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Effect of Preoperative and Postoperative Administration of Ondansetron in Prevention of Postoperative Nausea Vomiting in Laparoscopic Gynaecological Surgeries

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Abstract
Introduction: *Females undergoing laparoscopic gynecologic procedures are more vulnerable to get distressed by Post-operative Nausea and Vomiting (PONV). We conducted this study to evaluate the preoperative versus postoperative use of ondansetron, a commonly available, cost effective anti-emetic free of any side effects in the given dosage.*
Methods: *This randomized, double-blind study was conducted on ASA grade I and II patients after assigning them randomly into groups A and B. Group A patients received 4mg (2ml) Ondansetron as premedication before induction and 2ml normal saline at the end of surgery. Group B received 2ml normal saline as premedication before induction and 4mg (2ml) Ondansetron at the end of surgery. A standard anesthesia protocol was used in all the patients. They were assessed at regular intervals; 0-2 hours in PACU then at 2, 6, 8, 12 and 24 hours for the parameters, incidence of PONV (PONV score), number of patients requiring rescue antiemetic and time at which first rescue anti emetic was given, vitals and details of any side effects.*
Results: *There was no incidence of PONV in group B against 8 % in group A. The rescue antiemetic requirement was 8 % in group A, with no requirement in group B. Both the groups were vitally stable intra and postoperatively. No clinically and statistically significant side effects were observed. Patient satisfaction was also good in group B (100 %) against 96 % in group A.*
Conclusion: *Ondansetron 4mg intravenous effectively controls PONV with 100% patient satisfaction when given post-operatively compared to its preoperative use (96%). It can be highlighted for cost effectiveness and absence of any serious side effects in the dosage given.*
Keywords: *Ondansetron, Post-operative Nausea and Vomiting, Gynaecological laparoscopy.*

Introduction

Laparoscopic procedures are more preferred options for their advantage of being minimally invasive with small incision, less painful and hence early ambulation and discharge. However, many a times PONV becomes the mainstay to delay in discharge. It sometimes has been reported to be more distressing than the pain at surgical site. Unexpected extended hospital stay causes overall patient dis-satisfaction.

Outcome of post-surgical patients is crucial; therefore, awareness, risk assessment, prediction and implementation of institutional PONV management algorithm has become an essential part

of high quality patient care equivalent to providing pain relief.[1]

Ondansetron is the prototype of 5-HT_3 antagonist class; it blocks emetogenic impulses both at their peripheral origin and their central relay. Also it is easily available, less costly and acts effectively due to its good bio-availability. Therefore we decided to present this randomized double-blind study to compare the efficacy of Ondansetron as pre-medication for PONV in laparoscopic surgery versus its use post-operatively.

Materials and Methods

This prospective, randomized, double blinded, comparative study was conducted on patients undergoing elective laparoscopic gynaecological surgeries under general anaesthesia. It was approved by institutional ethics committee. A total number of 100 patients were divided into two groups of 50 each. All the patients were informed about their participation in the study and written informed and valid consent was obtained.

Sample size was calculated by using power analysis allowing an alpha error of 5% and a beta error of 20%. Thus minimum of 49 patients were required in each group. In our study 50 patients in each group were randomly assigned to one of 2 groups by a computer generated number table and received 4mg (2ml) Ondansetron as premedication before induction and 2ml normal saline at the end of surgery or 2ml normal saline as premedication before induction and 4mg (2ml) Ondansetron at the end of surgery. ASA I indoor patients posted for laparoscopic gynaecological surgeries of 1 to 1.5 hours duration were included.

Exclusion criteria applied were patient refusal, known hypersensitivity to Ondansetron, emergency surgeries, age greater than 65 and less than 18 years, history of nausea, vomiting or retching in 24 hours before anaesthesia, or those who received anti-emetic drugs 24 hours before anaesthesia, or known motion sickness, morning sickness or gastro-oesophageal reflux disease.

After pre-anaesthetic evaluation, examination and relevant investigations, patients were explained about general anaesthesia (GA) hence likely occurrence of nausea, vomiting, retching, pain & sedation.

Patients were selected from computer generated random number table and 50 patients were assigned to each group. Study medication was prepared by a person not involved in postoperative monitoring of PONV. Two syringes of 2ml volume each were prepared for every patient.

Group A- Patients received 4mg (2ml) Ondansetron as premedication before induction and 2ml normal saline at the end of surgery.

Group B- Patients received 2ml normal saline as premedication before induction and 4mg (2ml) Ondansetron at the end of surgery.

Decoding was done at the end of study for statistical analysis.

Adequate starvation was confirmed; Pulse oximeter, ECG and NIBP were attached for intraoperative monitoring and baseline parameters. Intravenous cannula was inserted & premedication with glycopyrrolate 0.005 mg/kg, midazolam 0.03 mg/kg, fentanyl 0.001 mg/kg and either of the study drugs was given. Standardized protocol of general anaesthesia was pre-oxygenation for 3 minutes, induction with propofol 1.5-2 mg/kg. After confirming bag and mask ventilation patient was administered injection succinylcholine 1.5 mg/kg intubation done with appropriate size endotracheal tube. Anaesthesia was maintained with 50:50: oxygen: nitrous oxide and sevoflurane 1.5-2.5% as inhalational agent. Muscle relaxation was maintained by intermittent bolus doses of vecuronium (0.08 mg/kg). The patients were mechanically ventilated to keep EtCO2 between 35-40 mm Hg and nasogastric tube was inserted. For laparoscopic surgical procedure, peritoneal cavity was insufflated with carbon dioxide to keep intra-abdominal pressure <14 mm of Hg. At the end of surgery, neuromuscular block was reversed using glycopyrrolate (0.01 mg/kg) and neostigmine (0.05 mg/kg) and patients subsequently extubated after suctioning and removing the nasogastric tube. For postoperative analgesia, intramuscular diclofenac 75 mg was given. All patients were observed and all

episodes of PONV (PONV score), pulse, mean blood pressure and respiratory rate were recorded for 0-2 hours in post-anaesthesia care unit and every 2 hourly for next 8 hours, then at 12 and 24 hours in ward. The number of episodes of nausea, retching and vomiting and side effects if any were observed1. and noted at specific time intervals. Time to the first rescue antiemetic was also noted in each group. IV metoclopramide 10 mg was used as the rescue anti emetic.

Assessment of PONV:

The terms nausea, vomiting, retching, emetic episode were defined as follows-

Nausea– an unpleasant sensation associated with the awareness of the urge to vomit.

Retching- laboured, rhythmic, spasmodic, contractions of respiratory muscles without expulsion of gastric contents from mouth.

Vomiting- defined as laboured, rhythmic, spasmodic, contractions of respiratory muscles with forceful expulsion of gastric contents from mouth.

Effect of the drug on PONV was noted according to the PONV Score.[2]

No nausea, vomiting or retching=0, only nausea=1, only retching=2, retching and one episode of vomiting=3 and more than one episodes of vomiting=4.

Nausea & vomiting were observed postoperatively at 0 hours, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours and 24 hours after patient responded to verbal commands. Patients were asked if they felt nauseated in each period, with two possible outcomes: “yes” if they did for at least 10 minutes or “no”. Every episode of nausea, vomiting and vomiting requiring rescue anti emetic were recorded and results were assessed.

Statistics

Data analysis was done by using SPSS (Statistical Package for social sciences) version 20:0. Qualitative data variables were expressed by using frequency and Percentage (%) and quantitative variables by using mean and SD. 2 independent sample t-test was used to compare the significant difference between group A and group B for quantitative data variables. Chi-square and/or Fisher's exact test was used to find the significant difference between group A and Group B for qualitative data variables, p-value < 0.05 was considered as significant

Observations and Results

This study was conducted on 100 patients undergoing elective laparoscopic gynaecological surgeries under general anaesthesia. We studied the optimal timing of Ondansetron administration (preoperative versus postoperative). Study was assessed in terms of incidence of PONV in terms of nausea, retching and vomiting and the time in hours when each occurred, using PONV score. Number of patients requiring rescue antiemetic and time at which first rescue anti emetic was given was noted. Pulse, mean blood pressure, respiratory rate and details of side effects like headache, dizziness and drowsiness were also observed.

Comparison of age in study groups by using 2 independent sample t-test (p-value > 0.05) showed no significant difference between mean age (years) in group A and group B. Mean age of patients in group A was 34.68±9.36 and that in group B was 33.74 ±9.12**.**

Table. No 1 - Comparison of time of 2nd medication, Reversal time, Time of eye opening and Time of following commands (min) in study groups (Zero minutes= Time of pre-medication)-

Time of second medication, reversal, eye-opening, time of following commands was compared in two groupsby using 2 independent sample t-tests. Calculated p-value > 0.05 indicates there is no significant difference between group A and group B with respect to above parameters (min).

Time (min)	Group A		Group B		p-value
	Mean	SD	Mean	SD	
Time of 2nd Medication	54.42	18.19	55.18	18.75	0.837
Reversal time	58.38	18.17	59.82	18.47	0.695
Time of eye opening	60.38	18.17	62.40	18.38	0.582
Time of following commands	62.36	18.16	63.68	18.30	0.718

Table 2- Comparison of extubation time, duration of surgery and time of orientation in two groups (Zero minutes= Time of pre-medication)

Time of extubation, duration of surgery, and time of orientation was compared in two groups by using 2 independent sample t-tests. Calculated p-value > 0.05 shows no significant difference between group A and group B with respect to above parameters.

Extubation Time (min)	**Group (n=50)**	**Time**		**p-value**
		Mean	SD	
	Group A	63.18	18.14	0.492
	Group B	65.7	18.4	
Duration of surgery (min)	**Group (n=50)**	**Time**		**p-value**
		Mean	SD	
	Group A	56.54	18.28	0.956
	Group B	56.34	18.27	
Time of orientation (min)	**Group (n=50)**	**Time**		**p-value**
		Mean	SD	
	Group A	57.34	18.15	0.444
	Group B	70.14	18.26	

Table 3- Comparison of Mean Pulse Rate, Mean Blood Pressure and Mean Respiratory Rate at 2 hours to 24 hours

Pulse rate, blood pressure and respiratory rate at 2 hours up to 24 hours postoperative were compared in two groups by using 2 independent sample t-tests. Calculated p-value > 0.05 of all three parameters shows that there is no significant difference between these in both groups at 2 hours to 24 hours.

Mean Pulse rate Mean BP Mean R. Rate	Group A (n=50)		Group B (n=50)		p-value
	Mean	SD	Mean	SD	
2 hours	77.56 80.76 13.64	5.18 4.85 1.19	78.52 80.80 13.16	5.49 5.11 1.46	0.371 0.968 0.075
4 hours	78.32 81.28 13.36	4.49 4.67 1.17	77.46 81.14 13.00	11.32 4.57 1.29	0.619 0.880 0.148
6 hours	78.12 81.61 13.60	4.99 4.80 1.21	78.60 80.82 13.12	5.24 5.06 1.35	0.640 0.731 0.064
8 hours	78.64 81.40 13.68	5.24 4.73 1.24	78.60 80.88 13.20	5.26 4.78 1.40	0.970 0.568 0.072
12 hours	78.26 81.32 13.64	4.97 4.53 1.19	78.78 80.80 13.20	5.00 4.80 1.46	0.603 0.579 0.102
24 hours	77.88 81.36 13.68	5.07 4.47 1.17	78.40 80.70 13.24	5.22 4.87 1.45	0.615 0.482 0.098

Table 4- Comparison of PONV score in both groups at 2 hours to 24 hours-

PONV score was compared in both groups from 2 hours till 24 hours postoperative. It was found that 1 patient in group A had only nausea at 2 hours (score=1), whereas at 4 hours three patients had PONV (Total 8%).

The occurrence of PONV was nil in Group B. Total 8% patients required rescue anti emetic medication.

By using Chi-square test p-value > 0.05 indicates that there is no statistically significant difference in PONV score in group A and group B at 2 hours to 24 hours.

Time	Groups	0	1	2	3	p-value
2 hours	A B	49 50	1 0	0 0	0 0	0.999
4 hours	A B	47 50	2 0	1 0	0 0	0.240
6 hours	A B	50 50	0 0	0 0	0 0	-
8 hours	A B	50 50	0 0	0 0	0 0	-
12 hours	A B	50 50	0 0	0 0	0 0	-
24 hours	A B	50 50	0 0	0 0	0 0	-

Patient satisfaction was compared in both groups after asking PONV status. In group A 47 out of 50 patients reported 'excellent' and 3 reported 'good'. In group B all 50 patients reported 'excellent'. By using Chi-square test p-value > 0.05 (p=0.242) showed that there was no statistically significant difference in the grade of patient satisfaction in both groups.

Discussion

Prophylaxis is widely administered after routine surgeries to prevent potential adverse outcomes of inadequately controlled PONV. The etiology of PONV is complex and multifactorial involving numerous patient and anaesthesia related risk factors.[3] Reported incidence of nausea and vomiting was 51% after prior use of ondansetron during laparoscopic procedure compared to 92% in placebo group[4]. We studied ondansetron for our cases of gynaecological laparoscopy for its appropriate timing of use.

Jun Tang et al[5] studied the optimal timing of ondansetron administ ration, the cost-effectiveness,

cost-benefits, and the effect on patients' quality of life after discharge. In a placebo-controlled, double-blind study, authors studied 164 patients undergoing outpatient gynecological laparoscopic procedures with a standard protocol. Patients were randomized to receive placebo (Group A), ondansetron 2 mg at the start and 2 mg after surgery (Group B), ondansetron 4 mg before induction (Group C), or ondansetron 4 mg after surgery (Group D). The effects of these regimens on the incidence, severity, and costs associated with PONV and discharge characteristics were determined, along with the patients' willingness to pay for anti-emetics. Compared with ondansetron given before induction, that given after surgery, was associated with lower nausea scores and earlier intake of normal food. This prophylactic regimen was also associated with the highest patient satisfaction and lowest cost-effectiveness ratios. Incidence of PONV was low in 24-h follow-up period. When ondansetron was given as a "split dose," its prophylactic antiemetic efficacy was not significantly different from that of the placebo group. They concluded, the prophylactic administration of ondansetron after surgery, rather than before induction, may be associated with increased patient benefits. Therefore in our study ondansetron 4 mg effective dose was used and its optimal timing of administration (preoperatively vs postoperatively) with effect on PONV and patient satisfaction was studied.

Antiemetic activity of prophylactic administration of ondansetron 4 mg, tropisetron 5 mg and granisetron 3 mg with that of metoclopramide 10 mg and placebo in 132 patients posted for laparoscopic cholecystectomy was compared by Naguib et al[6]. All study drugs were given as a short intravenous infusion ten minutes before the induction of anesthesia. Perioperative anesthetic care was standardized in all patients. PONV was assessed at regular intervals for 24 hours post-anesthesia. If patients experienced nausea and/or vomiting, rescue antiemetic treatment (metoclopramide 10 mg IV) was administered. The percentage of emesis-free patients was 65.5%, 52%, 48%, 29.2% and 27.6% in the respective study groups. Prophylactic antiemetic treatment with ondansetron resulted in a lower incidence ($P = 0.02$) of PONV than with metoclopramide or placebo. The times at which rescue antiemetic was first received were longer ($P < 0.01$) in ondansetron group than in the placebo and metoclopramide groups.

Constipation and headache are reported as side effects of ondansetron [7]; our study patients had no clinically significant side effects. Ondansetron given postoperatively was more effective in control of PONV. In our study total incidence of PONV was 8% which is far less than that observed by other observers.

In the first two post-operative hours, our study showed no incidence of PONV in both the groups. At 2 hours and 4 hours postoperatively PONV incidence was 2% and 6% respectively in group A. Group B had no incidence of PONV at 2 and 4 hours. In both the groups no PONV incidence was observed at 6, 8, 12 and 24 hours. This implied that the maximum incidence of PONV was observed in 2 to 4 hours postoperative period and incidence declined further in 24 hours. Thus our observations are consistent with Boudner & Honakavaara[8]. Though there is no significant difference of PONV score in both the groups at 2 hour ($p>0.05$) and 4 hour ($p>0.05$), the high incidence of PONV in group A (8%) against no incidence in group B shows that ondansetron given postoperatively is more effective in prevention of PONV.

Patient satisfaction was also high in group B 100% against 96% in group A; these observations were consistent with those byJun Tang et al[5]

In the present study, the need for rescue antiemetic was 8% in group A against no requirement in group B. As the plasma half-life of ondansetron is 3-5 hours, patients receiving it postoperatively will benefit more.

According to Oddby-Muhrbeck E[2] the number of patients that remain PONV free represent a more useful primary endpoint of any PONV study. The NNT score (Number Needed Treatment) along with number of PONV events was also calculated and overall patient satisfaction were considered secondary endpoints.

From the analysis of various observers, there is still a chance that scoring systems available can prove inferior at different settings. The initial trials uniformly reported that the risk scores developed in one center can be transferred to other settings without losing their predictive properties. Some reports have also suggested customizing risk scores for specific settings to maintain accuracy. For adults the score developed by Koivuranta M et al[9] and Apfel CC[10] appear to be popular for their simplified calculations. The outcome in terms of incidence of PONV can be improved by enhancing the efficiency of scoring systems by the anesthesiologists when they decide about giving either single or multimodal prophylaxis. Thus the resources can be focused on patients who are in real need by observing a stepwise and score based antiemetic approach.

According to consensus guidelines 2014[3] optimal PONV prophylaxis includes general prevention by using two anti-emetics.

Conclusion

At the end of the study we conclude that ondansetron is effective in prevention of PONV, in patients undergoing elective laparoscopic gynaecological surgeries under general anaesthesia when given postoperatively. Also the requirement of rescue antiemetic is decreased, thus being cost effective with good patient satisfaction profile.

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