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Sublingual Ondansetron vs. IV Ondansetron for Post-Operative Nausea in Laparoscopic Surgeries: A Non-Inferiority Study

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ABSTRACT

An orally disintegrating tablet (ODT) of Ondansetron offers an appealing option for preventing and managing post-operative nausea and vomiting (PONV) when compared to intravenous Ondansetron. This study aimed to establish that ODT Ondansetron is not inferior to intravenous Ondansetron in patients undergoing elective laparoscopic surgeries under general anaesthesia. Additionally, it sought to compare the need for rescue analgesics and the occurrence of complications between these two treatment groups. A prospective, randomized non-inferiority study was conducted with a cohort of 128 patients undergoing elective laparoscopic surgeries under general anaesthesia. These patients were randomly allocated into two groups, with 64 individuals in each. Group I received ODT Ondansetron 4mg sublingually half an hour before induction, while Group II received intravenous Ondansetron 4mg at the time of induction. PONV was assessed during two times. 0-6 hrs and 6-24 hrs post-surgery. Statistical analysis included an unpaired t-test to compare means and chi-square and Fisher's exact tests to compare proportions. A $p<0.05$ was deemed statistically significant. Both groups of patients were similar in terms of baseline characteristics such as age, gender, type of procedures, ASA grades, PONV score, weight and duration of surgery. The difference in the requirement for rescue antiemetics between the two groups was not statistically significant. Likewise the incidence of complications was comparable between the two groups. The study concluded that ODT Ondansetron is non-inferior to intravenous Ondansetron in effectively preventing PONV.

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Key Words
Antiemetics, analgesics, laparoscopy, ondansetron, vomiting

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INTRODUCTION

In patients undergoing surgical procedures under general anaesthesia the occurrence of postoperative nausea and vomiting (PONV) is a common concern. Approximately one-fourth of these patients experience PONV but in high-risk cases, this figure can escalate to as high as 80%. The most frequently reported complaint among these patients is the sensation of nausea and the act of vomiting following surgery, which can sometimes be more distressing than the pain experienced post-surgery. While PONV typically resolves on its own, neglecting it may lead to serious complications such as subcutaneous emphysema, suture dehiscence and gastric content aspiration, potentially resulting in delayed patient discharge. In response to this issue, efforts have been made to reduce PONV, including the use of less emetic anesthetic agents, improved pre- and post-operative medications, early identification and management of risk factors and advancements in surgical techniques. Despite these advances, PONV still remains a concern. For instance the incidence of PONV in patients undergoing laparoscopic surgeries is reported to be around 70-85%, owing to factors related to anaesthesia, patient factors and the nature of the surgical procedures[1,2].

Currently, there is a growing global trend favouring laparoscopic surgeries due to their advantages over open surgeries, such as fewer sutures, reduced post-surgical pain, earlier patient mobility, quicker hospital discharge and improved cosmetic outcomes. However, as mentioned earlier, PONV remains a common issue in these surgeries and vomiting is known to lead to electrolyte imbalances, dehydration and other complications[3].

Efforts to prevent PONV have included the use of drugs like butyrophenones and antihistamines but their efficacy has been limited, mainly due to side effects like dysphoria, extrapyramidal symptoms and dry mouth[4].

5-hydroxy tryptamine-3 (5HT3) receptor antagonists, specifically Ondansetron, are the primary pharmacological agents used today for managing PONV. Ondansetron belongs to the 5HT3 receptor antagonist class and is the most commonly employed one. Traditionally, Ondansetron is administered intravenously during the peri-operative period. This intravenous route is preferred to ensure patients remain nil by mouth, a prerequisite for surgery, as some patients may not tolerate oral medications or oral administration could trigger PONV before surgery, which is unacceptable[5].

However, studies have demonstrated that orally disintegrating tablets (ODT) of Ondansetron are equally effective as intravenous Ondansetron[6-8]. ODT Ondansetron presents an attractive alternative in the realm of drug administration for preventing and managing post-operative nausea and vomiting compared to intravenous ondansetron. Patients simply need to place the tablet in their mouth and it dissolves automatically, offering convenience. Notably, there's no requirement for water and this feature doesn't interfere with patient's fasting status. As it is absorbed through the oral mucosa, itboasts high bioavailability[9,10].

This unique aspect of ODT Ondansetron makes it an appealing choice and to further expand the available data beyond what is found in the existing literature, more studies are needed to confirm that ODT Ondansetron is as effective as intravenous Ondansetron. Additionally, ODT Ondansetron is cost-effective, with a 4mg tablet costing only 10 INR compared to 35 INR for intravenous Ondansetron 4mg. Consequently, the present study was conducted to establish that ODT Ondansetron is not inferior to intravenous Ondansetron in patients undergoing elective laparoscopic surgeries under general anaesthesia.

MATERIAL AND METHODS

The present study was a prospective, randomized non-inferiority trial. The study enrolled patients undergoing elective laparoscopic surgeries under general anaesthesia. All patients received standard protocol-based care.

During the study period, a total of 128 cases undergoing elective laparoscopic surgeries under general anaesthesia were included in the study. They were randomly assigned, with 64 patients in each of the two groups. Inclusion criteria comprised patients with ASA grades I and II, aged between 20-60 years, of either gender, or undergoing elective laparoscopic surgery. Exclusion criteria included patients with a history of motion sickness or PONV, recent use of anti-emetic drugs within the past 24 hrs, current treatment involving steroids or opioids, pregnant individuals and obese patients.

Group I patients received ODT of Ondansetron 4 mg sublingually 30 min before induction, while Group II patients were administered Ondansetron 4 mg intravenously at the time of induction. Pre-anesthetic evaluation and written informed consent were carried out and patients fasted for 8 hrs before surgery. Ranitidine tablets (150 mg) were administered at 6 AM on the day of surgery. Premedication included glycopyrrolate (0.004 mg kg^{-1}), midazolam (0.02 mg kg^{-1}) and fentanyl (2 mcg kg^{-1}). Anaesthesia induction consisted of propofol (2 mg kg^{-1}), followed by neuromuscular blockade with vecuronium (0.1 mg kg^{-1}). Standard anaesthesia protocols were followed.

PONV was assessed in two time periods 0-6 hrs and 6-24 hrs post-surgery. Nausea was evaluated using a numerical rating scale ranging from zero to ten, with

zero indicating no nausea and ten representing the most severe nausea[5]. Nausea was defined as a subjective sensation of unpleasantness associated with an urge to vomit[8]. Vomiting was defined as the forceful expulsion of gastric contents or retching (labored, spasmodic contractions of respiratory muscles without expulsion of gastric contents). Separate episodes of vomiting were considered if they were separated by more than one minute. PONV was defined as at least one episode of either nausea or vomiting or both within the first 24 hrs postoperatively[5].

The PONV score was utilized for rating PONV severity, categorized as follows zero for no nausea and vomiting, one for nausea without vomiting, two for both nausea and vomiting and three for more than two episodes of vomiting within half an hour[11].

Patients with a PONV score exceeding two were administered rescue anti-emetic treatment in the form of dexamethasone 8 mg intravenously. Post-operative pain management utilized drugs that would not impact the study results, thus avoiding the use of tramadol or morphine.

Continuous data were presented as means with standard deviations and analyzed using an unpaired t-test (two-tailed) to compare the two groups. Categorical data were presented as frequencies and percentages and compared using the chi-square test and Fisher's exact test. A $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the patients in group I was approximately 38.5±11.5 years, while it was around 37.0±10.0 years in group II. The distribution of the sample by age groups and gender was determined to be statistically not significant (Table 1).

The PONV score in both groups exhibited a similar pattern, with no discernible difference and the count of patients falling under ASA grades I and II also demonstrated similarity ($p>0.05$) (Table 2).

Within the initial six-hour period, one patient from each group needed rescue anti-emetics. In total, seven patients from group I and six patients from group II required such intervention and this disparity was not considered statistically significant ($p>0.05$) (Table 3).

Six patients from group I and seven patients from group II experienced episodes of nausea, while seven patients from group I and six patients from group II encountered vomiting. However, none of these discrepancies were identified as statistically significant ($p>0.05$) (Table 4).

DISCUSSIONS

We administered a 4mg dose of Ondansetron based on the study conducted by Honkavara *et al*.[12], which compared two Ondansetron doses (4 mg and 8 mg). Their findings indicated that the incidence of PONV was similar in both dose groups, concluding that 4 mg of Ondansetron is a suitable alternative to 8 mg. Hedge *et al*.[5] compared the ODT of Ondansetron with intravenous Ondansetron and found a significantly higher incidence of PONV in the intravenous group compared to the ODT group. However, in our study, we did not observe a significant difference between the two groups. Bhashyam *et al*.[13] conducted a similar study and reported comparable incidences of PONV and side effects in both groups, consistent with

Table 1: Age and Gender distribution of study population

	Group I		Group II		Total		
Variable	No	Parentage	No	Parentage	No	Parentage	p-value
Age							
21-30 years	17	13.28	14	10.94	31	24.22	0.69
31-40 years	12	9.38	14	10.94	26	20.31	
41-50 years	15	11.72	19	14.84	34	26.56	
51-60 years	20	15.63	17	13.28	37	28.91	
Gender							
Male	38	29.69	35	27.34	73	57.03	0.45
Female	26	20.31	29	22.66	55	42.97	

Table 2: PONV and ASA wise distribution of study population

	Group I		Group II		Total		
Variable	No	Parentage	No	Parentage	No	Parentage	p-value
PONV scoring							
0-6 hrs	4	3.13	4	3.13	8	6.25	1
6-24 hrs	4	3.13	4	3.13	8	6.25	1
0-24 hrs	8	6.25	8	6.25	16	12.50	1
ASA Grade							
I	30	23.44	34	26.56	64	50.00	0.71
II	34	26.56	30	23.44	64	50.00	

Table 3: Rescue Antiemetics requirement in study population

	Group I		Group II		Total		
Rescue antiemetics required	No	Parentage	No	Parentage	No	Parentage	p-value
0-6 hrs	2	1.56	2	1.56	4	3.13	1
6-24 hrs	5	3.91	4	3.13	9	7.03	0.71
0-24 hrs	7	5.47	6	4.69	13	10.16	0.68

Table 4: Occurrence of complications in two groups

Complications	Group I	Group II	p-value
Nausea	6	7	0.67
Vomiting	7	6	0.67
Headache	2	3	0.75
Dizziness	4	3	0.71

our findings. Sadawarte *et al*.[14] also noted in their study that vomiting and nausea incidences were similar in patients receiving oral and intravenous Ondansetron, mirroring our results. They observed that patients tolerated Ondansetron well in either form, with no reported side effects.

In our study, patients in the ODT and intravenous groups were similar in terms of age, sex, type of surgery, ASA grades and weight (p>0.05). The average duration of the operative procedure was 96.90±18.95 min for patients in the ODT group and 94.1±20.46 min for patients in the intravenous group and this difference was not statistically significant (p>0.05).

We found an equal incidence of nausea in both groups during the first six hours, consistent with the findings of Hegde *et al*.[5], Bhashyam *et al*.[13] and Sadawarte *et al*.[14]. Hegde *et al*.[5] reported a higher incidence of nausea in the intravenous group compared to the ODT group but the difference was not statistically significant. Similarly, the clinically and statistically non-significant incidence of nausea in the intravenous group during 6-24 hrs was comparable to the ODT group, aligning with the findings of Hegde *et al*.[5], Bhashyam *et al*.[13] and Sadawarte *et al*.[14]. Hegde *et al*.[5] also found that ODT 8mg and intravenous 4mg Ondansetron groups had similar incidence of nausea during the 7-24 hrs after surgery. In our study, the incidence of nausea in the first 24 hrs in the ODT group was similar to that in the intravenous group (p>0.05), consistent with the findings of Hegde *et al*.[5], Bhashyam *et al*.[13] and Sadawarte *et al*.[14]. Bhashyam *et al*.[13] noted a significantly higher incidence of nausea and vomiting in the placebo group compared to the ODT group at various time intervals.

The incidence of vomiting in the first six hrs was 6% in both groups, similar to the findings of Hegde *et al*.[5], Bhashyam *et al*.[13] and Sadawarte *et al*.[14]. Hegde *et al*.[5] found that patients who received placebo had a significantly higher incidence of vomiting in the first six hours compared to patients in the ODT 8 mg group and intravenous group. We observed that the incidence of vomiting during 6-24 hrs was 10.93% in the ODT group and 9.37% in the intravenous group but the difference was not statistically significant. Similar findings were reported by Hegde *et al*.[5], Bhashyam *et al*.[13] and Sadawarte *et al*.[14]. Overall, in the first 24 hrs the incidence of vomiting was not statistically significant. There was no significant difference in the requirement for rescue anti-emetics, consistent with the observations of Bhashyam *et al*.[13], who noted that patients consuming rescue anti-emetics were similar in both the group G and ODF group.

The incidence of PONV in our study, as measured by the PONV score during 0-6 hrs, 6-24 hrs and 0-24 hrs, was similar in both groups, in line with the findings of Hegde *et al*.[5], Bhashyam *et al*.[13] and Sadawarte *et al*.[14].

Both ODT and IV Ondansetron had non-serious adverse effects such as short-duration headache, constipation, dizziness, diarrhea and prolongation of the QTc interval. In our study, the incidence of headache was slightly lower in the ODT group than in the IV group, which was not statistically significant. Additionally, the incidence of dizziness was slightly higher in the ODT group than in the IV group and this difference was also not statistically significant. These findings align with the study conducted by Hegde *et al*.[5], Bhashyam *et al*.[13], where no significant differences were found between the groups. Headache in our study was managed by the administration of a single dose ofparacetamol 10 mg kg^{-1} IV.

CONCLUSION

In conclusion, based on the findings of the current study, it can be affirmed that ODT Ondansetron is as effective as IV Ondansetron in preventing PONV in patients undergoing elective laparoscopic surgeries under general anaesthesia. Furthermore, ODT Ondansetron demonstrates a favorable side effect profile. It is a safe, cost-effective, well-tolerated option that is comparable in efficacy to IV Ondansetron 4 mg for preventing PONV in this patient population.

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