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Efficacy of orally disintegrating tablet of ondansetron 4mg sublingually compared to ondasetron 4mg intravenousin the management of post-operative nausea and vomiting in patients undergoing elective laparoscopic surgeries under general anesthesia: A non-inferiority study

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ABSTRACT:

Background: Orally disintegrating tablet (ODT) of ondansetronis an attractive option for prevention and management of post-operative nausea and vomiting (PONV) compared to intravenous ondansetron. It is given sub-lingually and automatically gets dissolved and hence convenient. There is no need of water and hence it does not interfere with the fasting status of the patients. As it is absorbed by oral mucosa, its bioavailability is high. This is unique thing about ODT of ondansetronand hence attracts its use.

Objective: Present study was carried out to prove that ODT of ondansetronis not inferior to intravenous ondansetron in patients undergoing elective laparoscopic surgeries under general anesthesia and to compare the requirement of rescue analgesics and complication in these two groups

Methods: Prospective, randomized non-inferiority study was carried out among 100 patients undergoing elective laparoscopic surgeries under general anaesthesia at department of Anaesthesiology, Malla Reddy Narayana Multi-speciality Hospital. The patients were randomly assigned as 50 cases each in two groups. Group I patients were given ODT of ondansetron 4mg sublingually half an hour before induction. Group II patients were given ondansetron 4mg intravenously at the time of induction. PONV assessed in two periods of 0-6 h and 6-24 h. The difference in two group means was tested by using unpaired t-test. Difference in proportions was tested using chi square test, Fisher's extract test. p value < 0.05 was considered as significant.

Results: Both the group patients were comparable in terms of baseline characteristics like age, sex, procedures performed, ASA grades, PONV score, weight and duration of surgery (p > 0.05). The difference for requirement of rescue antiemetics in two groups was not significant (p > 0.05). The incidence of complications was also comparable in two groups (p > 0.05)

Conclusion:ODT of ondansetron was found to be non-inferior to IV ondansetron in preventing PONV.

Key words:anesthesia, efficacy, laparoscopic surgery, nausea, ondansetron

Key messages:ODT ondansetron can be used to prevent post operative nausea and vomiting instead of IV ondansetron as both are equally good and this will also be useful in those who do want to avoid intravenous injections as much as possible.

INTRODUCTION

In patients undergoing operative procedures under general anesthesia, postoperative nausea and vomiting (PONV) is common issue. About one fourth of such patients are affected by PONV, but it may go up to 80% in high risk cases. Most commonly reported complaint is nausea and vomiting after surgery. Most of the times, it is worse than pain experienced after surgery. Fortunately, PONV is self-limiting but there is risk of serious complications if not attended like subcutaneous emphysema, dehiscence of sutures, gastric contents aspiration etc. Discharge of the patients may also be delayed. Attempts are on to tackle this problem and as a result there is more and more use of anesthetic agents which are less emetic, improvedpre- and post-operative medication, identifying risk factors early and their management, robust surgical techniques etc. which has reduced the incidence of PONV during the recent times. Even with these advances, PONV tends to occur even today. It has been reported that incidence of PONV among patients undergoing laparoscopic surgeries is around 70-85% due to factors related to anesthesia, patients and operative procedures. [1, 2]

Now a days there is an increasing trend towards the laparoscopic surgeries globally due to the advantages it offers over the open surgeries like a smaller number of stitches, reduced pain after surgery, early mobility, early chances of hospital discharge and cosmetics and some other advantages. But as stated above, PONV is common in these kinds of surgeries also and vomiting is known to lead to imbalance of electrolytes, dehydration and many other complications. [3]

For prevention of PONV; drugs like butyrophenones, antihistaminic etc. were tried but with limited success. This was due to the side effects of these drugs like dysphoria, extra pyramidal symptoms, dry mouth etc. [4]

5-hydroxy tryptamine-3(5HT3) receptor antagonists are the first line pharmacological agents which are commonly used now a days to manage the PONV. Ondansetron belongs to 5-hydroxy tryptamine-3(5HT3) receptor antagonists' group and it is the commonly used one. Ondansetron is generally administered by intravenous route during peri-operative period. Intravenous route is preferred to keep patient's nil by mouth which is a pre requisite for surgeries and some patients may not tolerate oral routes or oral administration may lead to PONV itself before surgery which is not acceptable. [5] However, studies have shown that oral disintegrating tablets of ondansetron are as effective as intravenous ondansetron. [6, 7, 8]

Orally disintegrating tablet (ODT) of ondansetronis an attractive option in the field of administration of the drugs for prevention and management of post-operative nausea and vomiting compared to intravenous ondansetron. It needs to be kept in mouth and it gets automatically dissolved and hence convenient. There is no need of water and hence it does not interfere with the fasting status of the patients. As it is absorbed by oral mucosa, its bioavailability is high. [9, 10]

This is unique thing about ODT of ondansetronand hence attracts its use. In view to have more and more data apart from what is available in the literature, more studies are required to prove that ODT of ondansetronis as good as intravenous ondansetron. ODT of ondansetron 4mg costs only 10 INR compared to 35 INR for intravenous ondansetron 4mg and also saves cost related to intravenous use.

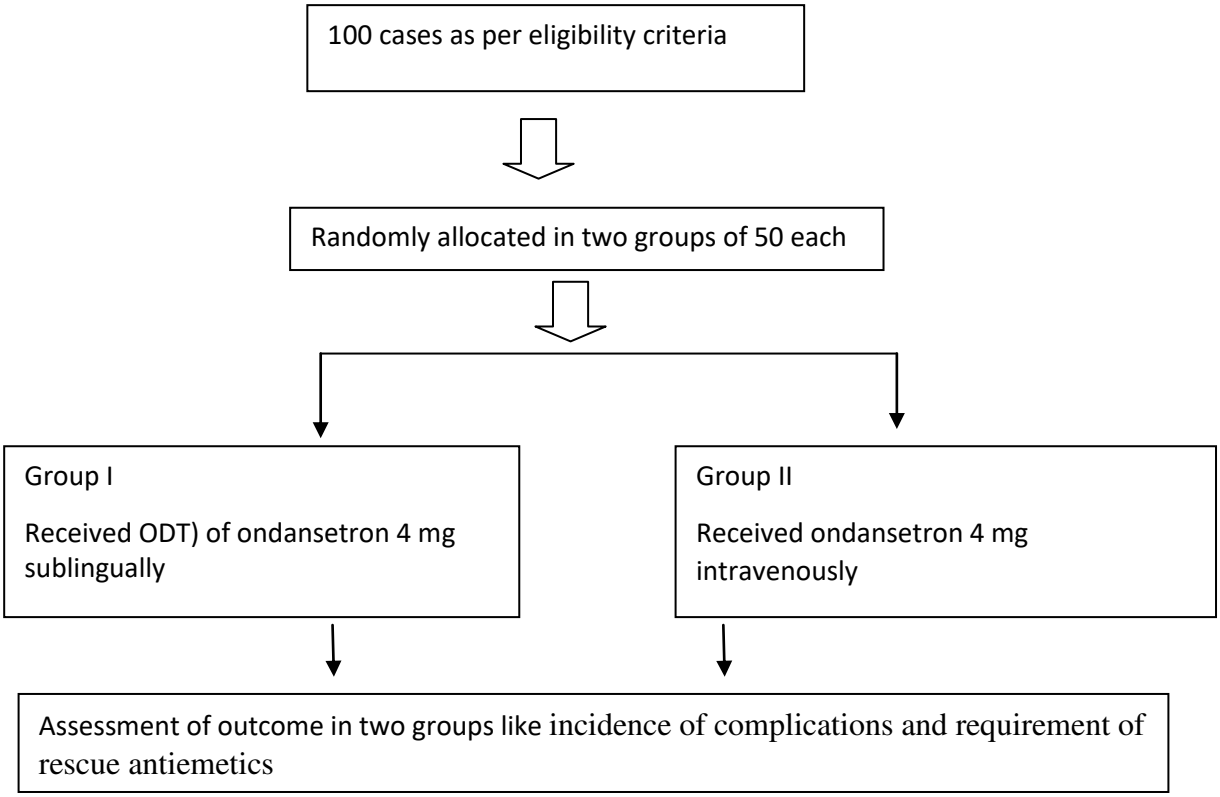
Hence present study was carried out to prove that ODT of ondansetronis not inferior to intravenous ondansetron in patients undergoing elective laparoscopic surgeries under general anesthesia.

METHODS

Present study was prospective, randomized non inferiority study carried out at department of Anaesthesiology, Malla Reddy Narayana Multi-speciality Hospital among patients undergoing elective laparoscopic surgeries under general anaesthesia from November 2017 to October 2018.

Institutional ethics committee approval was obtained. Written informed consent was taken from all study participants. All patients were managed as per the standard protocol

During the study period, it was possible to study 100 cases undergoing elective laparoscopic surgeries under general anaesthesia. They were randomly assigned as 50 cases each in two groups. patients with ASA grade I & II, Age group of 20 to 60 years of either gender and Undergoing elective laparoscopic surgery were included. Patients with past history of motion sickness or PONV, Taken anti-emetic drugs in last 24 hours, Presently taking treatment consisting of steroid or opioid, Pregnant and Obese patients were excluded.



The patients were randomly assigned as 50 cases each in two groups. Group I patient were given Orally disintegrating tablet (ODT) of ondansetron 4 mg sublingually half an hour before induction. Group II patients were given ondansetron 4 mg intravenously at the time of induction.

Pre anesthetic evaluation was carried out. Written informed consent was taken. Patients were fasted for 8hrs prior to surgery. Tablet ranitidine (150mg) was administered in the morning at 6AM on the day of surgery. Patients in the first group received (ODT) of ondansetron 4mg sublingually 30 min prior to surgery.

Premedication was achieved with glycopyrrolate(0.004mg/kg), midazolam(0.02mg/kg) and fentanyl(2mcg/kg). The patient was preoxygenated with 100% oxygen with appropriate size face mask for 3 min. Anaesthesia was induced with propofol(2mg/kg). Neuromuscular blockade was achieved by vecuronium(0.1mg/kg). Anesthesia was induced as per the standard protocol.

PONV assessed in two periods of 0-6 h and 6-24 h.For evaluation of nausea, numerical rating scale was used. The scale ranged from zero to ten. Zero meant there was no nausea experienced by the patient while as the number increased, the experience of nausea also increased with worst rating as ten. [5] Nausea was defined as, "a subjective feeling of unpleasant sensation associated with awareness of urge to vomit".[8]

An event of vomiting was defined as,"vomiting (forceful oral expulsion of gastric contents) or retching (laboured, spasmodic, rhythmic contractions of the respiratory muscles without expulsion of gastric contents)." [8] "If the events of vomiting separated by >1min, they are considered as separate episodes".[5]

PONV was defined as,"at least one episode of either nausea or vomiting or both during the first 24 h postoperatively." [5]PONV was rated using the PONV score (no nausea and vomiting

means zero; nausea is there but no vomiting as one, both present is two and three is presence of more than two vomiting in half an hours) described by Mathew et al.[11]

Those patients were given rescue anti-emetic (dexamethasone 8mg intravenously) who had PONV score of more than two. Post operative pain management was done using those drugs which will not affect the study results. Hence drugs like tramadol/morphine were not used.

Continuous data were expressed as a mean and standard deviation and were analysed using unpaired t-test(two-tailed t-test) for comparison between the two groups. Categorical data were expressed as frequency and percentages and compared using chi square test, Fisher's extract test. Probability value (p value) was used to determine the level of significance; p value < 0.05 was considered as significant.

RESULTS

The mean age of the patients in group I was 38.3±11.6 years whereas it was 37.2±10.1 years in group II. The distribution of the sample by groups and age groups was found to be statistically not significant (p=0.798). There were 30 male patients (60%) and 20 female patients (40%) in group I and 27 male patients (54%) and 23 female patients (46%) in group II. The distribution of the sample among both the groups was found to be statistically not significant (p=0.545). (Table 1)

The PONV score in both the groups was comparable with no difference and the number of patients with ASA grades I and II were also similar (p> 0.05) (Table 2)

The average weight of the patients in group I patients was 59.68$\pm$10.03 kg and the average weight of the patients in group II was 58$\pm$9.2 kg and this difference was statistically not significant (p>0.05). Similarly, the duration of surgery was also comparable in two groups (p > 0.05) (Table 3)

in the first six hours one patient from each group required rescue anti-emetics. In 6-24 hours', time, four patients in group I and three patients in group II required rescue antiemetics and this difference was not found to be statistically significant (p>0.05). Overall, five patients from group I and four patients from group II required rescue antiemetics and this difference was not found to be statistically significant (p>0.05) (Table 4)

Five patients from group I and six patients from group II developed nausea while six patients from group I and five patients from group II had vomiting. Two from group I and three from group II had headache and three from group I and two from group II had dizziness. All these differences were not found to be statistically significant (p>0.05) (Table 5)

DISCUSSION

We used ondansetron 4mg dose based on the findings of a study by Honkavara P et al [12] who compared two doses of ondansetron (4mg and 8mg). they reported that incidence of PONV was similar in both the groups and concluded that 4mg ondansetron can be used instead of 8mg.

Hedge HV et al [5] have compared the ODT of ondansetron with that of intravenous ondansetron and noted that incidence of PONV was significantly more in intravenous group compared to ODT group. We found no significant difference in two groups.

Bhashyam S et al [13] also carried out a similar study and found that incidence of PONV as well as incidence of side effects was comparable in both the groups. We also found similar findings.

Sadawarte P et al [14]observed from their study that vomiting and nausea incidence was comparable in two groups of patients receiving oral and intravenous ondansetron which is similar to the findings of the present study. They noted that patients were able to tolerate ondansetron given either intravenous or oral and there were no side effects reported.

In present study, patients in the ODT group and intravenous group were similar in terms of age, sex, type of surgery they underwent, grades of ASA, and weight (p>0.05). Average duration of operative procedure was 100.90±17.77 minutes for patients in ODT group compared to 93.1±21.56 minutes for patients in intravenous group and this difference was not found to be statistically significant (p>0.05).

Equal incidence of nausea was observed in two groups during first six hours (P=1) and this finding is comparable to finding by Hegde HV et al, [5] Bhashyam S et al [13] and Sadawarte P et al. [14] Hegde HV et al [5] found that incidence of nausea was more in intravenous group compared to ODT group but the difference was statistically not significant.

clinically and statistically not significant (p= 0.695) nausea incidence in 6-24 hours in intravenous group was similar to the nausea incidence in ODT group and this finding is comparable to finding by Hegde HV et al, [5] Bhashyam S et al [13] and Sadawarte P et al. [14] Hegde HV et al [5] found that ODF 8mg and intravenous 4mg ondansetron groups had similar incidence of nausea in 7-24 hours after surgery.

Incidence of nausea in first 24 hours in the present study in the ODT group was found to be comparable to incidence of nausea in first 24 hours among intravenous group (p > 0.05). Similar findings were reported by Hegde HV et al, [5]Bhashyam S et al [13] and Sadawarte P et al.[14] Bhashyam S et al [13] noted that there was significantly higher incidence of nausea and vomiting in placebo group compared to ODF group at various intervals of time.

Incidence of vomiting in the present study in first six hours was 6% in both the groups (p=1). Hegde HV et al, [5]Bhashyam S et al [13] and Sadawarte P et al [14] also reported similar findings. Hegde HV et al [5] found that patients who received placebo had significantly higher incidence of vomiting in first six hours compared to patients in the ODF 8mg group (p = 0.002) and also it was significantly more in intravenous group (p=0.044)

We observed that incidence of vomiting in 6-24 hours was 6% and 4% in ODT group and intravenous group respectively but the difference was statistically not significant (p=0.646). Hegde HV et al, [5]Bhashyam S et al [13] and Sadawarte P et al [14] also reported similar findings.

Overall, in first 24 hours, the incidence of vomiting was 12% in ODT group compared to 10% in intravenous group but this difference was not found to be statistically significant (p>0.05).

10% of patients in the ODT group and 8% of patients in intravenous group required rescue anti-emetics and this difference was not significant (p=0.726). Bhashyam S et al [13]observed that patients consuming rescue anti-emetic were similar in group G and ODF group.

Incidence of PONV in the present study which was measured by PONV score during 0-6 hours, 6-24 hours and 0-24 hours was equal in both the groups. Similar findings were reported by Hegde HV et al, [5]Bhashyam S et al [13] and Sadawarte P et al.[14]

Both ODT and IV ondansetron has non-serious adverse effects like short duration head ache, constipation, dizziness, diarrhea and prolongation of QTc interval. In our study incidence of headache, was slightly less in ODT than in IV group which was found to be statistically not significant (p=0.646) and the incidence of dizziness was slightly high in ODT than in IV

group which was found to be statistically not significant (p=0.646) and related to study conducted by Hegde HV et al [5], Bhashyam S et al [13] in which no significant difference found in the groups. Headache was managed by administration of single dose of paracetamol 10mg/kg IV in our study.

CONCLUSION

So, from the results of the present study it can be concluded that ODT ondansetron is equally efficacious with IV ondansetron to prevent postoperative nausea and vomiting in patients undergoing elective laparoscopic surgeries under general anaesthesia with favourable side effect profile. ODT ondansetron is safe, cost effective, well tolerated and comparable in efficacy with IV ondansetron 4mg in prevention of PONV in patients undergoing elective laparoscopic surgeries under general anesthesia.

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Table 1: Distribution of study subjects as per age and sex

Variable		Group I	Group II	Total	Chi square	P value
Age (years)	21-30	13 (26) *	11 (22)	24 (24)	1.0103	0.798
	31-40	9 (18)	11 (22)	20 (20)		
	41-50	12 (24)	15 (30)	27 (27)		
	51-60	16 (32)	13 (26)	29 (58)		
Sex	Male	30 (60)	27 (54)	57 (57)	0.3672	0.545
	Female	20 (40)	23 (46)	43 (43)		

*figures in the parentheses indicate percentages

Table 2: Distribution of study subjects as per ASA grade and Postoperative nausea and vomiting (PONV) score

Variable		Group I	Group II	Total	Chi square	P value
PONV score	0-6 hours	3 (6) *	3 (6)	6 (6)	0	1
	6-24 hours	3 (6)	3 (6)	6 (6)	0	1
	0-24 hours	6 (12)	6 (12)	12 (24)	0	1
ASA grade	I	23 (46)	25 (50)	48 (48)	0.1603	0.688
	II	27 (54)	25 (50)	52 (52)		

*figures in the parentheses indicate percentages

Table 3: Distribution of study subjects as per weight and duration of surgery

Variable	Group I	Group II	T value	P value
Weight (kg)	59.68±10.03	58±9.2	0.8728	0.3849
Duration of surgery (min)	100.9±17.8	93.1±21.6	1.971	0.052

Table 4: Distribution of study subjects as per requirement of rescue antiemetics

Required rescue antiemetics	Group I	Group II	Chi square	P value
Yes (0-6 hours)	1 (2) *	1 (2)	0	1
Yes (6-24 hours)	4 (8)	3 (6)	0.1536	0.695
Yes (0-24 hours)	5 (10)	4 (8)	0.1221	0.726

*figures in the parentheses indicate percentages

Table 5: Comparison of incidence of complications in two groups

Complications	Group I	Group II	Chi square	P value
Nausea	5 (10) *	6 (12)	0.1021	0.749
Vomiting	6 (12)	5 (10)	0.1021	0.749
Headache	2 (4)	3 (6)	0.2105	0.646
Dizziness	3 (6)	2 (4)	0.2105	0.646

*figures in the parentheses indicate percentages