study involving one hundred ASA I-II patients undergoing major gynaecological surgery.

Objective: To study anti-emetic efficacy of intravenous (IV) ondansetron (4 mg), droperidol (2.5 mg), metoclopramide (10 mg), and placebo.

Patients and Methods: 100 ASA physical status I-II undergoing major gynaecological surgery were randomized to receive intravenously (IV), one of the four test drugs 10 minutes before the end of anaesthesia. The incidence of postoperative nausea and vomiting following a standard anaesthetic technique was assessed.

Results: A significantly large number of patients who received ondansetron (88%) and droperidol (72%) were free of emetic sequelae when compared to placebo (41%); $p < 0.05$ (power of this observation is approximately 80% at the given significance level). Metoclopramide was ineffective. Patients given droperidol were significantly more sedated than those receiving ondansetron; $p < 0.05$. This is not surprising, as the dose of droperidol used in this study was higher than that currently recommended because we found lower doses to be ineffective in controlling nausea and vomiting in this group of patients.

Conclusion: It was concluded that, of the drugs studied ondansetron is the best choice for anti-emetic prophylaxis after major gynaecological surgery.

Keywords: pharmacology, ondansetron, droperidol, complications, nausea and vomiting

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INTRODUCTION

A major problem with the modern anaesthesia despite all the advancements, which unfortunately is not considered to be a big problem, is postoperative nausea and vomiting (PONV). Estimates in the literature of the incidence of PONV vary from 14% to 82%[1], according to the design of the study, the type of operations performed, the anaesthetic procedures used, and the type of patients studied. A recent audit of more than 1,800 cases at 161 hospitals in the UK estimated the overall incidence of PONV at 36%[2].

Typically, PONV lasts for up to 24 hours after surgery, during which time the patient is likely to experience between one and five episodes of retching and vomiting. A few patients experience persistent vomiting for up to 48 hours. The feeling of nausea may be severe, and is often distressing for the patient[3-5].

Persistent vomiting, besides distress and exhaustion, can cause sequelae like dehydration and interfere with nutrition and oral therapy. Respiratory obstruction and the inhalation of stomach contents are also a danger in patients with an impaired level of consciousness. Forceful vomiting has also resulted in dehiscence of abdominal wounds and even rupture of the oesophagus[6]. It can also cause significant increase in the cost of patient care as PONV takes up the nurse's time, there is delay in discharge of the patient, delay ambulation and can increase the chance of re-operation.

The present study was designed, keeping in mind the increased frequency of PONV in females, to compare the efficacy of three different agents and a placebo in terms of efficacy and adverse effects. Droperidol was studied, as it had been found to be effective, in low dose, by Kortilla[7], and Motensen[8], although atropine had been given to these patients before the induction of anaesthesia. This study examined the effect of droperidol without the influence of pretreatment with anticholinergic drugs. Metoclopramide was evaluated, but the patients did not receive any opioid before operation since Dundee and Clarke[9] have suggested that the duration of action of metoclopramide is too short to protect patient from the emetic effect of opioid premedication. Ondansetron was used in the study, as this is the selective 5-HT_3 antagonist already well established in the prevention of chemotherapy-induced nausea and vomiting. It is well tolerated and not associated with extra-pyramidal side effects.

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PATIENTS AND METHODS

After obtaining departmental ethics committee's approval, 100 women undergoing major gynaecological surgery were included in this randomized placebo-controlled study. All patients were from ASA I or II and aged between 16 and 70 years. Patients were asked to participate in the study after routine anaesthetic assessment, and informed that the purpose of the study was to assess the effect of different drugs on the postoperative state. Patients taking drugs with anti-emetic effects were excluded.

Midazolam 7.5 mg was given by mouth 2 hours before operation, and a similar anaesthetic technique was used throughout. Fentanyl (1 μg/kg) was administered IV and anaesthesia was induced with sleep dose of thiopentone. Endotracheal intubation was facilitated by suxamethonium (1.5 mg/kg, up to a maximum of 100 mg). Anaesthesia was maintained with 66% nitrous oxide and isoflurane in oxygen. Neuromuscular blockade was maintained with atracurium. Analgesia was topped up by intermittent boluses of fentanyl. Ten minutes before the neuromuscular blockade was antagonized at the end of the procedure, one of the drugs under study was given IV. The test drug was chosen in a double blind, randomized fashion. The drug used was one of the following: ondansetron 4 mg (Group A), droperidol 2.5 mg (Group B), metoclopramide 10 mg (Group C), or placebo (saline) (Group D). Residual neuromuscular blockade was antagonized with atropine 1.2 mg and neostigmine 2.5 mg.

Table I. Demographic data of the patients (mean ± SEM)

	Group A [n = 25]	Group B [n = 25]	Group C [n = 24]	Group D [n = 24]
Age (year)	48.5 ± 19	50.5 ± 17	49.7 ± 14	51.2 ± 13
Weight (kg)	55.4 ± 17	56.4 ± 15	58.2 ± 13	54.7 ± 17
Duration of surgery (min)	174 ± 30	160 ± 45	170 ± 38	168 ± 48

Table II. Types of major gynaecological surgery performed in each group

	Group A [n = 25]	Group B [n = 25]	Group C [n = 24]	Group D [n = 24]
VAGINAL				
Hysterectomy	4	3	4	5
Repair	2	3	3	2
ABDOMINAL				
Hysterectomy	10	9	8	9
Laparotomy	6	7	6	7
Laparoscopy	3	3	3	1

During recovery from anaesthesia, the patients were observed for 6 hours by trained members of the nursing staff, and were directly questioned every 15 minutes during the first hour, every hour subsequently for 6 hours, regarding the occurrence of nausea, vomiting (including retching), sedation and abnormal movements. The observer was blinded to the study drug. Emetic symptoms and signs were graded as follows: 1, no nausea; 2, mild nausea; 3, severe nausea; and 4, retching and/or vomiting. Grades 3 and 4 were considered as severe forms of PONV. Any nausea or vomiting was treated using prochlorperazine 12.5 mg intramuscularly (IM). Postoperative pain was noted using visual analogue scale (VAS) and analgesia given on request, as keterolac 30 mg IM. After the first dose, keterolac was continued 8th hourly for three doses.

An anaesthetist saw all patients on the day after operation. They were questioned about the occurrence of nausea, vomiting, sedation, abnormal movements or postoperative pain during the previous 24 hours. They were also asked to assess their postoperative state as satisfactory or unsatisfactory with regard to nausea and vomiting. Absence of nausea or mild nausea unassociated with retching and/or vomiting was classified as 'satisfactory'. Other factors taken into account were the presence of drowsiness and 'hangover'.

Where appropriate, comparisons were made using Chi square test and $p < 0.05$ was taken as significant.

RESULTS

One hundred patients were involved in the study initially; one patient each in the metoclopramide group and placebo group were excluded, because they had to be given opioid analgesic as the pain could not be controlled with keterolac.

There was no statistically significant difference between the groups with regard to patients' age and weight (Table I). The type of surgery performed, and the number of patients in each group who underwent abdominal or vaginal procedures was comparable (Table II).

The incidence of emetic sequelae in the untreated group was 58.3% (14 out of 24). Patients receiving ondansetron 4 mg had significantly less postoperative nausea and vomiting than those treated with placebo ($p = 0.002$) or metoclopramide 10 mg ($p = 0.004$). Those receiving droperidol also had significantly less incidence of nausea and vomiting compared to placebo ($p = 0.031$). Patients who received droperidol were noted to be significantly more sedated in the postoperative period compared to those receiving ondansetron ($p = 0.05$), metoclopramide ($p = 0.002$), or placebo ($p < 0.0001$). There was no difference between the groups in the occurrence of abnormal movements (Table III). In the

droperidol group, the incidence of postoperative pain in the first six hours was significantly less as compared to the placebo ($p < 0.0001$), ondansetron ($p = 0.001$), or metoclopramide ($p < 0.0001$). In the droperidol group, the number of patients requesting analgesic within 6 hours of surgery was significantly less than placebo ($p < 0.0001$), ondansetron ($p = 0.001$), metoclopramide ($p = 0.005$).

The postoperative state (Table IV) was reported to be significantly more satisfactory in the patients receiving ondansetron compared to those receiving placebo ($p < 0.0001$), or metoclopramide ($p = 0.033$). Those receiving droperidol did not show statistically significant difference in the postoperative state as compared to the placebo or metoclopramide and dissatisfaction was largely attributable to unpleasant drowsiness and 'hangover'.

Table III. Number of patients having nausea-vomiting during the first six hours after operation

	Group A [n=25](%)	Group B [n=25](%)	Group C [n=24](%)	GroupD [n=24](%)
Nausea and vomiting	3* (12)	6* (24)	13 (54)	14 (58)
Free of emetic sequelae	22* (88)	18* (72)	11 (46)	10 (42)
Sedation	6 (24)	17* (68)	5 (21)	4 (16)
Pain	22 (88)	10 (40)	20 (83)	23 (96)
Abnormal movements	2 (8)	3 (12)	2 (8)	4 (16)
No analgesic within 6 h	3 (12)	15* (60)	4 (16)	2 (8)

*Significant difference from placebo: *P < 0.05 (Chi square)*

Table IV. Postoperative State

	Group A [n=25](%)	Group B [n=25](%)	Group C [n=24](%)	GroupD [n=24](%)
Satisfactory	23* (92)	20 (80)	15 (63)	14 (58)
Unsatisfactory	2	5 (20)	9 (37)	10 (42)

DISCUSSION

The aetiology of postoperative vomiting is multifactorial. The vomiting centre of the brain controls the coordinated sequence of respiratory and gastrointestinal events that leads to vomiting. The vomiting centre receives input via the nervous system from many sources, including the chemoreceptor trigger zone (CTZ), the oropharynx, the gastrointestinal tract, the respiratory and circulatory systems, pain receptors and the cerebral cortex. Many of the drugs used in anaesthesia and pain control can stimulate the vomiting centre via the CTZ. The CTZ is outside the blood-brain barrier, so it is directly exposed to circulating drugs, and to metabolic disturbances. Both central and peripheral receptors for 5-HT_3 and dopamine appear to play an important role in PONV[10].

PONV is said to be related to duration of anaesthesia[11], and obese patients and those cared for by inexperienced anaesthetists are also more likely to vomit postoperatively[11,12]. Anaesthetic dosage may be an important aetiological factor[6]. Nausea and vomiting are also said to occur more commonly in patients with a history of PONV or a strong history of motion sickness; sudden movement or change of position[13], or even transport back to the ward, which may also be precipitants[14].

Postoperative vomiting is more common in women than in men, a difference that is thought to be hormonal in origin and specifically associated with the gonadotropins[11]. Premenopausal and postmenopausal women are similarly affected but the frequency decreases after 70 years, when it is identical to that in men[15].

This multifactorial aetiology of PONV requires studies to take into account the contributions made by anaesthetic technique, type and duration of surgery, postoperative analgesic regimen, and a multitude of patient factors. This single centre study is unique in that it attempts to keep the variables to a minimum by studying female paitents presenting for a single intraabdominal operation, using a standardised premedicant, anaesthetic technique, and postoperative analgesic regimen.

The present study found that prophylactic IV ondansetron and droperidol to be effective at reducing the incidence of PONV after major gynaecological surgery.

Mortensen[8] reported a reduction in the incidence of emetic sequelae from 57% to 18% with the use of prophylactic IV droperidol 2.5 mg and 5 mg. In this study results using 2.5 mg were comparable. The dose of droperidol used in this study was higher than that currently recommended, as in our clinical experience, we found lower doses to be ineffective in controlling nausea and vomiting in this group of patients. However, a significant incidence of sedation was noted in the patients receiving droperidol.

Prophylactic IV ondansetron has been reported to be superior to placebo for the prevention of PONV[16-18]. Ondansetron has also been reported to be superior to both droperidol and metoclopramide for the prevention of PONV after minor gynaecological surgery[19] and day case gynaecological laparoscopy[20]. A multicentre trial of prophylactic IV ondansetron found 4 mg and 8 mg to be equally effective for the prevention of PONV[18]. The present study confirms that prophylactic ondansetron 4 mg is effective at reducing the incidence of emetic sequelae after major gynaecological surgery.

This study found metoclopramide to be ineffective (when compared to placebo) for prophylaxis. The short duration of action of metoclopramide may explain its lack of efficacy at preventing PONV[22]. The lack of prophylactic efficacy and the occurrence of side effects prompt review of the use of metoclopramide for the prevention of PONV.

The cost factor is one of the major deterrents to the use of ondansetron. There is at least a seven to tenfold difference in the cost of ondansetron compared to other commonly used anti-emetics. Thus, with regard to routine IV prophylaxis against PONV, we do not see a frontline role for ondansetron when lower cost options are available.

In summary, the efficacy of anti-emetic prophylaxis with IV ondansetron, droperidol, and metoclopramide was evaluated for the prevention of PONV after major gynaecological surgery. When compared to placebo, a significantly greater number of patients given ondansetron 4 mg and droperidol 2.5 mg was free of emetic sequelae and did not require rescue antiemetics. Metoclopramide 10 mg was ineffective for the prevention of PONV. We conclude that ondansetron is the best drug for anti-emetic prophylaxis for major gynaecological surgery.

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