COMPARATIVE TRIAL OF COMBINED METOCLOPRAMIDE AND DEXAMETHASONE VERSUS DEXAMETHASONE IN POSTOPERATIVE NAUSEA AND VOMITING IN GYNAECOLOGICAL SURGERY

***Orewole O. T., **Aremu S. K., *Bolaji B. O., *Kolawole I. K.,**

*Anaesthesia Department, University of Ilorin Teaching Hospital
**ENT Department, Federal Medical Centre, Ido-Ekiti,Ekiti State
Corresponding Author: Dr Aremu SK
ENT Department, Federal Medical Centre, Ido-Ekiti, Ekiti State.
Mobile : +2348033583842, Email : shuaib.aremu@gmail.com

ABSTRACT

AIM: Metoclopramide is a drug that has been used in the dose of 10 mg iv for postoperative nausea and vomiting (PONV) prophylaxis for many years and has been reported to be ineffective at this dose. That a higher dose of this drug, when used in combination with 8 mg dexamethasone, is more effective when compared with 8 mg dexamethasone only is worth validating and this study was designed to do. The aim is to compare the effectiveness of adding 50 mg metoclopramide (in two divided doses) to 8 mg intravenous dose of dexamethasone versus 8 mg dexamethasone only as a prophylactic anti-emetic in gynaecological surgery under spinal anaesthesia at University of Ilorin Teaching Hospital, Ilorin.

MATERIAL AND METHOD: This was a prospective, controlled study in which seventy-four ASA physical status 1 and 2 eligible gynaecological patients with 37 patients per group, were randomly allocated to either the metoclopramide and dexamethasone group or the dexamethasone only group for the purpose of this study. A simple random technique of balloting was used for randomization of the study population. Every participant was preloaded with one

litre of normal saline. Spinal Anaesthesia was established with 3 ml of 0.5 percent hyperbaric bupivacaine and 25 µg of fentanyl. Both groups received 8 mg dexamethasone iv immediately after induction of spinal anaesthesia. The test group received 25 mg of metoclopramide iv after establishment of spinal anaesthesia and another dose of 25 mg metoclopramide iv at the end of surgery while the control group received normal saline at both times respectively. Data on PONV were collated for 24 hours postoperatively using a study pro-forma. Vital signs such as pulse, SaO_2 and BP as well as postoperative pain were monitored according to the study protocol.

During the 24-hour period of the study, patients in the metoclopramide group were found to have a lower incidence of PONV (11% Vs 44%, p=0.003). This is statistically significant. During the early postoperative period (0-4 h) and late period (5-24 h), the incidence of PONV remained higher in the dexamethasone only group; (30.6% Vs 8.3%) and (13.9% Vs 2.8%) respectively. The differences between the two groups were statistically significant for 0-4 h (P = 0.02) but not significant for 5-24 h (P = 0.09).

CONCLUSION: Intravenous 50 mg metoclopramide in two divided doses added to 8 mg dexamethasone is more effective than 8 mg dexamethasone only in reducing the incidence of PONV in women undergoing gynaecological surgery under spinal anaesthesia.

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INTRODUCTION

Although, many physicians continue to view postoperative nausea and vomiting (PONV) as a minor complication that poses little problem, most patients view this complication as more debilitating than the surgery itself.[1] Patients often rate postoperative nausea and vomiting as worse than postoperative pain.[2, 3] Prevention of postoperative nausea and vomiting has been found to improve satisfaction among patients who are likely to experience them.[4] This complication is not only unpleasant and aesthetically displeasing to patients and their care givers but, when severe, is associated with electrolyte imbalance, dehydration, bleeding, wound dehiscence and rarely, pulmonary aspiration of gastric contents.[1]

Most gynaecological surgeries are associated with high incidence of PONV.[1] In Ibadan, Nigeria, the incidence of post operative nausea and vomiting within twenty four hours of surgery was 14.6% and 19.6%, respectively with female preponderance (66% of the patients who vomited were females) ($p < 0.05$).[5] At the University of Ilorin Teaching Hospital, the incidence of PONV in gynaecological surgery was put at 30%.[6]

The efficacy of antiemetics is known to be improved by combining two or three interventions.[7,8] An example of such combination is dexamethasone and metoclopramide.[8] Tzeng et al compared low-dose dexamethasone with metoclopramide and normal saline and noticed that the total frequency of nausea and vomiting in the dexamethasone group was significantly lower than the metoclopramide and saline groups.[9]

Jan Wallenborn et al also investigated the efficacy and safety of three doses of metoclopramide (10 mg, 25 mg, and 50 mg) on the assumption that each patient would receive basic antiemetic prophylaxis of 8 mg dexamethasone.[8]They found that 25 mg or 50 mg metoclopramide added to

the basic intervention of 8 mg dexamethasone was effective, safe, and cheap. Fifty milligrams metoclopramide was however found to be more effective than 25 mg over 24 hours postoperatively. In their study the 50 mg was given as a single dose intra-operatively but suggested that if given in divided doses of 25 mg intra-operatively and 25 mg immediately after surgery it would be as effective and may further reduce the side effect of this drug.

There is the need for a similar but modified study in this environment to verify this research and determine if indeed dividing the 50 mg metoclopramide into two equal doses will produce additive antiemetic effect with minimal adverse effects. This is because both metoclopramide and dexamethasone are relatively cheap and readily available in our environment.

The general objective of the study was to find out if both 50 mg metoclopramide in two divided doses and 8 mg dexamethasone would be more effective than 8 mg dexamethasone as prophylactic antiemetic in patients undergoing gynaecological surgery.

The specific objective are :

1. To determine the efficacy of a combination of 50 mg metoclopramide (in two divided doses) and 8 mg dexamethasone in the prevention of PONV in patients undergoing gynaecological surgery.

2. To assess the side effects of metoclopramide and dexamethasone used in the study.

MATERIAL AND METHOD

STUDY AREA

The study was conducted at the University of Ilorin Teaching Hospital, Ilorin (UITH).

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and consent for this study were obtained from the Ethical Review Committee of the Hospital. Approval and informed consent of every participating patient were obtained before recruitment of each patient was commenced.

STUDY DESIGN

This was a prospective, randomised, controlled study of combined metoclopramide+dexamethasone versus dexamethasone in the prevention of postoperative nausea and vomiting.

Each eligible patient was randomly allocated to either metoclopramide+dexamethasone or dexamethasone+normal saline groups (n=37 each) using a simple random technique of balloting. The duration of the study was between June 2009 and May 2010.

SAMPLING TECHNIQUE

Study sample was obtained from a consecutive series of patients slated for elective gynaecological surgery under spinal anaesthesia at the University of Ilorin Teaching Hospital (UITH). A simple random technique of balloting was used.

SAMPLE SIZE DETERMINATION

In a previous study done by Kolawole, the incidence of PONV in gynaecological surgeries at University of Ilorin Teaching hospital (UITH) was 30%.[6]

Using the Department of Anaesthesia records of surgical procedures done in a period of four years between January 2002 and December 2005 at UITH, the estimated population of elective gynaecological surgery was about 160 per annum and patients load for six months was about 80. Patient load for six months was used but data collection was spread over one year to give room for any logistics problems that might crop up during data collection.

The target population was less than 10,000. The formula: $n = Z^2pq/d^2$ was first used to calculate the desired sample size (n) when the population is more than 10,000.[78]

n = the desired sample size when population is greater than 10,000

Z = the standard normal deviate, usually set at 1.96(or more simply at 2.0), which corresponds to 95% confidence interval.

p = the proportion in the target population estimated to have a particular characteristic (30% or 0.30).[6]

q = 1.0 – p

d = degree of accuracy desired (0.05)

$n = (1.96)^2(0.30)(0.70)/(0.05)^2$

=323

The sample size for this study was subsequently calculated using the formula[78]:

nf =n/1+ (n/N).

Where:

nf = the desired sample size when population is less than 10,000

n= the desired sample size when the population is more than 10,000=323

N = the estimate of the population size = 80

The sample size nf = 323/ {1+ (323/80)} = 65

Minimum sample size of 65 patients was calculated

Using the attrition rate of 10%, 72 patients was calculated. Seventy-four patients divided into two equal groups of 37 patients per group were eventually used for the study.

STUDY POPULATION

Seventy-four ASA physical status I and II female patients aged 18 years and above who were scheduled for gynaecological surgery under spinal anaesthesia participated in this study over a period of one year.

EXCLUSION CRITERIA

Patients with ASA classification higher than 2, those who were lactating, pregnant or who had history of PONV, motion sickness or had received an anti-emetic or steroids within the previous 24 hours were excluded from this study. Others with gastrointestinal diseases, extrapyramidal disease, history of malignant hyperthermia, hepatic insufficiency, pheochromocytoma,

mechanical ileus, sickle cell disease, psychiatric illnesses and substance abuse including smoking as well as patients on anticancer treatment were also excluded from the study. Also excluded were patients who refused to participate in the study, those who refused spinal anaesthesia, patients with coagulopathy or other bleeding diathesis, patients with infection at the site of injection of intrathecal drugs, severe hypovolaemia, increased intracranial pressure, severe aortic stenosis, severe mitral stenosis and those with previous history of adverse reaction to dexamethasone, metoclopramide and bupivacaine.

STUDY PROTOCOL

PREOPERATIVE ASSESSMENT/ PREMEDICATION

Consented Patients aged 18 years and above and who were scheduled for gynaecological surgery under spinal anaesthesia were recruited into the study during preoperative round on the ward.

Each patient was reviewed a night before surgery by the investigator. Adequate history including Bio data was taken. Previous medical history to exclude history of motion sickness, previous PONV and other exclusion criteria was taken and thorough physical examination was carried out. American Society of Anesthesiology (ASA) physical status classification was determined. Height and the weight were also measured and recorded. The anaesthetic procedure as well as benefits and possible adverse effects of the study drugs, anaesthetic drugs and that of the procedure were explained to the patients. Consent for spinal anaesthesia and voluntary participation in the study was obtained from each patient. Patients were fasted from midnight and 10 mg of oral diazepam prescribed for premedication a night before and on the morning of surgery.

IN THE THEATRE

On arrival at operation suite, the patients were allowed to randomly pick a ballot paper from a box containing seventy four (74) ballot papers. 37 papers were labelled A for dexamethasone+Normal Saline (control group) and 37 were labelled B for dexamethasone+metoclopramide combination (metoclopramide or treatment group) in sealed envelopes. All safety anaesthetic precautions were taken. Patients were connected to the multiparameter monitor and the following vital signs were monitored noninvasively: arterial oxygen saturation, blood pressure, and heart rate using the PM-800 Express patient monitor (S Henzen Mindray Bio-medical Electronics Co.,Ltd). Intravenous access was secured with 16G cannula and the drugs withdrawn appropriately.

Study medications were prepared in a double-blind fashion in identical 5 ml syringes. A doctor in the Department of Anaesthesia prepared the drugs while the investigator administered the medications. The observer was another resident doctor who monitored the patient, measured and collated data on the outcome variables (nausea, vomiting, time and vital signs).

Patients were preloaded with 1 litre of normal saline over 30 minutes after which they were put in a sitting position for the spinal anaesthesia. The back of each patient was cleaned with antiseptic lotion and spirit and then draped. The appropriate lumbar inter-space was located between L2 and L5 and the spinal anaesthesia was induced in each patient using 3 ml of 0.5% hyperbaric bupivacaine and 25 µg of fentanyl. This was done using size 26 G Quincke spinal needles. Both groups received 8 mg of iv dexamethasone after induction of anaesthesia. The treatment group then received metoclopramide 25 mg iv in a 5 ml syringe while the control group was given 5 ml 0.9% saline iv in identical 5 ml syringe. The level of spinal block was

tested for using sensation to light touch and cold temperature. The maximum level of block was at the 5^{th} thoracic spinal level.

Hypotension (defined as reduction in systolic blood pressure > 30 mmhg or diastolic blood pressure >15 mmhg from base line) was treated with normal saline and where necessary with iv ephedrine 3 mg boluses. Normal saline was used for intraoperative fluid management and whole blood was administered whenever blood loss was more than calculated allowable blood loss. At the closure of the skin, another 25 mg iv metoclopramide in 5 ml syringe was given to the treatment group (metoclopramide group) while the control group received 5 ml 0.9% saline iv. Patients breathed spontaneously room air supplemented with 100% oxygen by facemask whenever SaO_2 was < 95%. Patients pulse rate, blood pressure and arterial oxygen saturation were monitored intraoperatively every 5 minutes using the PM-800 Express patient monitor (S Henzen Mindray Biomedical Electronics Co., Ltd). At the end of surgery patients were transferred to the recovery room where monitoring of patients continued for 1 hr. Patients were then transferred to the ward for further observation. Morphine 5 mg iv 4 hourly, diclofenac 75 mg im daily and paracetamol 600 mg 6 hourly iv were employed for postoperative pain management. Rescue anti-emetic ondansetron 4 mg iv bolus was recommended for patients who vomited once or more.

Pain was assessed using the verbal rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = excruciating pain) at 15 minute intervals during patients stay in the recovery room and at 4 hour, 12 hour, 16 hour and 24 hour in the ward by direct questioning by a trained observer (another resident doctor) blinded to the study. Breakthrough pain was controlled with additional doses of morphine titrated at 2 mg iv as required. The total amount of morphine administered to each patient was recorded. Nausea and vomiting were assessed immediately after

surgery and at 30-min intervals in the recovery room for 1 hour. In addition, nausea and vomiting were evaluated at 4 hour, 12 hour, 16 hour and 24 hour by direct questioning and by spontaneous complaint of the patients. Nausea and vomiting were evaluated on a 3-point ordinal scale (0 = none, 1 = nausea, and 2 = vomiting). No distinction was made between vomiting and retching (i.e., a retching event was considered as a vomiting event).

The primary end point was a total effective antiemetic response (i.e., complete response), defined as no PONV and no administration of rescue antiemetic medication for 24 hour postoperatively. Secondary end points included the proportion of patients who experienced an episode of nausea, retching or vomiting, and the number of patients who needed antiemetic rescue. The details of adverse effects throughout the study (0-24 hour after anaesthesia) were assessed each time PONV was assessed.

A simplified risk score was calculated preoperatively for each patient.[40,75] This predictive score of PONV considers four predictors: female sex, history of PONV or motion sickness, non-smoking and expected use of opioids; patients were assigned one point each for the risk factors. In a cross-validation study, patients with a risk factor of 0 had a 10% risk for PONV, those with a score of 1 had a risk of 21%; of 2, 39%, of 3, 61% and of 4, 79%[40]. All the patients used in this study were female, non smoker and were expected to use opioids. With the presence of 3 risk factors, the calculated risk for PONV was 61%.

SPECIAL DEFINITIONS

For the purpose of this study, and to ensure uniformity and standardization, duration of anaesthesia was defined as the period between intrathecal injection of hyperbaric bupivacaine

and the time when the patient could feel pain at the surgical site. The duration of surgery was taken as the period between skin incision and end of skin closure.

DATA COLLECTION

Nausea and vomiting and pain were assessed for 24 hrs starting from immediate postoperative period, in the recovery room and in the ward.

Nausea and vomiting were evaluated on a 3 point ordinal scale (0-none; 1-nausea; 2-vomiting and/or retching. No nausea, no vomiting and no anti-emetic medication in the first 24-hour post-operative period was defined as a successful end-point.

Pain intensity was assessed using verbal rating scale. An ordinal scale of 0-4 (0- no pain, 1- mild pain, 2- moderate pain, 3- severe pain and 4- excruciating pain) was used.

STATISTICAL ANALYSIS

Data entry was done using the statistical package for the social sciences (SPSS 15.0 for windows evaluation version. SPSS Inc.).Two-sample independent student's t-test (2-tailed) were used to analyse continuous patients' variables like age, weight, duration of anaesthesia/surgery, including their mean + SD (Standard Deviation). However, chi-squared test or Fisher's Exact test were used appropriately for discreet variables like symptoms of PONV (nausea, vomiting). A p-value of less than 0.05 was considered significant.

Seventy four patients (37 patients each in study and control groups) were recruited into the study. However, two of them were disqualified because their spinal anaesthesia wore off and anaesthesia was converted to general anaesthesia. Data obtained from seventy-two patients were analysed.

From the analytic statistics of the patients' characteristics (Table 1) it is apparent that patients in both groups had comparable demographic and clinical profiles.

Table 1. Patient Demographics

	Metoclopramide Group	Control Group	P- Values
Age (yr)	44 ± 9	41 ± 10	0.124
Weight (kg)	70 ± 17	64 ± 15	0.108
Height (cm)	163 ± 6	159 ± 5	0.026
BMI (kg/m^2)	27 ± 6	25 ± 6	0.357
PCV (%)	35 ± 4	36 ± 4	0.978
Parity	3 ± 2	3 ± 2	0.529
ASA Score*	1	1	0.605
DOA (min)	158 ± 20	162 ± 37	0.507
DOS (min)	129 ± 23	130 ± 40	0.855
Morphine* (mg)	39 ± 5	40 ± 4	0.518

n = 36 in each group.

Morphine* = 24 hr morphine consumption

Values are mean ± SD in each group.

ASA score*- Mode values used

Two-sample independent student t-test confirms that continuous quantitative variables such as weight (P = 0.108), body mass index (BMI) (P = 0.357), duration of anaesthesia (P = 0.507),

duration of surgery (P = 0.855) and total morphine consumption in 24 hours (P = 0.518) were not statistically different between the two groups.

RESULTS

MAIN FINDINGS

During the first 24 h after anaesthesia, the percentage of patients with complete response was 88.9% in the Metoclopramide Group (Dexamethasone+Metoclopramide) and 55.6% in the Control Group (Dexamethasone+Normal Saline) (P = 0.002).Table 2 shows the types of operation done for the patients.

Table 2. Types of Operation

Types of operation	Metoclopramide Group n (%)	Control Group n (%)
Abdominal hysterectomy	20 (55.6)	16 (44.4)
Vaginal hysterectomy	3 (8.3)	1 (2.8)
Myomectomy	11(30.6)	12 (33.3)
VVF* repair	0 (0)	1 (2.8)
Ovarian cystectomy	1 (2.8)	3 (8.3)
Tuboplasty	1 (2.8)	2 (5.5)
Manchester repair	0 (0)	1 (2.8)

n = 36 in each group.

P = 0.633

The incidence of nausea, vomiting and the number of patients rescued in each group is also shown in Table 3.

Table 3. Patients Having Complete Response, Nausea, Vomiting, or Rescue Antiemetic Medication During The First 24 Hours After Anaesthesia

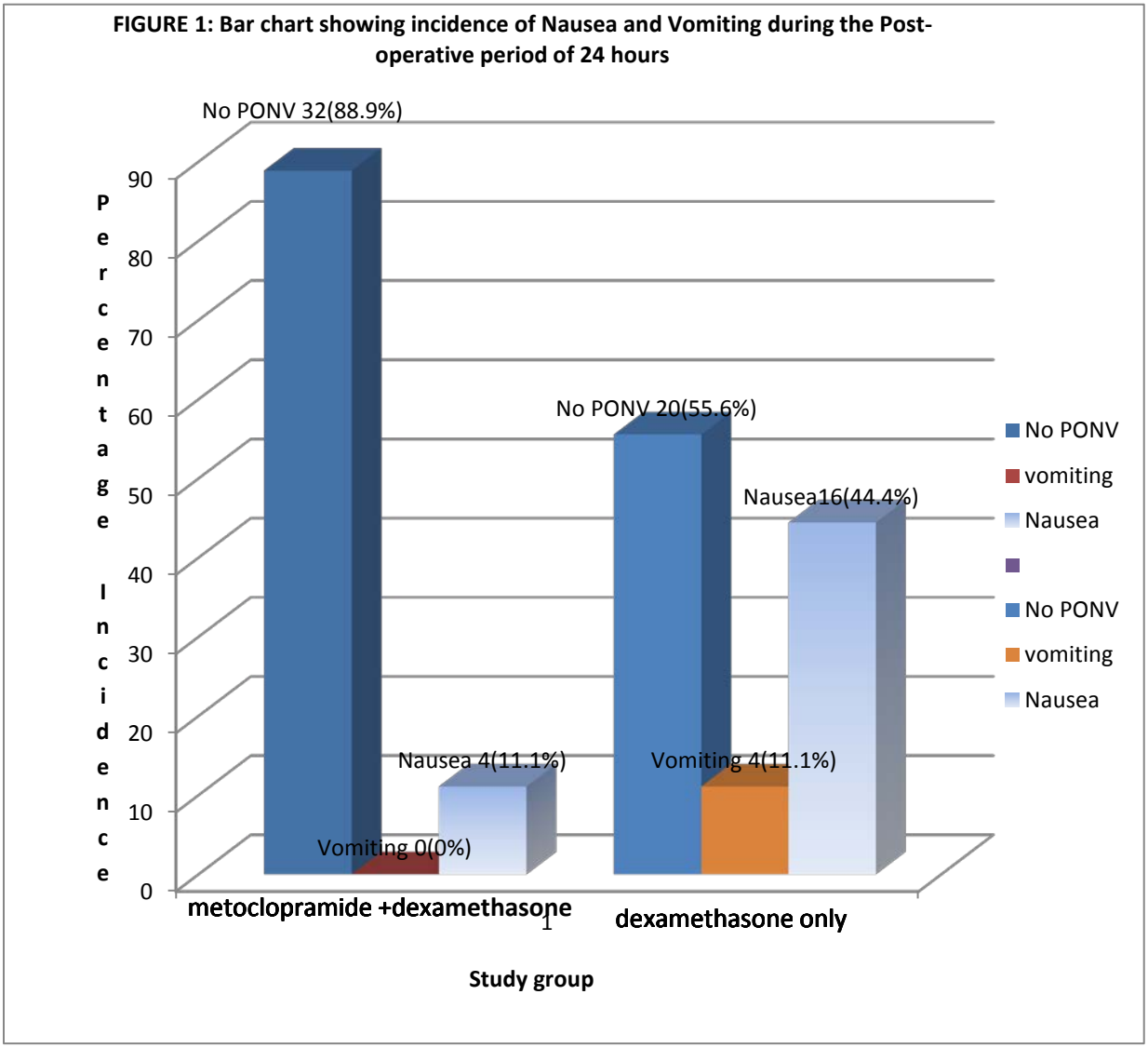
	Metoclopramide Group n (%)	Control Group n (%)	P-Values
Complete response	32 (88.9)	20 (55.6)	0.002
Nausea+Vomiting	4 (11.1)	16 (44.4)	0.003
Nausea	4 (11.1)	16 (44.4)	0.003
Vomiting	0 (0)	4 (11.1)	0.57
Multiple Nausea	0 (0)	11 (30.6)	0.003
Multiple Vomiting	0 (0)	1 (2.8)	0.218
Rescue	1 (2.8)	5 (13.9)	0.199

n = 36 in each group.

The incidence of PONV (nausea and/or vomiting) in the Metoclopramide Group was 4 (11.1%) while it was 16 (44.4%) in the Control Group (P = 0.003). Similarly, 4 patients (11.1%) in the Metoclopramide Group had nausea while 16 patients (44.4%) in the Control Group had nausea (P = 0.003). No patient (0%) vomited in the Metoclopramide Group while 4 patients (11.1%) vomited in the Control Group (P = 0.57). This result showed that nausea was the more common feature of PONV than vomiting in both groups in the first 24 hour.

Figures1 graphically illustrates the intra-group differences in outcomes during the total study period (0-24 hour). Patients with complete response and less incidence of PONV are in clear majority in the Metoclopramide Group.

FIGURE 1: Bar chart showing incidence of Nausea and Vomiting during the Post-operative period of 24 hours



The incidence of vomiting was lower in the Metoclopramide Group than the Control Group for the same period of 0-24 h (0% Vs 11.11%). This was however not statistically significant (P = 0.57).

During the early postoperative period (0-4 h) and late period (5-24 h) (Table 4 and Figures 2 and 3), the incidence of PONV continued to be higher in the Control Group than the Metoclopramide Group i.e. 30.6% Vs 8.3% and 13.9% Vs 2.8% respectively. The difference was statistically significant for the period 0-4 hour (P = 0.02) while not significant for the period 5-24 hour (P = 0.09). It is also noted that incidence of early PONV is higher than late PONV in both groups.

Table 4. Incidence of Early and Late Postoperative Nausea and Vomiting

	Metoclopramide Group n (%)	Control Group n (%)	P- values
Early PONV (0-4 hr)			
Complete response	33 (91.7)	5 (69.4)	
PONV	3 (8.3)	11(30.6)	0.02
Late PONV (5-24 hr)			
Complete response	35 (97.2)	31 (86.1)	
PONV	1 (2.8)	5 (13.9)	0.09

n = 36 in each group.

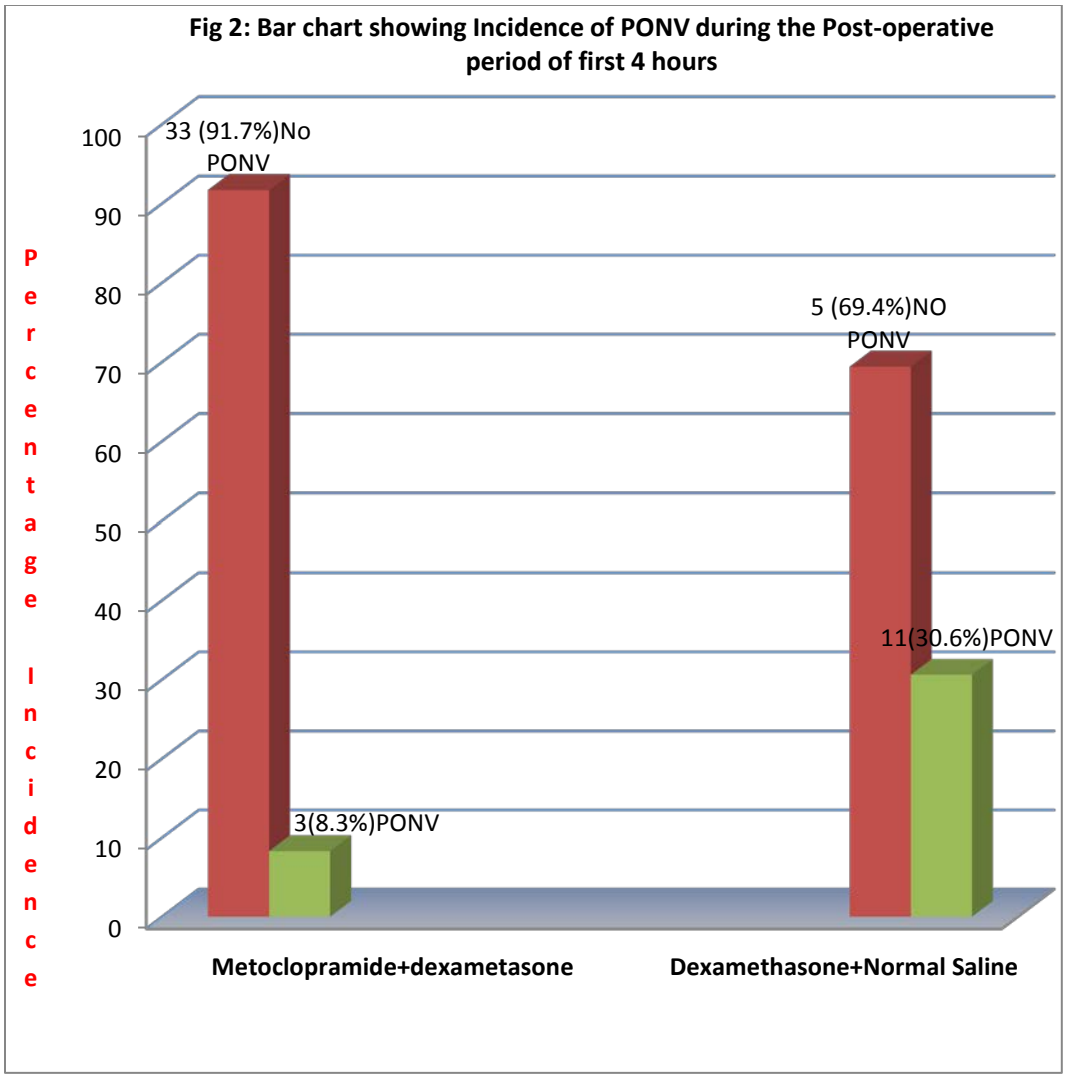
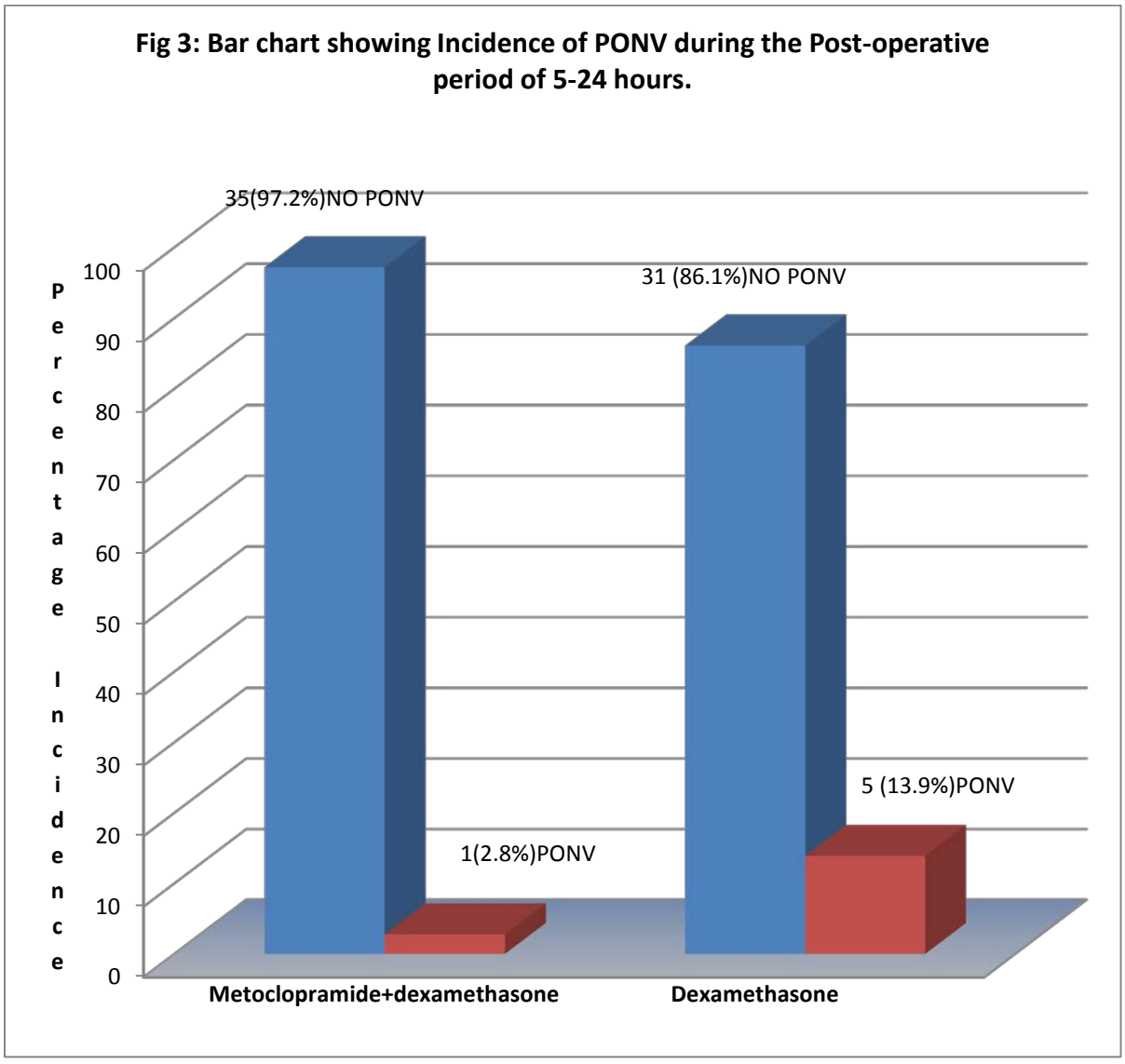


Fig 2: Bar chart showing Incidence of PONV during the Post-operative period of first 4 hours
Percentage Incidence
100
90
80
70
60
50
40
30
20
10
0
33 (91.7%)No PONV
3(8.3%)PONV
5 (69.4%)NO PONV
11(30.6%)PONV
Metoclopramide+dexametasone
Dexamethasone+Normal Saline
NO PONV
PONV



Eleven patients (30.6%) had multiple episodes of nausea (greater than once) in the Control Group while no patient had multiple episodes of nausea in the Metoclopramide Group (P =

0.003). One patient (2.8%) in the Control Group also had multiple episodes of vomiting whereas no patient (0%) in the Metoclopramide Group had multiple episodes of vomiting (P = 0.218) (Table 3).

The number of patients that required rescue antiemetic in the Metoclopramide Group was 1 (2.8%) while 5 patients (13.9%) required it in the Control Group. This was however not statistically significant (P = 0.199). All the patients that required rescue antiemetic responded favourably to one dose of the antiemetic used (4 mg ondansetron iv bolus).

OTHER FINDINGS

Table 5 shows the relationship between PONV and Age as well as that between PONV and Obesity. The patients were categorized into those with age < 50 yr and age ≥ 50 yr. The number of patients that were less than 50 yr was 51 while 21 patients were ≥ 50yr. The incidence of PONV in age < 50 yr was 28% while the incidence in ≥ 50 yr category was 29%. This was not statistically significant (P = 0.66).

Patients were also categorized into two groups based on the body mass index. There were 53 patients with BMI < 30 and 19 patients with BMI ≥ 30. The incidence of PONV among obese patients (BMI ≥ 30) was 15.8% while it was 20.8% among non obese patients. This was however not statistically significant (P = 0.87).

Table 6 shows the incidence of pain in the two groups. The incidence of pain in the Metoclopramide Group was 33.3% and 55.6% in the Control Group. The difference was not statistically significant (P = 0.96).

Table 6. Incidence of Pain in Study Groups

	Metoclopramide Group n (%)	Control Group n (%)
Pain	12 (33.3%)	20 (55.6%)
No Pain	24 (66.7%)	16 (44.4%)

n = 36 in each group

P = 0.96

Table 7 shows relationship between PONV and Pain. Among patients who were free of pain in the period 0-24 hour, 20% had PONV while 80% had no PONV. The difference was also not statistically significant (P = 0.099). Only one patient reported severe pain and the incidence of PONV in patients with severe pain was 100% (P = 0.278). This patient was in the Control Group.

Table 7. Incidence of PONV and Postoperative Pain in 24 hrs

	PONV n (%)	NO PONV n (%)	P-Values
No Pain	8(20%)	32(80%)	0.099
Mild Pain	9(36%)	16(64%)	0.256
Moderate Pain	2(33.3%)	4(66.7%)	0.537
Severe Pain	1(100%)	0(0%)	0.278

Adverse Effects

Table 8 shows the incidence of adverse effects in the study groups. The most frequent side effects were hypotension, dizziness and drowsiness which were relatively mild. No difference in the incidence of side effects was observed between the two groups.

DISCUSSION

Postoperative nausea and vomiting (PONV) is still the most troublesome event encountered in the recovery room, despite advances in prevention and treatment.[79] Furthermore, the ongoing trend towards ambulatory procedures has increased the focus on PONV as its occurrence may delay discharge or cause unanticipated hospital admission.[80],[81] PONV is a very common morbidity after gynaecological procedures as reported by various studies in the past.[12, 82,83] In this study, a highly pro-emetic setting was inadvertently provided to test the clinical efficacy of combination of two readily available, cheap and relatively safe anti-emetics in our environment.

This study was designed as a prophylactic trial rather than a therapeutic one. Researchers have suggested restricting prophylactic trials to high risk patients and/or procedures.[84] This is to prevent unnecessary exposures of patients to drugs and to prevent avoidable side effects and/or adverse reactions. Gynaecological procedures rightly belong to this category. Apfel simplified risk scores for the patients studied put the expected PONV risk at 61% (high risk).[75] This was because of the presence of three risk predictors of female gender, non-smoking and use of postoperative opioid. The Apfel score consist of four predictors: female gender, history of motion sickness or PONV, non-smoking, and the use of postoperative opioids. If none, one, two, three, or four of these risk factors were present, the incidences of PONV were 10%, 21%, 39%,

61% and 79% respectively.[75] Although interventions in this study were able to reduce the incidence of PONV in both the metoclopramide and the dexamethasone only groups to 11% and 44% respectively from the calculated Apfel score of 61% risk, none of the two interventions were able to totally abolish PONV.

It is obvious from the obtained results that the two groups involved patients with similar and comparable demographic and clinical profile. Each of these characteristics has a p-value > 0.05 (Table 1). These include number of patients in each group, age, weight, and BMI. Others are duration of anaesthesia/surgery and total dose of morphine administered post operatively. There were mild decreases in pulse rate and BP immediately after induction of spinal anaesthesia. These were assumed to be due to the spinal anaesthesia. Administration of normal saline was enough to correct the fall in BP. One patient in the dexamethasone group required the use of iv ephedrine 3 mg bolus to correct the hypotension. It may therefore be reasonable to say that the differences observed in the incidences of PONV between the two groups were due to the study drugs each group was exposed to, and not to any of the above variables, chance-finding or any other confounding variable.

In this study, the most noticeable finding is that combination of metoclopramide and dexamethasone is more effective than dexamethasone alone in preventing PONV in gynaecological surgery whether at 0-4 hour, 5-24 hour, or 0-24 hour period of the study (Tables 3-4 and Figures 1-3). The difference in both groups was statistically significant throughout the 24 hour. At 0-24 hour, the incidences of PONV were 44% and 11% in the Control Group and Metoclopramide Group respectively (P = 0.003, Table 3). This is in agreement with previous findings that combination therapy is better at preventing PONV in high risk patients/procedures.[1, 8, 70] The incidences of PONV in both groups (11% and 44% for

Metoclopramide Group and Control Group respectively) show that gynaecological procedures are highly emetogenic.

During the early postoperative period 0-4 hour and late period (5-24 hour)(Table 4), the incidence of PONV remained higher in the Control Group than the Metoclopramide Group for the above two periods i.e 30.6% Vs 8.3% and 13.9% Vs 2.8% respectively. The differences between the two groups was statistically significant for 0-4 hour (P = 0.02) but not significant for 5-24 hour (P = 0.09). One of the set objectives of this study was to test the hypothesis that 50 mg metoclopramide (in two divided doses) added to 8 mg dexamethasone is effective for the prevention of postoperative nausea and vomiting. This study reaffirmed the hypothesis (P = 0.002).

Metoclopramide has been used for almost 40 years to prevent PONV.[69] The affinity for doperminergic D2-receptors explains the antiemetic effect of metoclopramide.[85] In adults, the most often studied regimen to prevent PONV is 10 mg metoclopramide iv. There have been conflicting reports on the efficacy of 10 mg metoclopramide in the prevention of postoperative nausea and vomiting. In a meta analysis by Henzi et al, it has been shown that this dose had no significant antinausea effect.[69] This review by Henzi, et al involved 66 studies and 3260 patients who received 18 different regimens of metoclopramide and 3006 controls who received placebo or no treatment. There was no evidence of dose-responsiveness with oral, im, intranasal or iv metoclopramide in children and adults. The doses used in adults were 5-30 mg iv while 0.10-0.50 $mgkg^{-1}$ were used in children. The best documented regimen is 10 mg iv.[69]

High-dose metoclopramide has been used successfully as an antiemetic in highly emetogenic chemotherapy (treatment with Cisplatin, for instance).[86] Metoclopramide in larger doses is said

to have anti-5-HT receptor action.[87] Knudsen et al also found metoclopramide to be effective in counteracting emesis following spinal anaesthesia supplemented with intrathecal morphine.[88] This observation was confirmed by Pitkanem, and co-workers.[89]

Studies have also been done comparing the efficacy of metoclopramide plus other drugs combinations with other antiemetics. Eberhart et al compared dimenhydrinate (an antihistaminic) and metoclopramide alone and in combination for prophylaxis of PONV.[90] Metoclopramide in a dose 0.3 $mgkg^{-1}$ was used for the study. Neither metoclopramide nor dimenhydrinate alone reduced the incidence of PONV in male patients after endonasal surgery. However, the combination of both drugs revealed a moderate additive effect: PONV was reduced from 37.5% in the placebo group to 15.0%.[90]

Yoshitaka et al studied the effects of 8 mg dexamethasone on antiemetics in female patients undergoing gynaecological surgery.[91] The study demonstrated that incidence of complete response, no PONV, and no administration of rescue antiemetic medication was greater in patients who had received granisetron plus dexamethasone (96%) than in those who had received droperidol (49%) or metoclopramide plus dexamethasone (51%) ($P = 0.001$).[91]

The doses of metoclopramide used in many previous studies are relatively low and optimum dose of metoclopramide used in combination with another antiemetic (e.g. dexamethasone) could be highly effective in the prophylaxis for postoperative nausea and vomiting.

This hypothesis was put to test by Jan Wallenborn et al in their study.[8] Jan Wallenborn et al investigated the efficacy and safety of three doses of metoclopramide (10 mg, 25 mg, and 50 mg), on the assumption that each patient would receive basic antiemetic prophylaxis of 8 mg dexamethasone. They found that 25 mg or 50 mg metoclopramide added to the basic intervention

of 8 mg dexamethasone was effective, safe, and cheap.[8] 50 mg metoclopramide was however found to be more effective than 25 mg over 24 hours postoperatively. In their study the whole 50 mg was given as a single dose intra-operatively but in the present study, metoclopramide was given in two divided doses of 25 mg each at the beginning and end of surgery respectively.

Another meta-analysis reported that 10 mg metoclopramide was clinically ineffective and did not improve when combined with 8 mg dexamethasone.[69] Larger dosages, however, were as effective as ondansetron or droperidol when added to dexamethasone (odds ratios around 0.5).[7]

Metoclopramide is a relatively safe drug. Jan Wallenborn et al recorded low incidence of extrapyramidal symptoms while no incidence of extrapyramidal symptom was noted in this study. This is probably due to larger sample size used in the previous study.[8] It is also possible that giving the drug in two divided doses rather than as a bolus prevented the incidence of extrapyramidal effects in this study.

Jan Wallenborn et al found that metoclopramide also reduced the number of multiple episodes of nausea and vomiting and the need for rescue drugs.[8] Similarly in this study Metoclopramide reduced the number of multiple episodes of nausea (0% in Metoclopramide Group Vs 30.6% in the Control Group) and vomiting (0% in the Metoclopramide group Vs 2.8% in the Control Group) and the need for rescue drug (2.8% in the Metoclopramide Group Vs 13.9% in the Control Group) (Table 3). However, this was only statistically significant for multiple episodes of nausea (P = 0.003) and not statistically significant for multiple episodes of vomiting (P = 0.218) and the need for rescue drug (P = 0.09).

There have been conflicting reports on the efficacy of dexamethasone in the prevention of PONV. Several studies have found that dexamethasone is effective in prevention of PONV.[13,92,93]

In these studies, the antiemetic effect of dexamethasone was reported to be equal to or even better than that of serotonin subtype 3 (5-HT3) receptor antagonists such as ondansetron and granisetron.[92, 93] Dexamethasone also reduced the occurrence of postoperative nausea and vomiting (PONV) in patients undergoing tonsillectomy, thyroidectomy, cholecystectomy and hysterectomy.[13, 14, 28] However in another study, Jann-Inn Tzeng et al concluded that dexamethasone (8 mg) alone does not prevent PONV in women undergoing dilatation and curettage.[27] Dexamethasone was however found to enhance the antiemetic effect of droperidol[27]. Although dexamethasone has been used in the prophylaxis of chemotherapy related emesis in a wide dose range (8 – 32 mg), [92, 93] a single fixed dose of 8 mg was most frequently used in the prevention against PONV.[13, 14, 28]This was the reason why a single fixed dose of dexamethasone of 8 mg was chosen in this study.

Reviews dealing with PONV have discussed almost exclusively general anaesthesia and largely ignored regional anaesthesia. This contrasted with the increasing popularity of regional anaesthesia. A multitude of medications, such as synthetic opioids, α_2-agonists, and cholinesterase inhibitors, have been introduced in an attempt to enhance the action of local anaesthetics. The decision about their usefulness will not only rely on their effects on nerve blockade and pain relief, but also on their influence on side effects such as PONV.

Patients in this study had their surgery under spinal anaesthesia. Two patients whose anaesthesia was converted to general anaesthesia were excluded from the study. Regional anaesthesia has been reported to be less emetogenic than general anaesthesia.[55-60] Intrathecal fentanyl was used for all patients in this study. It is possible that this could have further increased the risk of PONV in the patients that were studied.[71] Intrathecal morphine is however more emetogenic than intrathecal fentanyl.[5]

Age

Twenty-one patients (29.2%) had age ≥ 50years while fifty-one patients (70.8%) had age < 50 years. In this study, age had no effects on the incidence of PONV (P = 0.66, Table 5). Jan Wallenborn et al noticed that early postoperative nausea and vomiting was less frequent in patients aged 50 or more but late episodes were more frequent, as were adverse reactions.[8] There was no similar finding in this study. There was no difference in the incidence of PONV between patients aged 50 or more and patients aged less than 50 years throughout 24 hours (Table 5).

Table 5. Incidence of PONV compared with Obesity and Age

	PONV (n)	NO PONV (n)
Age		
P = 0.66		
Age < 50 yr	14	37
Age ≥ 50 yr	6	15
Obesity		
P = 0.87		
Obese (BMI ≥ 30)	3	16
Not Obese (BMI < 30)	11	42

Soyannwo et al could not find significant relationship between age and PONV in their study.[5] Similarly, Berg Van den et al could not establish relationship between age and postoperative vomiting in their study.[32] Cohen et al[17] showed that the incidence of vomiting is no doubt higher in paediatric age groups when compared to adults. In a recent study, Alesandro CS et al also found PONV to be significantly associated with younger age (P = 0.034).[94] All the patients in the present study were adults with age range of 21- 63 years unlike some previous studies that included patients with younger age range and larger population sample.[94] Watcha and White concluded that the relationship between emesis and age is not as clear as relationship between gender and postoperative nausea and vomiting in adult population.[12]

Obesity

Body mass index (BMI) had no effects on postoperative nausea and vomiting in this study (P = 0.87). Obesity has actually been disproved as a patient-related PONV risk factor .[95] Interestingly, the systematic review that did so found that the belief in increased body mass index as a risk factor apparently largely stemmed from a “chain reaction” of 14 review articles misquoting or misinterpreting 4 original studies.[95]

Postoperative pain

Postoperative pain after gynaecological surgery may precipitate or aggravate PONV. Morphine, paracetamol and diclofenac were used for postoperative pain management in this study to minimise the influence of pain on PONV. In the Metoclopramide Group, 12 (33.3%) patients had pain in the first 24 hour while 24(66.7%) were free of pain (Table 6). On the other hand, 20 (55.6%) patients in the Control Group had pain during the 24 hour period and 16 (44.4%) patients were free of pain. There was no statistically significant difference in the incidence of

pain between the two groups (P = 0.96). Therefore, pain could not have been responsible for the higher incidence of PONV noticed in the Control Group.

Table 7 shows that among patients who experienced pain (mild, moderate and severe) and those who did not, there was no statistically significant difference in the incidence of PONV. In a similar vein, Stadler et al could not establish relationship between PONV and postoperative pain.[96]Some studies have however established postoperative pain as risk factor in PONV.[12]

More patients in the Control Group (55.6%) had pain within 24 hours postoperatively compared with the Metoclopramide Group (33.3%) (P = 0.96, Table 6). Although the difference was not statistically significant, the observed result may be due to the analgesic effect of metoclopramide that has been reported by some investigators.[97,98] Ramaswamy et al found that metoclopramide produced a significant analgesic effect when tested by both acetic acid induced writhing and hot plate test.[97] This effect was reduced by naloxone suggesting opioid involvement. Furthermore, bromocriptine which inhibits the release of prolactin attenuated the effect of metoclopramide indicating that this drug could act by releasing prolactin.[97] Lisander agreed that metoclopramide may enhance analgesic effect of opioids and established that VAS-pain scores tended to be smaller in patients that had metoclopramide compared with those that had no metoclopramide. He however could not conclusively demonstrate clinically relevant analgesic effect of metoclopramide.[98]

Type of surgery

This study was conducted on patients undergoing major gynaecological surgery ranging from total abdominal hysterectomy to Manchester repair (Table 2). There was relative even distribution of types of surgery between the two study groups (P= 0.633). Some investigators

have established types of surgery as a risk factor in PONV.[12] Whereas several other studies have suggested that differences in the incidence of PONV are mainly due to patient- or anesthesia-specific factors, regardless of the type of surgery.[99] However in a more recent study, Ruiz et al found that the type of surgery, when categorized anatomically, was associated with an increased frequency of early PACU antiemetic administration.[100]

Adverse events

The adverse effects seen during the study are shown in Table 8.The most frequently reported side effects were dizziness and drowsiness which were relatively mild. No difference in the incidence of adverse effects was observed among the groups. Only one patient in the Metoclopramide Group had significant hypotension which responded to intravenous administration of ephedrine 3 mg bolus and Normal Saline. No episode of extrapyramidal symptom was recorded throughout the study period. No patient complained of headache or vertigo in the both groups, although it might have been difficult to differentiate headache caused by spinal anaesthesia from that due to metoclopramide had there been an incidence in the Metoclopramide Group.

Table 8. Adverse Effects

	Metoclopramide Group (n)	Control Group (n)
Any adverse effects	11	10
Mild Hypotension	8	8
Moderate Hypotension	1	0
Dizziness	1	1
Drowsiness	1	1

n = 36 in each group.

In a review of several randomized placebo-controlled studies by Henzi et al, they found no significant difference between metoclopramide and placebo for adverse drug reactions such as extrapyramidal symptoms, sedation and drowsiness, dizziness and vertigo, headaches.[31]Only one adult patient who had received 20 mg metoclopramide was found to have extrapyramidal symptom while no extrapyramidal symptom was found in children in their study.

There was no episode of intraoperative vomiting in both groups during the present study.

Conclusion and Recommendation

Patients at high risk of PONV should receive special considerations with respect to the prophylactic use of antiemetic drugs. Due to different sites of action of antiemetic drugs, a combination therapy using two antiemetics (acting at different sites) together with less emetogenic anaesthetic procedure is more effective than monotherapy. A Combination of 8 mg dexamethasone and 50 mg metoclopramide in two divided doses given intravenously is effective in the prevention of PONV and it is strongly recommended for patients with high risk of developing PONV. It is found to be safe and cheap and this is in agreement with previous study. It is recommended that 25 mg metoclopramide be given after induction of anaesthesia and 25 mg at the closure of the skin.

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