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A PROSPECTIVE RANDOMIZED CONTROL TRIAL TO STUDY THE EFFECT OF TIMING OF PRE-OPERATIVE ADMINISTRATION OF DEXAMETHASONE AND ONDANSETRON ON POST-OPERATIVE NAUSEA AND VOMITING FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Background: *Post-operative nausea and vomiting (PONV) are potential complications in patients after laparoscopic cholecystectomy. The incidence rate of PONV after laparoscopic cholecystectomy (LC) is higher than that after other types of surgery. Recent interest has been focused on the use of various antiemetics, acting at different receptors at a specific time during surgery. It has been seen that ondansetron is more effective in the initial hours of the postoperative period and dexamethasone is found to be more effective in the late postoperative period after surgery. The present study was aimed to compare the effect of timing of dexamethasone and ondansetron alone when given 45 minutes before induction or given just before induction of anesthesia for control of PONV in laparoscopic cholecystectomy.* ***Methods:*** *This was a randomized prospective study of 200 patients of both sexes in the age group of 20-60 years. Patients were ASA I –II scheduled for elective laparoscopic cholecystectomy. All the patients enrolled for the study were counselled and due informed consent was taken. The data were recorded into an excel sheet and exported to SPSS software (v21.0; IBM, USA). The study was done to compare the effect of timing of dexamethasone and ondansetron alone when given 45 minutes before induction or given just before induction for control of PONV in laparoscopic cholecystectomy, to compare the severity of PONV in all the groups and to compare the amount of rescue anti-emetic consumed in the first 24 hours postoperative period among four groups(A,B,C,D). Categorical variables were presented as frequency and percentages and compared using Chi-Square test. Quantitative variables were expressed as mean and SD, and compared using One-way ANOVA followed by Bonferroni's post-hoc correction. P-value <0.05 was considered significant.*

Results: *The incidence of PONV in group A (dexamethasone 8 mg i.v. given 45 minutes before induction) and group B (ondansetron 4mg i.v. given 45 minutes before induction) was twenty-eight percent (28%) and sixty eight percent (68%) respectively in twenty-four hours of surgery (P<0.001) which is found to be significant. The incidence of PONV in group C (dexamethasone 8 mg i.v. just before induction) and D (ondansetron 4 mg i.v. just before induction) was thirty-six percent (36%) and fifty percent (50%) respectively in twenty-four hours of surgery (P<0.01) which is significant. Incidence of PONV in Ondansetron (45 min before induction of anesthesia) was 68% compared with 50% in ondansetron (just before induction) (P<0.01). Whereas it was 28% and 36% respectively with dexamethasone (P=0.39). The number of doses of rescue antiemetics required in group A (dexamethasone 8 mg i.v. 45 minutes before induction) in 0 to 6 hours were 15 and in group C (dexamethasone 8 mg i.v. just before induction) it was 16 (P=0.91). Only 1 patient required rescue antiemetic till 24 hours in both groups from 6 to 24 hours. The number of doses of rescue antiemetic required in group B (ondansetron 4 mg i.v. 45 minutes before induction) during 0 to 6 hours were 31 whereas in group D (ondansetron 4 mg i.v. just before induction) was 14 (P<0.01). There after both the groups required 14 doses of rescue antiemetics each. So, timing of administration of ondansetron is significant. Patients of all the groups had no complaint of PONV at 24 hours of surgery. The time for demand of first rescue antiemetic was 195.71±54.83 in group A (dexamethasone 8 mg 45 minutes before induction) and 199.53±66.79 in group C (dexamethasone 8 mg i.v. just before induction) (P=0.755). So, timing of administration of dexamethasone is non-significant. The time for the demand of first rescue antiemetic was 74.27±27 in group B (ondansetron 4 mg i.v. 45 minutes before induction) and 128.71±12.64 in group D (ondansetron 4 mg i.v.*

just before induction) (P<0.0001). So, timing of administration of ondansetron is significant. ***Conclusion:*** *Based on our study it was concluded that, dexamethasone has a longer duration of action and better efficacy as an antiemetic in comparison with ondansetron in the prevention of postoperative nausea and vomiting. The timing of administration of dexamethasone with reference to induction of anesthesia has no bearing on the incidence of vomiting and rescue antiemetic requirements. The ondansetron appears to have a shorter duration of action and is associated with a higher incidence of PONV in the first six hours in comparison to dexamethasone. Timing of administration of ondansetron is important in laparoscopic cholecystectomy before surgery as it has bearing on the incidence of vomiting and rescue antiemetic required. It was also found that administration of ondansetron just before induction delays the onset of PONV, resulting in relatively lower incidence in the first 6 hours, in comparison to administration of ondansetron 45 minutes before induction.*

KEYWORDS: Post-operative nausea and vomiting (PONV), Dexamethasone, Ondansetron, laparoscopic cholecystectomy, ASA.

INTRODUCTION

Post-operative nausea and vomiting (PONV) are potential complications in patients after laparoscopic cholecystectomy. The incidence rate of PONV after laparoscopic cholecystectomy (LC) is higher than that after other types of surgery.[1,2] An incidence of 46-75% has been reported in patients undergoing laparoscopic cholecystectomy who did not receive any antiemetic medication.[3] It is a major cause of distress within 24 hours of surgery in 40-70% of patients undergoing laparoscopic cholecystectomy. The factors which result in the increased incidence of PONV are patient characteristics, surgical procedure, anesthesia technique, and postoperative care.[4,5] Several risk factors which are associated with PONV are female gender, history of the previous PONV, motion sickness, non-smoking status, anaesthetic adjuvants like (volatile anaesthetics, nitrous oxide, opioids, ketamine, neostigmine >2.5 mg in perioperative period), longer operating time, intraabdominal surgeries including gynecologic and laparoscopic surgery are associated with a higher incidence of PONV.[6] Laparoscopic cholecystectomy is the gold standard treatment of gall bladder disease. Because it has been proven that it is cost-effective compared to open cholecystectomy.[7] Despite being a minimally invasive procedure high incidence of PONV in these patients becomes the major cause of morbidity.[8] The incidence of PONV for female patients is three times that for males due to increased estrogen, and progesterone levels during their menstrual cycles.[9] Patients with history a of motion sickness have increased chances of PONV due to a low threshold for nausea and vomiting.[10] Surgical factors particularly in LC have intraperitoneal insufflation of CO2, leading to stretching of peritoneum and subsequent nausea and vomiting.[11] The factors which increase PONV after LC includes pain, dizziness, ambulation, oral intake, and opioids. Post-operative nausea and vomiting result mainly due to stimulation of various receptors in the chemoreceptor trigger zone (CTZ), which is outside the blood-brain barrier and is in contact with CSF. Its stimulation can send emetogenic triggers to the brainstem's vomiting centre to activate the vomiting reflex. The various receptors in CTZ are serotonin ($5\text{-}HT_3$), dopamine (D_2), Mu (M_1), histamine (H_1) and neurokinin (NK_1).[12] Therefore, drugs that block any single receptor type may not be completely effective to prevent PONV. Drugs that are being used for PONV prophylaxis include serotonin receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron, and ramosetron). These drugs peripherally block gut vagal afferents and act centrally in the area prostema.[13] D_2 receptor antagonists (dopamine, metoclopramide, domperidone, droperidol) also act by blocking central dopamine receptors and block H_1 and $5HT_3$ receptors. NK_1 receptor antagonists (aprepitant, netupitant/palonosetron, rolapitant, akynzeo) act mainly at nucleus tractus solitarius and areas of reticular formation blocking NK_1 receptors.[15] Antihistaminic drugs (cinnarizine, cyclizine, diphenhydramine, dimenhydrinate, doxylamine, hydroxyzine) act by blocking acetylcholine receptors in vestibular apparatus and histaminic receptors in nucleus tractus solitaries.[14] Anticholinergic drugs (hyoscine/scopolamine) act by inhibiting the binding between neurotransmitter acetylcholine and central muscarinic receptors in the cerebral cortex and pons to induce antiemetic effects.[15]

Benzodiazepines (midazolam/ lorazepam) act by causing sedation, reducing anxiety and depression of vomiting centres. Corticosteroids (dexamethasone) block the synthesis of prostaglandins leading to reduction of central serotonin activity and change of permeability of blood-brain barrier to plasma proteins. Glucocorticoid receptors on both sides of the nucleus tractus solitarius in the brain stem act to conduct the main antiemetic effect of dexamethasone.

Prophylactic use of dexamethasone has been found to be effective in reducing the incidence of PONV during 24 hours after laparoscopic cholecystectomy. It can potentiate the effect of other antiemetics by various mechanisms like prostaglandin antagonism, decreased release of endorphins, and reduction in bradykinin levels. Recent interest has been focused on the use of various antiemetics, acting at different receptors at a specific time during surgery. It has been seen that ondansetron is more effective in the initial hours of the postoperative period and dexamethasone is found to be more effective in the late postoperative period after surgery. The present study was aimed to compare the effect of timing of dexamethasone and ondansetron alone when given 45 minutes before induction or given just before induction of anesthesia for control of PONV in laparoscopic cholecystectomy.

MATERIALS AND METHODS

After approval by the institutional ethics committee, this study was carried out on 200 patients of both sexes in the age group of 20-60 years. Patients were ASA I –II scheduled for elective laparoscopic cholecystectomy. Aim and objectives of the study were to compare the effect of timing of dexamethasone and ondansetron alone when given 45 minutes before induction or given just before induction for control of PONV in laparoscopic cholecystectomy, to compare the severity of PONV in all the groups, to compare the amount of rescue anti-emetic consumed in the first 24 hours postoperative period among four groups and to note any untoward effects of the drugs. Factors for inclusion criteria were: Patients in the age group of 20-60 years, ASA I –II, patients willing to give consent for the study, no history of motion sickness, no history of previous PONV, non-smoker, Following groups of patients were excluded from the study group: Patients not willing to participate in the study, Patient on treatment with antiemetics like cyclizine, cinnarizine, scopolamine, granisetron, steroids etc. Or those who received antiemetic 48 hours before surgery, active smoker, patients with gastro-esophageal reflux disease, patient with history of PONV, pregnancy or lactation, Body mass index >35 kg/m^2 , patients with Baseline prolonged QTc interval and patients with electrolyte imbalance. After obtaining the consent and subject fulfilling the inclusion criteria, the patients were allocated in four groups randomly of 50 patients each after the informed consent. ***Group A*****:** 8 mg dexamethasone 45 minutes before induction. ***Group B*****:** 4 Mg ondansetron 45 minutes before induction. ***Group C***: 8 mg dexamethasone just before induction. ***Group D***: 4 mg ondansetron just before induction. This randomization and group allocation were computer generated by co-guide. The anesthesia provider gave drug to patient according to the group of patients. The observer was blinded to the drugs infused. However, in case of any untoward reaction or complication in postoperative period the code of the drug was opened and the patient /subject was excluded from the study. The patients were explained on the use of verbal rating scale (VRS, 0= not satisfied, 10=fully satisfied) and were instructed for overnight fasting. All patients were given premedication with oral alprazolam 0.5mg at 10 pm and at 6 am in morning on the day of surgery (with a sip of water). Patients were observed for 24 hours after surgery for any episode of nausea and vomiting every one hourly for two hours and six hourly for 24 hours. The severity of postoperative nausea and vomiting was assessed on a Numerical rating scale. (NRS 0-3). Score 0 – no nausea and no retching, Score 1 – complaining of sickness and retching, Score 2 – vomiting once or twice in 30 minutes, Score 3 – vomiting >2 times in 30 minutes.

Rescue antiemetic inj metoclopramide 10 mg iv was given to the patients with a PONV score of ≥2 or on the demand of the patient. Patient satisfaction with the management of PONV symptoms using 10 points verbal rating scale was accessed (VRS, 0=not satisfied, 10=fully satisfied). Side effects in all four groups e.g. headache, constipation, dizziness, diarrhoea, hallucinations and extrapyramidal symptoms were recorded.

Statistical analysis

The data were recorded into an excel sheet and exported to SPSS software (v21.0; IBM, USA). Categorical variables were presented as frequency and percentages and compared using Chi-Square test. Quantitative variables were expressed as mean and SD, and compared using One-way ANOVA followed by Bonferroni's post-hoc correction. P-value <0.05 was considered significant.

OBSERVATION AND RESULTS

A total of 200 patients were divided into four groups as mentioned above. Our study observed that mean age of the patients in group A (dexamethasone 8 mg 45 minutes before induction), group B (ondansetron 4 mg 45 minutes before induction), group C (dexamethasone 8 mg just before induction), and Group D (ondansetron 4 mg just before induction) was 46.5±14.0 years, 43.4±11.2 years, 44.7±9.2 years, and 44.8±8.7 years respectively.

Table 1: Comparison of age between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
Age (years)	46.5±14.0	43.4±11.2	44.7±9.2	44.8±8.7
P value	0.551#			

Data presented as mean±SD

Out of 200 patients, 37.5% patients (n=75) were males. In group A (dexamethasone 8 mg 45 minutes before induction), females were significantly higher in comparison to other groups (P=0.028).

Table 2: Comparison of gender distribution between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
Male	10	20	22	23
Female	40	30	28	27
P value	0.028*			

Our study observed that the mean duration of surgery of the patients in group A (dexamethasone 8 mg 45 minutes before induction), group B (ondansetron 4 mg 45 minutes before induction), group C (dexamethasone 8

mg just before induction), and Group D (ondansetron 4 mg just before induction) was 51.9±7.7 minutes, 55.0±8.9 minutes, 51.3±6.7 minutes, and 51.6±7.5 minutes respectively. There was no significant difference in the duration of surgery between different groups of patients (P=0.064).

Table 3: Comparison of duration of surgery between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
Duration of surgery (minutes)	51.9±7.7	55.0±8.9	51.3±6.7	51.6±7.5
P value	0.064#			

Data presented as mean±SD

In this study, 10% of patients in group B (ondansetron 4mg 45 min before induction) and 8% in group D (ondansetron 4mg just before induction) complaint of sickness and retching while 4% of patients in both groups had an incidence of vomiting. In group A (dexamethasone 8 mg 45 min before induction) and group C (dexamethasone 8 mg just before induction), none of the patients had any incidence of nausea and vomiting. At baseline, the PONV score was comparable between the groups (P=0.364). The PONV score at baseline between groups was non-significant.

Table 4: Comparison of PONV score at baseline between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	50	45	50	46
Complaining of sickness and retching	0	3	0	2
Vomiting once or twice in 30 minutes	0	1	0	1
Vomiting >2 times in 30 minutes	0	1	0	1
P value	0.364#			

Data presented as numbers.

Table 5: Comparison of PONV score at 2 hours between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	45	46	43	46
Complaining of sickness and retching	3	2	5	2
Vomiting once or twice in 30 minutes	1	2	2	1
Vomiting >2 times in 30 minutes	1	0	0	1
P value	0.851#			

Data presented as numbers.

Table 6: Comparison of PONV score at 4 hours between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	47	41	46	45
Complaining of sickness and retching	2	5	3	3
Vomiting once or twice in 30 minutes	1	2	1	1
Vomiting >2 times in 30 minutes	0	2	0	1
P value	0.720#			

Data presented as numbers.

Table 7: Comparison of PONV score at 6 hours between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	45	46	45	48
Complaining of sickness and retching	3	3	3	2
Vomiting once or twice in 30 minutes	1	1	2	0
Vomiting >2 times in 30 minutes	1	0	0	0
P value	0.798#			

Data presented as numbers.

Table 8: Comparison of PONV score at 12 hours between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	49	42	48	43
Complaining of sickness and retching	1	7	2	5
Vomiting once or twice in 30 minutes	0	1	0	2
Vomiting >2 times in 30 minutes	0	0	0	0
P value	0.103#			

Data presented as numbers.

Table 9: Comparison of PONV score at 18 hours between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	50	46	50	47
Complaining of sickness and retching	0	2	0	2
Vomiting once or twice in 30 minutes	0	2	0	1
Vomiting >2 times in 30 minutes	0	0	0	0
P value	0.243#			

Data presented as numbers.

Table 10: Comparison of PONV score at 24 hours between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	50	50	50	50
Complaining of sickness and retching	0	0	0	0
Vomiting once or twice in 30 minutes	0	0	0	0
Vomiting >2 times in 30 minutes	0	0	0	0
P value	-			

Data presented as numbers.

Table 11: Comparison of overall PONV score at 24 hours between groups.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
No nausea and vomiting	36	16	42	25
Complaining of sickness and retching	9	22	13	16
Vomiting once or twice in 30 minutes	3	9	5	6
Vomiting >2 times in 30 minutes	2	3	0	3
P value	0.003**			

Data presented as numbers.

Table 12: Time to first Rescue antiemetic.

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
Time (Min)	195.71±54.83	74.27±15.1	199.53±66.79	128.71±12.64
P value	<0.001***			
	Group A vs. Group B <0.0001; Group A vs. Group C =0.7553 Group A vs. Group D <0.0001; Group B vs. Group C <0.0001 Group B vs. Group D <0.0001; Group C vs. Group D <0.0001			

Overall total doses of rescue antiemetic during 24 hours

Over the period of 24 hours, total numbers of rescue anti-emetic doses in patients in group A (dexamethasone 8 mg 45 minutes before induction), in group B (ondansetron 4 mg 45 minutes before induction), in group C (dexamethasone 8 mg just before induction), and in group D (ondansetron 4 mg just before induction) were 16, 45, 18, and 32 respectively. We also observed that the total number of doses was significantly higher in group B (ondansetron 4 mg 45 minutes before induction) and D (ondansetron 4 mg just before induction) in comparison to group A (dexamethasone 8 mg 45 minutes before induction) and C (dexamethasone 8 mg just before induction) (P=0.026). The results of the comparison of the total number of doses of rescue antiemetic among all four groups were significant.

Table 13: Rescue antiemetics (total number of doses)

	Group A (n=50)	Group B (n=50)	Group C (n=50)	Group D (n=50)
Baseline	0	5	0	5
2-hour	6	6	7	5
4-hour	3	13	4	6
6-hour	6	7	5	2
12-hour	1	9	2	9
18-hour	0	5	0	5
24-hour	0	0	0	0
Total	16	45	18	32
P value	0.026*			

DISCUSSION

Post-operative nausea and vomiting (PONV) are potential complications in patients after laparoscopic cholecystectomy. The incidence rate of PONV after laparoscopic cholecystectomy (LC) is higher than that after other types of surgery.[16] It is a significant cause of distress within 24 hours of surgery in 40-70% of patients undergoing laparoscopic cholecystectomy. Laparoscopic cholecystectomy is the gold standard treatment of gallbladder disease. PONV is the second most common complaint after pain being the most common.[17] PONV remains an important problem in modern anesthesia because of the multitude of consequences such as delayed recovery, unplanned hospital admission, pulmonary aspiration, dehydration, wound dehiscence and prolonged hospital stay. Cholecystectomy, gynaecological and laparoscopic surgeries are associated with an increased risk of PONV. Surgical factors particularly in LC required intraperitoneal insufflation of CO2, leading to stretching of peritoneum and subsequent nausea and vomiting. Despite the high incidence of PONV, there are relatively few published studies that compare the effect of timing of antiemetic drugs in specific disorders. The present study was aimed to compare the effect of timing of dexamethasone and ondansetron alone when given 45 min before induction or given just before induction for control of PONV in laparoscopic cholecystectomy. The dexamethasone proved to be far more efficacious in preventing PONV compared to ondansetron when given pre-emptively. Dexamethasone when given 45 minutes before induction the incidence of PONV was twenty-eight percent whereas when ondansetron was given 45 minutes before the incidence of PONV was sixty-eight percent. Gupta et al[8] (2005) compared the role of pre-operative dexamethasone as prophylaxis for PONV in laparoscopic surgery. The study included 200 patients divided into two groups; one group received 5mg of dexamethasone and the other group received 4mg ondansetron, 90 min before induction of anesthesia. It was observed that in group one 24% had nausea and 12% had vomiting as compared in group two 30% had nausea and 18% had vomiting after 24 hours of surgery. So, authors concluded that dexamethasone is more effective in the management of PONV than ondansetron. The results of this study were similar to our study with respect to the incidence of PONV.

Dexamethasone when given at the time of induction the incidence of PONV in this group was thirty-six percent, and in the ondansetron group when it was given at the time of induction it was fifty percent, again highlighting the fact that when given at the time of induction along with other anaesthetic agents the dexamethasone is more efficacious in preventing postoperative nausea and vomiting. In the dexamethasone group when administered 45 minutes before induction the total no of rescue antiemetic (inj metoclopramide 10 mg) required was fifteen in the first six hours and at the end of 24 hours, this incidence increased to sixteen from fifteen, which was not statistically significant. This highlights that the antiemetic effect of dexamethasone lasts 24 hours or longer.

D'Souza et al (2011)[18] conducted a prospective study comparing the efficacy of ondansetron and dexamethasone in preventing PONV in patients of laparoscopic gynecologic surgeries. In this study in 93 women, 3 groups were of patients who received 4 mg dexamethasone, 8 mg dexamethasone and 4 mg of ondansetron respectively. The incidence of PONV during the 24 hours postoperatively was highest (61%) in the ondansetron group. It was also observed that during the first 3 hours the incidence of PONV in the ondansetron group was also higher: 51.6 % as compared with 22.6 % and 36.6% in the dexamethasone 4mg and 8 mg groups. In dexamethasone 4mg group the incidence of request for rescue antiemetic was significantly lower as compared to other groups i.e., 0 % as compared to the 6.7% and 16.1% in the dexamethasone 8 mg and ondansetron 4 mg group respectively. The authors finally concluded that dexamethasone was much more cost-effective and efficacious in preventing PONV. The results of this study were similar to our study with respect to the incidence, duration of antiemetic effect and need for a dose of rescue antiemetic.

Wang et al[19] (2000) studied the effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting in a randomized controlled study. They evaluated the effect of 10 mg of iv dexamethasone on patients undergoing abdominal total hysterectomy under general anesthesia. Group 1 received dexamethasone before induction. Group 2 received dexamethasone at the end of anesthesia and group 3 received placebo (saline).

The incidence of PONV in 0 to 2 hours of post-period were as group 1 (15%) group 2 (45%) and group 3 (53%). And less no of rescue antiemetic requested by group 1 (8%) than group 2 (30%) and group 3 (35%) respectively. During postoperative period of 24 hours both in group 1 and 2 reported less frequent incidence of PONV (25% and 28%) and requested fewer no of rescue antiemetics (13% and 15%) than those in group 3 (35% and 38%). So, authors concluded that prophylactic i.v. administration of dexamethasone immediately before the induction of anesthesia rather at the end of anesthesia, was more effective in preventing postoperative nausea and vomiting. The result of this study is similar to our study in view of a smaller number of doses of rescue antiemetics required in the prevention of postoperative nausea and vomiting if dexamethasone is used in patients undergoing surgery. In the ondansetron group (B) where it was given 45 minutes before induction the total number of rescue antiemetic doses was forty-five, and the total no of rescue antiemetic doses decreased to thirty-two when it was given at the time of induction in the group (D), which is statistically highly significant. This highlights that the ondansetron is a relatively shorter-acting drug and timing of administration is important as more number patients required treatment of postoperative nausea and vomiting with the passage of time. Cruz et al(2008)[20] studied the effect of timing of ondansetron administration to prevent PONV in patients of plastic surgery. The study group received i.v 4mg of ondansetron prior to induction of anesthesia. And the control group received i.v 4 mg of ondansetron 30 min prior to the end of surgery.

The effect of PONV was noted in both groups. No significant difference was found in both the groups regarding early PONV i.e., first six hours ($p>0.05$). But a significant difference was found in late post-operative (i.e., from the sixth hour to twenty-four hours) nausea score between two groups (control group 17% vs study group 20%) and late postoperative vomiting score (control group 17% vs study group 8%). So, the authors concluded that late administration of ondansetron (before 30 minutes prior to completion of surgery) is effective in the prevention of PONV in the long duration of surgeries. The result of this study is similar to our study regarding late administration of ondansetron in the prevention of postoperative nausea and vomiting.

Sun et al[21] (1997) studied the effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery in which patients were divided into three groups. Group 1 received 5ml of saline (placebo) before induction of anesthesia and at the end of surgery. Group 2 received 4mg ondansetron in 5ml before induction of anesthesia and saline 5 ml at the end of surgery. Group 3 received saline 5ml before induction and 4mg of ondansetron in 5ml at the end of surgery. The incidence of PONV before induction in group 2 (20% ondansetron and 68% saline) and at the end of surgery in group 3 (60% saline and 4% ondansetron) compared to the placebo group (80% and 12%) respectively. Also, there was also less need for rescue antiemetic drugs in a group where it was given at the end of surgery 36% compared to 64% when ondansetron was given before induction. Therefore, the authors concluded that ondansetron is more effective in PONV if given at the end of surgery. A similar observation was noted in our study with ondansetron with reference to the timing of administration. The time for the demand of the first rescue antiemetic was 195.71±54.83 minutes in dexamethasone (group A) where it was administered 45 minutes before induction time. In our study when dexamethasone was administered at the time of induction (group C) the time for demand of first rescue antiemetic increased from 195.71±54.83 min to 199.53±66.79 minutes which was statistically not significant. This shows that the timing of administration of dexamethasone does not have any effect on the time of occurrence of postoperative nausea and vomiting. When ondansetron was administered 45 minutes before induction in (group B) the time for the demand of first antiemetic was 74.27 ±15.1 minutes, whereas when ondansetron was administered at the time of induction in (group D) the time of demand of first rescue antiemetic increased to 128.71±12.64 minutes which was highly significant. This highlights that the ondansetron has a shorter duration of action and the timing of administration with reference to induction of anesthesia is important. Dexamethasone is an inexpensive and effective antiemetic drug with minimal adverse effects after a single-dose administration. Prophylactic use of dexamethasone has been found to be effective in reducing the incidence of PONV during 24 hours after laparoscopic cholecystectomy. Ondansetron is a serotonin receptor antagonist. These drugs peripherally block gut vagal afferents and act centrally in the area prostema. It has been found to be effective in reducing the incidence of PONV after laparoscopic cholecystectomy up to 5-6 hours of surgery as the maximum duration of this drug is 4 to 6 hours. With better understanding pathophysiology of PONV and the pharmacology of drugs, the timing of these drugs seems important and logical in the management of PONV. In our study, there are few limitations. We have included only ASA I and II physical status patients in our study. ASA III and IV physical status patients could not be included in view of ethical issues, other limitations were due to fixed intraoperative anaesthetic techniques. For patients with certain diseases like diabetes and hypertension preoperative medication could not be stopped which also interfered with the incidence of postoperative nausea and vomiting.

CONCLUSION

Based on our study it was concluded that, dexamethasone has a longer duration of action and better efficacy as an antiemetic in comparison with ondansetron in the prevention of postoperative nausea and vomiting. The timing of administration of dexamethasone with reference to induction of anesthesia has no bearing on the

incidence of vomiting and rescue antiemetic requirements. The ondansetron appears to have a shorter duration of action and is associated with a higher incidence of PONV in the first six hours in comparison to dexamethasone. Timing of administration of ondansetron is important in laparoscopic cholecystectomy before surgery as it has bearing on the incidence of vomiting and rescue antiemetic required. It was also found that administration of ondansetron just before induction delays the onset of PONV, resulting in relatively lower incidence in the first 6 hours, in comparison to administration of ondansetron 45 minutes before induction.

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