Clinical Investigation

Efficacy of orally disintegrating film of ondansetron versus intravenous ondansetron in prophylaxis of postoperative nausea and vomiting in patients undergoing elective gynaecological laparoscopic procedures: A prospective randomised, double-blind placebo-controlled study

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ABSTRACT

Background and Aims: Ondansetron is one of the most widely used drugs for postoperative nausea and vomiting (PONV) prophylaxis. Orally disintegrating film (ODF) formulations are relatively recent innovations. We evaluated the efficacy of ODF of ondansetron for the prophylaxis of PONV. **Methods:** One hundred and eighty American Society of Anaesthesiologists-I or II women, in the age group 18-65 years, scheduled for elective gynaecological laparoscopic procedures were studied in a prospective randomised, double-blind, placebo-controlled trial. The patients were randomised into four groups: Placebo, intravenous (IV) ondansetron 4 mg, ODF of ondansetron 4 mg (ODF4) and 8 mg (ODF8) groups. PONV was assessed in two epochs of 0-6 and 7-24 h. Primary outcome measure was the incidence of PONV and secondary outcome measures were severity of nausea, need for rescue anti-emetic, analgesic consumption, time to oral intake, overall patient satisfaction and side effects such as headache and dizziness. PONV was compared using analysis of variance or Mann–Whitney U-test as applicable. **Results:** Data of 173 patients were analysed. The incidence of postoperative nausea was significantly lower ($P = 0.04$) only during the 0-6 h in the ODF8 group when compared with the placebo group. During the 0-6 h interval postoperatively, the ODF8 group had a significantly lower incidence of vomiting when compared with the placebo ($P = 0.002$) and the IV group ($P = 0.044$). During the 0-24 h interval postoperatively, ODF4 ($P = 0.01$) and ODF8 ($P = 0.002$) groups had a significantly lower incidence of vomiting compared to the placebo group. **Conclusions:** Orally disintegrating film of ondansetron is an efficacious, novel, convenient and may be a cost-effective option for the prophylaxis of PONV.

Key words: Laparoscopic surgical procedures, ondansetron, postoperative nausea and vomiting, randomized controlled trial

INTRODUCTION

Postoperative nausea and vomiting (PONV) continues to be a common problem after surgery. PONV is associated with high levels of patient discomfort and dissatisfaction in addition to the delayed discharge and increased health care cost.[1] Several patient related, anaesthetic and surgical factors are associated with an increased incidence of PONV. Women undergoing laparoscopic surgery represent one such high-risk group for PONV.[2] The reported incidence of PONV following laparoscopic surgery has been as high as 70-85%.[1,3] The 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists are the first-line drugs in the management of PONV.[1] Among

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the available 5-HT_3 receptor antagonists, ondansetron is the most widely used for PONV prophylaxis.

In the perioperative period, drugs used for the management of PONV are generally administered intravenously to allow compliance with any fasting requirements of surgery and also, most of the patients are unable to tolerate oral intake because of pain, sedation and PONV itself. Nevertheless, oral disintegrating tablets of 5-HT_3 receptor antagonists have been shown to be as effective as intravenous (IV) preparations.[4-6] Medications supplied in orally disintegrating film (ODF) formulations are relatively recent innovations in drug administration. ODF formulations are very convenient to use, result in high bioavailability as much of the drug is absorbed through the oral mucosa and, therefore, bypasses hepatic first-pass metabolism[7,8] and there is no requirement for oral intake of water as required for tablets. Due to these unique features, ODF formulation of ondansetron is an attractive option in the management of PONV. The U.S. Food and Drug Administration has approved oral soluble film of ondansetron for the prevention of postoperative, highly and moderately emetogenic cancer chemotherapy-induced, and radiotherapy-induced nausea and vomiting. However, there are no reports of efficacy of ODF of ondansetron in the management of PONV.

We undertook the current study to evaluate the efficacy of ODF of ondansetron for the prophylaxis of PONV and compare it to that of IV ondansetron. We hypothesized that the ODF of ondansetron will be as effective as IV ondansetron in preventing PONV in patients undergoing gynaecological laparoscopic procedures. The primary outcome measure was the incidence of PONV and the secondary outcome measures were severity of nausea, need for rescue anti-emetic, analgesic consumption, time to oral intake, overall patient satisfaction and side effects such as headache and dizziness.

METHODS

After obtaining approval for this study from the Institutional Ethics Committee and written consent from the patients, 180 consecutive American Society of Anaesthesiologists Physical Status Classification Class I or II women, in the age group 18-65 years, scheduled for elective gynaecological laparoscopic procedures under general anaesthesia were studied from March to September 2012 in a prospective randomized, double-blind, placebo-controlled trial. Patients with the previous history of PONV or motion sickness, patients who had received anti-emetic therapy within 24 h preoperatively, pregnant patients (except those undergoing medical termination of pregnancy with laparoscopic tubal ligation), patients on opioid and steroid treatment, and patients with a body mass index greater than 30 were not included.

After overnight fasting and premedication with oral ranitidine 150 mg the night before and on the morning of surgery, patients were randomised into four groups: Placebo, IV ondansetron 4 mg (IV), ODF of ondansetron 4 mg (ODF4) and ODF of ondansetron 8 mg (ODF8) groups using a block randomisation technique with varying block sizes and serially numbered, sealed envelopes. The envelopes were opened in the preoperative area just before administration of the study drug. All the patients were administered two ODFs in the preoperative area by one of the investigators just before shifting to the operating room. Patients in the ODF4 group received one ODF of ondansetron (containing ondansetron 4 mg) plus one placebo ODF, ODF8 group received two ODFs of ondansetron, whereas patients in the placebo and IV groups received two placebo ODFs. The placebo ODFs were formulated by the manufacturer of the ODF of ondansetron to have an identical appearance and flavour.

In the operating room, after securing an IV access and attaching routine monitoring, all patients were administered 2 ml of the IV study drug (0.9% normal saline in the placebo and ODF groups, and ondansetron 4 mg in the IV group) by the same investigator who administered the ODF and not involved in the postoperative outcome assessments. Anaesthesia was standardised. Anaesthesia was induced with fentanyl (2 μg/kg) and propofol (2 mg/kg). Neuromuscular blockade was achieved by vecuronium (0.1 mg/kg) or atracurium (0.5 mg/kg). Airway was secured by an appropriate size ProSeal Laryngeal Mask Airway (PLMA) or endotracheal tube (ETT). A nasogastric tube was inserted (through the gastric drain tube in case of PLMA or through the nose in case of ETT) in all patients, to aspirate the gastric contents and keep the stomach deflated during the procedure, which was removed at the end of surgery. Anaesthesia was maintained with propofol infusion and lungs were ventilated with oxygen in 50% nitrous oxide to maintain an end-tidal carbon dioxide level of 35-45 mmHg. Supplemental dose of

fentanyl (1 μg/kg/h) was administered if the surgery lasted more than an hour. IV diclofenac 75 mg was administered 30 min before the end of the procedure. Port-site skin was infiltrated with 2-3 ml of 0.25% bupivacaine per port at the end of the procedure. Upon completion of the procedure, neuromuscular blockade was reversed with neostigmine (50 μg/kg) and glycopyrrolate (10 μg/kg). The PLMA/ETT was removed upon return of consciousness and patients were shifted to the post-anaesthesia care unit (PACU). The duration of surgery and anaesthesia were noted.

Postoperatively, all patients were monitored for a minimum of 2 h in the PACU and kept nil-per-oral for 4 h. IV morphine (0.1 mg/kg) was administered if the pain relief was inadequate during the stay in the PACU. Diclofenac 75 mg was used 8-hourly for Analgesia, administered either orally or intravenously depending on the ability of the patient to tolerate oral intake. PONV was assessed in two epochs of 0-6 and 7-24 h by an anaesthesiologist who was not involved in administration of the study drugs, intraoperative management, and blinded to the group allocations. An 11-point numerical rating scale from 0 to 10 with 0 representing no nausea and 10 representing the worst imaginable nausea was used to evaluate the severity of nausea.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit. An event of vomiting was defined as vomiting (forceful expulsion of gastric contents from the mouth) or retching (laboured, spasmodic, rhythmic contractions of the respiratory muscles without expulsion of gastric contents).[6] If the events of vomiting were separated by >1 min, they were considered as separate episodes. PONV was defined as at least one episode of either nausea or vomiting or both during the 1st 24 h postoperatively. PONV was rated using the PONV score described by Mathew *et al*.[9] score 0 = no nausea, no vomiting, 1 = nausea present, no vomiting, 2 = nausea ±, vomiting present, and 3 = vomiting > 2 episodes in 30 min.

Patients with a PONV score of 2 or more were given IV dexamethasone 8 mg as a rescue anti-emetic. The PACU and ward nursing staffs, blinded to the group allocations, recorded the episodes of vomiting and administration of anti-emetic agents. Consumption of fentanyl (intraoperative) and morphine (postoperative), time to oral intake and time to first vomit (both counted from arrival to PACU), were recorded. Patients were asked about their overall satisfaction, and whether they experienced dizziness or headache. The patient satisfaction score was graded on an 11-point scale from 0 to 10 where 0 represented 'no satisfaction at all' and 10 represented 'complete satisfaction'.

Orally disintegrating film of ondansetron ('Emefilm', Delvin Formulations PVT Limited, Chennai, India) containing 4 mg of ondansetron is a pink, orally dissolving film with strawberry flavour, designed to be applied on the tongue where it dissolves in a few seconds and then is swallowed with saliva. 'Emefilm' does not require water to aid dissolution or swallowing (product monograph on Emefilm).

Continuous data was presented as mean standard deviation or median and interquartile range, as appropriate. Normality of quantitative data was checked by measures of Kolmogorov–Smirnov tests of normality. For normally distributed data, means of the groups were compared using one-way analysis of variance followed by *post-hoc* multiple comparisons. For skewed data or ordinal data, Kruskal–Wallis test followed by Mann–Whitney U-test for two groups was applied. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi-square or Fisher's exact test whichever is applicable. The sample size was calculated as follows: We expected the incidence of PONV to be at least 60% in the placebo group and 30% in the IV group. At least 43 patients in each group were required to achieve 80% power at 5% Type I error. A total of 180 patients were recruited to account for inadvertent data attrition. All analyses were performed using SPSS® version 17 (Statistical Packages for the Social Sciences, Chicago, IL, 2008) and a $P < 0.05$ was considered as significant.

RESULTS

One hundred and eighty women were randomised into four groups. Since there was postoperative protocol violation in six patients and one patient received intraoperative methyl ergometrine, they were withdrawn from the study [Figure 1]. Data of 173 patients were analyzed. The patient characteristics, types of surgical procedure, duration of surgery, duration of anaesthesia, duration of pneumoperitoneum, intraoperative consumption of fentanyl and airway (ETT/PLMA) usage were similar in all the four groups [Table 1]. Postoperative

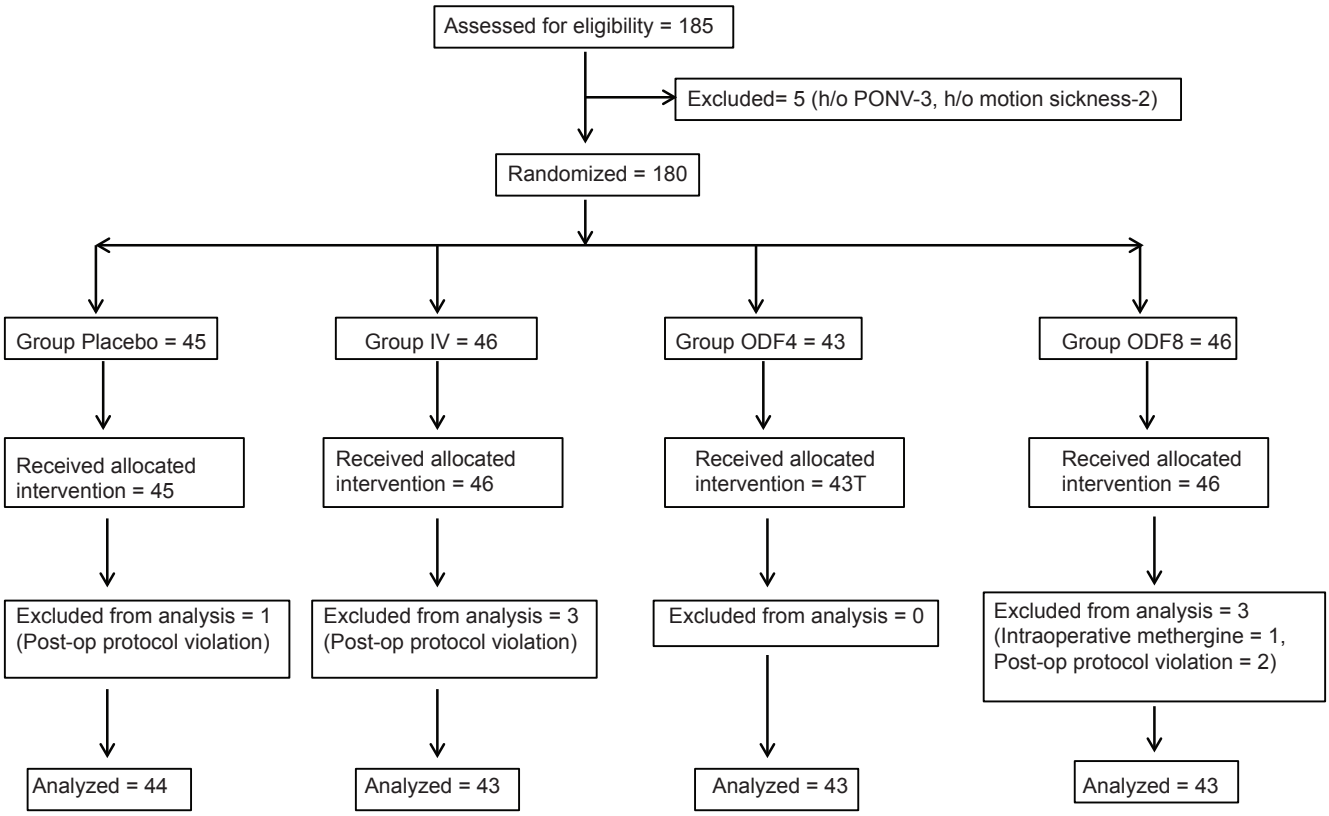


Figure 1: Group allocation and randomisation

Table 1: Patient characteristics, surgical and anaesthetic data

Parameter	Placebo (*n*=44)	IV (*n*=43)	ODF4 (*n*=43)	ODF8 (*n*=43)	*P* value
Age (year)	31.5 (7.3)	32.6 (9.1)	30.7 (7.4)	29.8 (6.4)	0.360
Weight (kg)	54.8 (10.2)	57.3 (10.9)	57.9 (11.8)	55.8 (12.4)	0.577
BMI (kg/m^2)	22.7 (3.8)	23.3 (4.2)	23 (3.9)	22.7 (4.2)	0.910
ASA PS I/II	39/5	38/5	40/3	38/5	0.868
Laparoscopic procedure					
Tubal ligation	14	14	19	20	0.251
MTP+tubal ligation	5	4	2	3	
Diagnostic laparoscopy	17	10	10	12	
Salpingectomy/ovarian cystectomy	2	10	6	2	
Hysterectomy	6	5	6	6	
Duration of anaesthesia (min)	84.9 (76)	82.3 (54.2)	75.6 (68)	77.3 (56.4)	0.900
Duration of surgery (min)	61 (72)	59 (51)	55 (64)	54 (53)	0.535
Duration of pneumoperitoneum (min)	50 (64)	47 (49)	46 (59)	38 (45)	0.471
Intraoperative fentanyl (μg)	178 (97)	179 (70)	179 (97)	177 (81)	0.656
Airway					
ETT	10	16	9	15	0.227
PLMA	34	27	34	28	

All values except ASA are expressed as mean (SD), ASA is in numbers. BMI – Body mass index; MTP – Medical termination of pregnancy; ASA PS – American Society of Anesthesiologists Physical Status; SD – Standard deviation; IV – Intravenous; ODF – Orally disintegrating film; PLMA – ProSeal laryngeal mask airway; ETT – Endotracheal tube

consumption of morphine, time to oral intake, time to first vomit, patient satisfaction score and the incidence of adverse effects were also comparable between the groups [Table 2]. One patient each in the IV and ODF4 groups who complained of a headache postoperatively had headache preoperatively as well. All except two patients described ODF as 'pleasant'. One patient described ODF to be excessively sweet and the other described it as sweet to begin with and bitter later on.

The incidence of postoperative nausea was significantly lower ($P = 0.04$) only during the 0-6 h in the ODF8

group when compared with the placebo group. The difference in postoperative nausea between the three study groups during the 0-6 h, 7-24 h and 0-24 h interval was not significant [Table 3].

During the 0-6 h interval postoperatively, the ODF8 group had a significantly lower incidence of vomiting when compared to the placebo ($P = 0.002$) and the IV group ($P = 0.044$). During the 7-24 h interval postoperatively, the ODF4 group had a significantly lower incidence of vomiting when compared to the placebo ($P = 0.04$). There was no significant difference between the ondansetron groups in the incidence of vomiting during the 7-24 h interval postoperatively. During the 0-24 h interval postoperatively, ODF4 ($P = 0.01$) and ODF8 ($P = 0.002$) groups had a significantly lower incidence of vomiting compared with the placebo group. However, here was no significant difference between the ondansetron groups in the incidence of vomiting during the 0-24 h. The overall incidence of PONV in the 0-24 h period postoperatively was 58% in the placebo group, 46.5% in the IV group, 51.2% in the ODF4 group and 34.9% in the ODF8 group. However, the difference was not statistically significant.

The severity of PONV, as indicated by the PONV score, in the 0-6 h interval was significantly less ($P = 0.008$) in the ODF8 group as compared to the placebo group. However, there was no significant difference in the PONV scores between the four groups in the 7-24 h interval. One patient in the placebo group had seven episodes of vomiting in the first 3 h postoperatively in spite of receiving rescue dose of dexamethasone. There were no Q-T interval abnormalities observed during the study.

DISCUSSION

Our results show that the ODF of ondansetron is useful in the prophylaxis of PONV during the 1st 24 h in patients undergoing gynaecological laparoscopic surgeries. ODF of ondansetron 4 mg could be the minimal effective dose. Furthermore, ODF of ondansetron 8 mg may be the optimal dose since ODF8 group had the lowest incidence of PONV among the three study groups. The ODF preparation was found to be well accepted by the patients as the majority of them described its taste as 'pleasant'.

The placebo group in our study had a lower incidence of PONV than the generally reported incidence of

Table 2: Postoperative data

Parameter	Placebo (*n*=44)	IV (*n*=43)	ODF4 (*n*=43)	ODF8 (*n*=43)	*P* value
Postoperative morphine (mg)	3.4 (3.9)	4.3 (4.5)	5 (4.5)	3.3 (3.8)	0.185
Time to oral intake (min)	302 (143)	271 (65)	265 (56)	258 (43)	0.271
Time to first vomit (min)	319 (206)	295 (223)	305 (155)	358 (141)	0.906
Patient satisfaction score	10 (5-10)	10 (5-10)	10 (4-10)	10 (5-10)	0.755
Dizziness	5 (11.4)	5 (11.6)	8 (18.6)	2 (4.7)	0.254
Headache	2 (4.6)	2 (4.7)	3 (7)	0	0.419

Values are expressed as mean (SD). Patient satisfaction score values are in median (range) whereas dizziness and headache are expressed as numbers (percentage). SD – Standard deviation; IV – Intravenous; ODF – Orally disintegrating film

Table 3: Postoperative nausea and vomiting

Time period	Placebo (*n*=44)	IV (*n*=43)	ODF4 (*n*=43)	ODF8 (*n*=43)
0-6 h				
Nausea	17 (38.6)	10 (23.3)	10 (23.3)	8 (18.6) (*P*=0.04*)
Nausea score	0 (0-5)	0 (0-0)	0 (0-0)	0 (0-0) (*P*=0.017*)
Vomiting	13 (29.5)	8 (18.6)	7 (16.3)	2 (4.7) (*P*=0.002*) (*P*=0.045†)
PONV score 0/1/2/3	26/5/7/6	31/4/8/0	30/6/6/1	35/6/2/0 (*P*=0.008*)
7-24 h				
Nausea	14 (31.8)	7 (16.3)	11 (25.6)	8 (18.6)
Nausea score	0 (0-2.75)	0 (0-0)	0 (0-1)	0 (0-0)
Vomiting	13 (29.5)	6 (14)	5 (11.6) (*P*=0.04*)	6 (14)
PONV score 0/1/2/3	26/5/12/1	33/4/4/2	30/8/4/1	33/4/6/0
0-24 h				
Nausea	22 (50)	16 (37.2)	19 (44.2)	14 (32.6)
Vomiting	22 (50)	13 (30.2)	10 (23.3) (*P*=0.01*)	8 (18.6) (*P*=0.002*)
Overall PONV	25 (58)	20 (46.5)	22 (51.2)	15 (34.9)

Values expressed as numbers (percentage), Nausea score is in median (inter-quartile range). *When compared with the placebo group; †When compared with the IV group. PONV – Postoperative nausea and/or vomiting; IV – Intravenous; ODF – Orally disintegrating film

PONV (70%-85%) in a similar group of patients.[1,3,10] The anaesthesia regime used could be the reason for the low incidence of PONV in our study and the statistically non-significant difference in the overall incidence of PONV in the 1st 24 h postoperatively. We used propofol, which is known to reduce the incidence of PONV.[11,12] The usage of PLMA in a higher number of patients could be another reason for the reduced PONV in our study. Hohlrieder *et al*.[13] concluded that the frequency of PONV, airway morbidity, and analgesic requirements is lower for the PLMA than the ETT in females undergoing breast and gynaecological surgery. We also limited the inspired nitrous oxide concentration to 50% which may reduce PONV, since nitrous oxide may contribute to PONV in a dose-dependent fashion. Mraovic *et al*.[14] reported that in patients undergoing gynaecologic laparoscopic surgery, the incidence of PONV at 24 h was 33%, 46% and 62% in patients who received 30% oxygen with air, 50% N_2O with oxygen and 70% N_2O with oxygen ($P = 0.018$), respectively. The authors had used sevoflurane with different concentrations of N_2O.

Orally disintegrating film of ondansetron 8 mg was the most effective drug in the 1st 6 h postoperatively. Subsequently, in the 7-24 h interval, this advantage was not observed. This indicates that beyond 6 h, the benefits of a single preoperative dose of ODF of ondansetron 8 mg may not last to the same extent. Therefore, we suggest that a second dose of ODF of ondansetron 8 mg 6 h postoperatively may be useful in reducing the incidence of PONV subsequently.

Orally disintegrating film of ondansetron may also be cost effective when compared to IV ondansetron. Each film of ODF containing 4 mg of ondansetron costs about 10, whereas an ampoule of ondansetron 4 mg costs about 35 in Indian rupees. However, these pricing may not be universal. IV medication also involves an additional expenditure in the form of a syringe, needle and biomedical waste.

We did not directly measure and compare the pain and anxiety postoperatively which may affect the incidence of PONV and we consider this as a shortcoming of our study. However, the anaesthesia protocol was standardised. We used a predefined dose of opioid and diclofenac for intraoperative as well as postoperative analgesia. The consumption of analgesics intra- and postoperatively was similar in all the four groups. This may have eliminated the variations in the incidence of PONV caused by pain and opioids. In spite of the higher incidence of PONV in the placebo group, the patient satisfaction score did not differ significantly between the four groups. The most frequently reported adverse events of 5-HT_3 receptor antagonists are dizziness and headache.[15] These adverse events observed in our study were similar in all the four groups.

Ondansetron 4 or 8 mg has been recommended for PONV prophylaxis although an 8 mg of ondansetron has been suggested to be the optimal dose in a meta-analysis.[16] We could have included one more group to receive IV ondansetron 8 mg. However, IV ondansetron 4 mg is the generally used dose in our institute considering the lower body mass of Indian patients compared to the western counterparts.

The half-life of ondansetron is approximately 3.5-4 h in adults.[17,18] Therefore, in operative procedures lasting more than 2 h, it might be more relevant to administer the drug towards the end of the surgery. Since the mean duration of the procedure in our study was about an hour, we assume that administering the drug preoperatively was appropriate.

The concern with the oral route perioperatively is bioavailability of the drug and hence, the efficacy. Some patients may swallow the ODF instead of allowing it to dissolve in saliva. This may reduce the efficacy of the drug. However, it takes only a few seconds for the ODF to dissolve and therefore, much of the drug will still reach the systemic circulation via the pharyngeal mucosa bypassing the first-pass metabolism.

There are a few limitations of our study. First, our calculation of the sample size was based on the expected PONV incidence of 60% in the placebo group and 30% in the IV group. However, the results of our study showed a 58% incidence of overall PONV in the placebo group and 46.5% in the IV group. This may have resulted in under powering, and therefore, a non-significant difference in the effectiveness of IV ondansetron 4 mg when compared to the placebo. Second, our study was not adequately powered to assess the efficacy of the individual drug regimen. Therefore, we cannot conclude about the optimal dose of ODF. Third, we used dexamethasone as a rescue anti-emetic. There is conflicting evidence with regard to the use of dexamethasone as a rescue anti-emetic because of a relatively slow onset of action.

Future studies with a larger sample size are required to find out the optimal dose of ODF. Further studies

may be conducted to evaluate the efficacy of ODF of ondansetron in patients undergoing day-care procedures. The usefulness of ODF of ondansetron may be of greater value in the setting of day-care procedures where the patients may experience nausea and vomiting after discharge from the hospital. These patients may easily be taught about the administration of ODF. The efficacy of ODF of ondansetron when administered in the postoperative period needs to be studied. Due to the convenience of administration and acceptance of the ODF by the patients, we speculate a conscious, oriented and pain free patient in the immediate postoperative period may be cooperative enough for administration of the ODF. Future researches may involve incorporating longer acting drugs such as ramosetron, palonosetron etc., into the ODF formulations with the convenience of a single daily dosing.

CONCLUSION

Orally disintegrating film of ondansetron is an efficacious, novel convenient and may be a cost effective option for the prophylaxis of PONV. ODF of ondansetron 4 mg could be the minimal effective dose and 8 mg dose may be the optimal. ODF is well accepted by the patients.

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