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RESEARCH ARTICLE
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A COMPARATIVE STUDY OF ONDANSETRON WITH ONDANSETRON AND DEXAMETHASONE IN PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV) IN LAPAROSCOPIC SURGERIES

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ABSTRACT

Background: Post-operative nausea and vomiting is the second most common symptom following surgeries and the incidence of PONV (Post-operative Nausea and Vomiting) is as high as 50-70% following laparoscopic surgeries. The combination of serotonin receptor antagonist ondansetron with dexamethasone given as prophylaxis has been proved efficacious in the prevention of PONV.

Aims and Objectives: To compare the efficacy of ondansetron alone with the combination of ondansetron and dexamethasone in the prevention of postoperative nausea and vomiting following elective laparoscopic surgeries under general anesthesia.

Methods: We randomly divided 80 patients undergoing elective laparoscopic surgeries under general anesthesia into two groups, with each group consisting of 40 patients with ASA I–II physical status. Group A received intravenous 4 mg ondansetron diluted in 4 ml normal saline and injected at the time of induction; group B was given a combination of intravenous 4 mg ondansetron and 8 mg dexamethasone by the same route. Both the groups were compared with respect to all these parameters.

Results: Postoperatively, 40% of patients in group A showed early nausea compared to 25% in group B. A significant reduction in the incidence of delayed nausea and delayed vomiting was observed with the addition of dexamethasone. A complete response was seen in 57.5% of the cases in the ondansetron group and 75% in the ondansetron and dexamethasone groups. Mean discharge times from the recovery room were comparable in both groups.

Conclusion: It can be concluded that the combination of ondansetron and dexamethasone is superior to ondansetron alone in the prevention of postoperative nausea and vomiting in elective laparoscopic surgeries under general anaesthesia.

Keywords: Ondansetron, Dexamethasone, PONV.

INTRODUCTION

Laparoscopic surgery is a principle technique for minimally invasive surgery of the abdomen, and it has been employed in multiple surgical procedures, is applicable to almost every surgical

subspecialty.[1] PONV, post-anesthetic shivering, and pain are the common postoperative patient complaints that can result in adverse physical and psychological outcomes. While PONV is considered a minor complaint and gets neglected many times, it can be quite distressing to the patient. It has been described as "a big little problem.[2]" Although PONV is rarely fatal, severe nausea and vomiting cause the risk of aspiration pneumonitis, dehydration, imbalance in electrolytes, dehiscence of wound, prolonged bleeding from the operation site, venous hypertension, hematoma, esophagus rupture, and blindness.[3,4,5] Even mild PONV can sometimes delay hospital discharge,[6] decrease patient satisfaction[7] and increase the use of medical resources. The first extensive description of the phenomenon of nausea and vomiting was published in 1948[8] by Sir John Snow.

During the Ether era, the incidence of PONV was as high as 75–80%. Change in anaesthesia practice from opioids to non-opioid or supplemented opioid anesthesia and deep ether anaesthesia to lighter and non-ether anaesthesia has led to a decrease in the incidence of PONV by almost 50%. Improvement of operative technique and identification of the patient's predictive emetogenic factors also contribute to decreased incidence of PONV. Despite the decreased incidence and severity, PONV still remains a problem of laparoscopic surgeries. In 1981, dexamethasone was first shown to be a useful antiemetic drug for cancer patients receiving chemotherapy.[9] It is one of the potent synthetic analogs of corisol. Antiemetic effects of dexamethasone may be due to central or peripheral inhibition of the production of serotonin, central inhibition of the synthesis of prostaglandins, changes in the permeability of the blood-brain barrier to serum proteins, or inhibition of the release of endogenous opioids.

The incidence of post-operative nausea and vomiting is still very high in spite of a few newer medications. It is in the range of 20-30%.[10,11] There is no single drug that can claim to be the miracle cure for this problem. Since new evidence suggests that the combination of antiemetics can act synergistically.[12-14] Combinations of drug therapy could be the answer to solve this problem. Since PONV has multiple aetiologies, targeting a single type of receptor may not be enough for many people. It is advantageous to administer medications with distinct mechanisms of action. To achieve the best outcome, different medication combinations are being tested. When combined with dexamethasone, a 5HT3 antagonist produces the best antiemetic effects.[15]

AIMS AND OBJECTIVES

The aim of the study was to compare the efficacy of ondansetron with a combination of ondansetron and dexamethasone in the prevention of postoperative nausea and vomiting in laparoscopic surgeries under general anesthesia. Primary Objectives were to compare the efficacy of a combination of ondansetron and dexamethasone with ondansetron alone in prevention of PONV in terms of early and delayed nausea, early and delayed vomiting, complete response, and requirement of rescue antiemetics.

Secondary Objectives were to study whether Dexamethasone could reduce pain on the day of surgery, to observe any side effects like headache, flushing and giddiness.

MATERIALS AND METHODS

This was a prospective randomized study conducted in the Department of Anaesthesiology at Mallya Hospital, Vittal Mallya Road, Bangalore, after obtaining approval from the institutional ethical and scientific committee over a period from June 2014 to April 2015. Eighty patients in the age group between 20 and 60 years of ASA I and II physical status undergoing elective laparoscopic surgeries under general anaesthesia was the study population. The types of surgeries included were laparoscopic cholecystectomy, laparoscopic appendicectomy, laparoscopic gynaecological surgeries (ovarian cystectomy and sterilization).

The number of patients in each group was calculated based on the data from a previous study by R. Thomas and N.Jones[16] in which a difference in response rates of 0.25 from a base line prevalence of 0.5 with 80% power at a two sided significance level of 5% was considered. With this assumption, 80% test power, and 5% margin of error, it was determined that 72 patients were needed in each study

group. The final patient number was 40 per group due to consideration of possible patient losses because of conversion of laparoscopic to open surgeries or failure to follow up. This work has used both descriptive and inferential statistical analysis. The results of categorical measures are shown in Number (%), and the results of continuous measurements are presented as Mean ± SD (Min-Max). The data was analysed using statistical tools, specifically SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0, and R environment ver. 2.11.1. Tables were created using Microsoft Word and Excel.

A simple randomization method was used, and the random numbers were generated using a computer-generated random number sequence using http://www.randomization.com. Patients were allocated into one of the two groups of 40 each in a double-blind manner.

1. Group A (n = 40) received 2 ml of Ondansetron 4 mg diluted to 4 ml with normal saline (total 4 ml).
2. Group B (n = 40) received 2 ml of ondansetron 4 mg and 2 ml of dexamethasone 8 mg (total 4 ml).

Inclusion Criteria and Exclusion Criteria

In this study, patients of ASA grade I and II physical status, patients between 20 and 60 years of age group, and patients weighing 40 to 80 kg were included. Patient refusal, pregnant women, patients with history of motion sickness, previous history of postoperative nausea and vomiting, patients who received antiemetic and/or opioids within 24 hours prior to surgery, patients on chronic steroid therapy, patients suffering from diabetes mellitus, renal and hepatic diseases, intestinal obstruction, and procedures converted from laparoscopic to open surgeries were excluded from the study.

Methodology

After taking written informed consent from the patients, a detailed clinical history was taken, and general and systemic examinations were done. History of any previous surgery, drug intake, or drug allergy was taken. Heamoglobin (Hb), total leukocyte count, random blood sugar, blood urea, serum creatinine, electrocardiogram, and chest X-ray were done on all the patients. During the preoperative visit, all patients were explained about the verbal rating scale and assessment of nausea accordingly. Tab. Alprazolam 0.5 mg was given as an anxiolysis the night prior to the surgery. No premedications were given on the day of surgery. All patients were kept fasting for 8 hours prior to surgery. In the operation theater, the anesthesia machine was checked. Appropriate sized endotracheal tubes, a working laryngoscope with medium- and large sized blades, a styllet, a suction catheter, and suction apparatus were kept ready before the procedure. Standard multiparameter monitoring (Datex Ohmedda Cardio Cap 5, madde in Finland) having continuous surface ECG, NIBP (Non-Invasive Blood Pressure) monitoring, pulse oximetry (SpO_2), and $EtCO_2$ (End Tidal Carbon Dioxide) were kept ready. Preoperative baseline values of heart rate, systolic and diastolic blood pressure, and oxygen saturation were taken prior to the start of anaesthesia. An intravenous line appropriate for surgery was secured, and crystalloid was started. The study drugs were prepared independently in 5-ml syringes and labeled as study drugs, and the administering anaesthesiologist was unaware of the identity of the drug loaded in the syringe. General anesthesia with controlled ventilation was given to all the patients. All the patients were given a standard premedication with Inj. Midazolam 0.03 mg/kg, Inj. Glycopyrrolate 0.05 mg/kg, and Inj. Fentanyl 1 mg/kg intravenously.

Patients in the two groups (group A and group B as described earlier) received the study drug as per the group allocation, intravenously at the time of induction. After preoxygenation with 100% oxygen for 3 minutes, anaesthesia was induced with Inj. Propofol 2 mg/kg intravenously, and intubation was facilitated with Inj. Suxamethonium 1.5 mg/kg intravenously. Standard intubation was done with an appropriate-sized endotracheal tube, and an end tidal CO2 monitor was connected. Ryles tube inserted for gastric emptying. Anaesthesia was maintained on a closed circuit with isoflurane 1-2%, O2, and nitrogen oxide at 50:50 and intravenous Vecuronium 0.01 mg/kg for the maintenance of paralysis. Once the pneumoperitonium was established, the intra-abdominal pressure was maintained at 12–14

mmHg throughout the surgery. Adequate hydration is maintained with crystalloids. Following the procedure, a residual neuromuscular blockade was relieved using injections of glycopyrrolate (0.005 mg/kg) and neostigmine (0.05 mg/kg). Once the patients' muscles had sufficiently recovered, they were extubated.

Monitoring

Introperative monitoring: ECG, SPO2, and EtCO2 were monitored continuously, and BP every 5 minutes in 1st hour and every 15 minutes thereafter. Duration of anesthesia, duration of surgery, and duration of CO2 insufflation were noted. Discharge time from the recovery room (discharge criteria based on modified Aldrete scoring system) is noted. Post-operative monitoring: patients were observed 24 hours postoperatively. Nausea, vomiting, and pain were recorded hourly for 4 hours and then at the end of 24 hours. Any other complications or side effects of the drugs were noted. Nausea was measured as per an 11 point verbal rating scale, with 0 = no nausea and 10 = nausea as bad as can be. Nausea occurring in the first 4 hours is taken as early nausea and 4 to 24 hours as delayed nausea.

Vomiting was scored depending on the number of episodes of vomiting. Retching is also considered an episode of vomiting. Vomiting was also divided as early vomiting occurring in 0-4 hours and delayed vomiting 4-24 hours. Repeated vomiting within 1 to 2 minutes was considered a single episode. Inj. Metaclopromide 0.15 mg/kg was given as rescue antiemetic. Pain was measured as per a visual analog scale. Pain in the first 4 hours was considered early pain and between 4-24 hours as delayed pain. Pain scale greater than 4 or, as per patient requirement, rescue analgesia with Inj. Diclofenac Sodium 75 mg IM was given.

Patients without any early or delayed nausea, not a single episode of vomiting, and not requiring rescue antiemetics in a 24-hour period were considered to have a complete response. The number of patients with complete responses in both groups was noted.

RESULTS

The mean age of both groups is comparable and does not bear a statistically significant difference ($p>0.05$).The gender distribution in both groups is comparable and does not bear any statistically significant difference. The weight distributions were comparable in both groups, with $p = 0.953$, which was statistically not significant. (P value > 0.05). Samples are matched for type of surgery with a p-value ($p = 0.675$, not significant). Types of surgeries are comparable in both groups (Table 1). The mean duration of anesthesia was statistically similar in both groups, with $P = 0.846$. The mean duration of surgery was comparable in both groups, with $P = 0.712$, not significant. The mean duration of carbon dioxide insufflation was similar in both groups, with a p-value of 0.482 (Table 2). Intraoperative heart rate changes are comparable in both groups, with a p-value of > 0.05. Heart rate did not bear any statistical significance.

SBP (mm Hg) in two groups of patients studied. No statistically significant difference was seen most of the time, except at 20 minutes and 25 minutes, where the p-value was significant. Intra-operative blood pressure in both groups was comparable. DBP (mm Hg) in two groups of patients studied. Intraoperative diastolic blood pressure was comparable in both groups with no statistically significant difference. P value>0.05. Intraoperative saturation of oxygen bears no statistical difference ($p > 0.05$), and hence SpO_2 in both groups is comparable. $ETCO_2$ (mmHg) in two groups of patients studied in which intraoperative end tidal carbon dioxide values do not bear statistical difference most of the time with p-value >0.05, except at 50 mins, 55 mins, where p-values were 0.047 and 0.035, respectively. At 60 minutes, p-value 0.088, suggestive of significance.

Hence, intraoperative end tidal carbon dioxide was comparable in both groups. Table 3 data shows that mean early nausea score is 1.98±2.13 in group A compared to 1.35±1.92 in group B with p-value 0.172, which was not statistically significant. The mean delayed nausea score was 1.43±1.89 in group A compared to 0.55±1.06 in group B, with a p-value of 0.013, which is statistically significant. Table 4 shows that in group A, early nausea was seen in 16 patients (40%), with mild nausea in 12 patients

(30%) and moderate nausea in 4 patients (10%). In group B, early nausea was seen in 10 (25%) patients, out of whom 7 (17.5%) patients had mild nausea and 3 (7.5%) patients had moderate nausea. No patients in both groups complained of severe nausea. In group B, delayed nausea was seen in 6 patients (Table 5) (15%). All 6 patients had mild nausea, and none had moderate or severe nausea. Data shows that the mean early vomiting score in group A was 0.20±0.41 compared to 0.10±0.30 in group B with a p-value of 0.215, which was not significant statistically (Table 6). The mean delayed vomiting score in group A was 0.13±0.33 compared to 0.02±0.016 in group B with a p value of 0.092, which is suggestive of significance. Mild early vomiting was seen in 8 patients (20%) of group A compared to 4 patients (10%) in the group. No patients had moderate and severe early vomiting in both groups.

Delayed vomiting in group A was seen in 5 patients (12.5%), compared to only one patient (5%) who had mild delayed vomiting. None in both groups had moderate or severe vomiting, both in the early and delayed periods. Data shows that 10 patients (25%) of group A needed rescue antiemetics compared to 4 patients (10%) of group B (Table 7). The requirement of rescue antiemetics was higher in group A than group B, with a p-value of 0.077, which was suggestive of significance. A complete response was seen in 23 patients (57.5%) of group A and 30 patients (75%) of group B. The difference was of statistically moderate significance with p = 0.025.3 (Table 8).

Comparison of incidence and severity of early and delayed pain in two groups reveals that 20 (50%) of patients in group A had no pain in the early period as compared to 55% (22/40) in group B. VAS score ≤ 4 seen 18 patients (45%) of group A compared to 17 patients (42.5%) of group B. 2 patients (5%) had VAS scores > 4 compared in group A to 1 patient (2.5%) in group B. No patients in both groups had a VAS score more than 6 with a p value of 0.977, which was not statistically significant. 75% (30) patients of group A had no delayed pain compared to 32 patients (80%) of group B. 10 patients (25%) had pain scoreless ≤ 4 compared to 9 patients (20%) patients of group B with a p-value of 0.827, which was not significant. No patients had a delayed VAS score more than 4. Comparison of requirement of rescue analgesics in two groups shows 19 patients (47.5%) of group A needed rescue analgesic compared to 12 patients (30%) of group B with a p-value of 0.108, which was not statistically significant. The mean discharge time of group A was 40.63±10.39 compared to 47.38±13.91 of group B. P value 0.615, which was not significant in comparing discharge time in two groups. Side effects were minimal in both groups, with 2 patients in group A having headaches and 1 patient having giddiness compared to group B, where none had headache and 2 patients had giddiness. None had flushing. Side effects in both groups were statistically not significant.

Surgery	**Group A**		**Group B**	
	No	**%**	**No**	**%**
Laparoscopic Appendicectomy	10	25.0	9	22.5
Laparoscopic Cholecystectomy	24	60.0	26	65.0
Laparoscopic Ovarian cystectomy	6	15.0	4	10.0
Laparoscopic sterilization	0	0.0	1	2.5
Total	40	100.0	40	100.0

Table 1: Types of Surgeries in Two Groups of Patients Studied

	Group A	**Group B**	**P-Value**
Duration of anesthesia (mins)	76.88±18.66	77.75±21.42	0.846
Duration of surgery (mins)	62.38±17.06	63.88±19.10	0.712
Duration of carbon dioxide insufflation (mins)	45.90±14.49	48.38±16.77	0.482

Table 2: Duration of Anesthesia, Surgery and Duration of Carbon Dioxide Insufflations in Two Groups of Patients Studied

	Group-A	Group-B	P-Value
Early Nausea Score	1.98±2.13	1.35±1.92	0.172
Delayed Nausea Score	1.43±1.89	0.55±1.06	0.013

Table 3: Comparison of Severity of Early and Delayed Nausea (Mean Nausea Score) between Two Groups

	Early Nausea			
	Group A		Group B	
	No	%	No	%
Mild	12	30	7	17.5
Moderate	4	10	3	7.5
Severe	0	0.0	0	0.0

Table 4: Comparison of Incidence of Early Nausea as Mild/Moderate/Severe between Two Groups

	Delayed Nausea			
	Grou A		Group B	
	No	%	No	%
Mild	9	22.5	6	15.0
Moderate	3	7.5	0	0.0
Severe	0	0.0	0	0.0

Table 5: Comparison of Incidence of Delayed Nausea as Mild/Moderate/Severe between Two Groups

	Group-A	Group-B	P-Value
Early Vomiting Score	0.20±0.41	0.10±0.30	0.215
Delayed Vomiting Score	0.13±0.33	0.02±0.016	0.092

Table 6: Comparison of Severity of Early and Delayed Vomiting (Mean Vomiting Score) between Two Groups

Rescue Antiemetics	Group A (N = 40)		Group B (N = 40)	
	No	%	No	%
No	30	75.0	36	90.0
Yes	10	25.0	4	10.0
Total	40	100.0	40	100.0

Table 7: Comparison of Requirement of Rescue Antiemetics in Two Groups

Complete Response	Group A (N = 40)		Group B (N = 40)	
	No	%	No	%
Yes	23	57.5	30	75.0
No	17	42.5	10	25.0
Total	40	100.0	40	100.0

Table 8: Comparison of Complete Response in Two Groups

DISCUSSION

The worst thing that can happen to a patient having surgery and anaesthetic is PONV. Even though we have a few newer drugs in our arsenal, the incidence of post-operative nausea and vomiting is still quite significant. In fact, it contributes so much to patient discontent that more than 70% of patients thought avoiding PONV was crucial.[17] Many anti-emetic regimens have been explored for prevention and utilised as treatments, either alone or in combination, with varying degrees of success.

For almost thirty years, individuals receiving chemotherapy have been treated with dexamethasone as an antiemetic with very few side effects. Dexamethasone is especially helpful for the prophylaxis of late nausea and vomiting, as it reduces the incidence of PONV following both abdominal and non-abdominal surgery.[15] Ondansetron works well to prevent vomiting. Although it seems to be more targeted at preventing nausea, dexamethasone also lowers the frequency of vomiting.[18] This could explain why prophylactic administration of ondansetron plus dexamethasone has been demonstrated to decrease the overall incidence of both nausea and vomiting, an effect that is probably cumulative. Laparoscopic procedures were used in this investigation because they are a separate predictor of PONV.[19] Since PONV is a known side effect of laparoscopic procedures, we felt it would be unethical to include a placebo in our investigation. Anxiety raises the probability of PONV.[20] In the trial, midazolam injection (0.03 mg/kg intravenously) was given as a premedication for anxiolysis. Dexamethasone in a dose of 8-10 mg has been used frequently in the prevention of PONV. Fujii et al. found a dose-dependent effect of dexamethasone with aplateau effect at 8 mg, which is also the most commonly used dose in many studies.[21] Hence, Dexamethasone 8 mg was used for the study. Ondansetron 4 mg was used as 4 mg is the recommended dose[22] for prevention of nausea and vomiting.

Research has demonstrated that the optimal time to administer dexamethasone was during the induction of anaesthesia. Regarding ondansetron, it was proposed that as the medication has an approximate half-life of 3.5–4 hours in adults, it might be pertinent to give it towards the end of surgical procedures lasting more than 2 hours.[23] It is believed that the timing of the antiemetic combination prior to induction would not impact the result, as the average length of the procedure in our study was approximately one hour. According to Mehernoor et al.,[24] giving patients who have already received a preventive dosage of the same antiemetic again does not effectively control developed PONV. Therefore, metoclopramide 10 mg, an antiemetic from a distinct pharmacological category, was utilised as a rescue antiemetic in this investigation.

In this study, 40% of patients in group A showed early nausea compared to 25% in group B. This is comparable to the study by Fazal Wadood[25] et al., which showed early nausea in 45% of patients in the ondansetron group compared to 25% in the combination of ondansetron and dexamethasone group in patients undergoing middle ear surgery. Delayed nausea was seen only in 15% of patients in group B compared to 30% in group A with a p-value of 0.013, which is statistically significant. Significant reduction of incidence of delayed nausea was observed with the addition of dexamethasone. These results are comparable to the study by Lopez[26] et al., where late nausea was seen in 38% of patients in the ondansetron alone group compared to 12% in the combination group. The combination group experienced decreased post-operative nausea, which is similar to the findings of V. Rajeeva et al.[27] In our study, the incidence of delayed vomiting is 12.5% and early vomiting is 20% in the ondansetron group. Similar results were seen by V. Rajeeva et al.,[26] who experienced 15% early emesis and 35% delayed emesis following ondansetron. 10% of early vomiting cases compared to 2.5% of late vomiting cases in the combo group, with a statistically significant p-value of 0.092.

This is similar to the same study as well; however, it differs with Lopez et al.[26] findings that no patient vomited during the first 24 hours, but 4% did so by then. The reason for the discrepancies in our results could be that patients in this study had significant gynecological surgery for a longer period of time than those in our study. 10 patients (25%) in group A required rescue antiemetics, (which is considered failure of prophylaxis) compared to only 4 patients (10%) in group B, with a p-value of 0.077, statistically significant. The mean discharge time from the recovery was comparable in both groups and of no statistical significance. Given their respective side effect profiles, dexamethasone and ondansetron were both well tolerated. Three cases of group A and two cases of group B had minor side effects that included headache, flushing, and giddiness. These side effects were statistically insignificant. A single dose of dexamethasone is considered safe. The study was not extended beyond 24 hours after recovery from anaesthesia and Not all the laparoscopic surgeries included in the study can be considered as the main limitations.

CONCLUSION

The present study compared the efficacy of the combination of dexamethasone and ondansetron with the efficacy of ondansetron alone in the prevention of postoperative nausea and vomiting following elective laparoscopic surgeries under general anesthesia in adults.

Different antiemetics have been studied as monotherapy or in combination of two or three drugs with different mechanisms of action. Ondansetron being a potent anti-emetic, along with Propofol used as an induction agent, which also has an antiemetic effect, prevents postoperative nausea and vomiting up to an extent. But the addition of dexamethesone further increases the efficacy, especially in the prevention of delayed nausea and vomiting, and also decreases the need for rescue antiemetics. Hence, the combination of ondansetron and dexamethasone is more advantageous than the monotherapy with ondansetron.

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