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Prevention of Post-Operative Nausea and Vomiting Following Laparoscopic Cholecystectomies - Comparative Evaluation of Some Common Anti-Emetics

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Abstract: *Post operative nausea and vomiting (PONV) are common even with the use of conventional antiemetics prophylactically. In a randomized double blind study, 90 patients aged 20-65 years belonging to ASA I or II class, undergoing laparoscopic cholecystectomy patients under general anesthesia were divided into 3 groups of 30 patients each and received either 40 mcg/Kg of Granisetron plus dexamethasone (Group A) or 0.1mg/Kg of Ondansetron plus dexamethasone (Group B) or 6ml of 0.9% Saline (Group C) pre- operatively. Patients were observed for 24 hours post operatively. The incidence of PONV was recorded to be 56.66% when no anti-emetic prophylaxis was used. A cumulative complete response (no nausea, no retching, no vomiting and no need of rescue anti emetic) was observed in 80% patients in granisetron-dexamethasone group as compared to 83.33% patients in ondansetron-dexamethasone group and only 43.33% in placebo group. Only 7(23.33%) patients in granisetron-dexamethasone group and 6(20%) patients in ondansetron-dexamethasone group required rescue anti emetics as compared to 15(50%) patients in placebo group. It was concluded that the incidence of PONV is significantly reduced by the prophylactic use of ondansetron-dexamethasone and granisetron-dexamethasone.*

Keywords: *Dexamethasone, Granisetron, laparoscopic cholecystectomy, Ondansetron, PONV,*

I. Introduction

Post-operative nausea vomiting (PONV) is a common problem and most frequent side effect during the first 24 hours after emergence from anaesthesia, it is usually self limiting but can cause significant morbidity.[1] The average rate of PONV is approximately 20-30%.In certain patient population undergoing specific outpatient procedures, the incidence can still be as high as 80% [2]. After laparoscopic cholecystectomy up to 70% patients have PONV if they are not on any anti-emetic prophylaxis [3].

The process of emesis is coordinated by a multiple array of central emetic receptors in the lateral reticular formation of the midbrain stem adjacent to chemoreceptor trigger zone and solitary tract nucleus. It has been speculated that blockade of these receptors is an important mechanism of action of the currently used anti-emetic drugs.[4] There are multiple contributing factors that stimulate the vomiting reflex in PONV; yet no single component is typically the causative factor. The anesthesia related factors associated with emesis included premedication, inhalational agents, opioids, postoperative pain, patient mobilization, hemodynamic instability and initiation of oral intake.[5] Surgery related factors include operative procedures, length of surgery, blood in G.I. tract, forcing oral intake, opioid analgesics, premature ambulation (postural hypotension) and pain.[6] Due to the multifactorial nature of PONV, the effectiveness of any single anti-emetic agent given prophylactically as monotherapy is limited. More recent studies have shown that the combination of anti-emetic medication acting at different emetogenic receptor sites significantly improves effectiveness compared with the single agent treatment. The purpose of combination therapy is to obtain homogenous multireceptor blockade. Dexamethasone has also been found to be an effective anti-emetic though exact mechanism is not known [7]. The combination of dexamethasone with 5-hydroxytryptamine (5-HT3) receptor antagonist is superior to a serotonin receptor antagonist alone in preventing post-operative nausea and vomiting [8].

In the present study we have used 5-HT3 receptor antagonists granisetron and ondansetron along with dexamethasone to find out an effective combination for prophylaxis of PONV following general anesthesia in laparoscopic cholecystectomy patients.

II. Patients And Methods

This prospective, randomized, double blind , placebo controlled trial included 90 patients aged 20-65 years, belonging to either ASA I or II class, undergoing laparoscopic cholecystectomy under general anesthesia.

A proper approval from the local ethics committee and informed consent was taken from the patients

included in the study. The patients were randomly allocated into three groups of 30 patients each and received one of the following treatment regimens:

Group A – Patients received Granisetron 40 mcg/kg I.V. plus Dexamethasone 8 mg I.V (diluted to a volume of 6ml).

Group B –Patients received Ondansetron 0.1 mg/kg I.V. plus Dexamethasone 8 mg I.V (diluted to a volume of 6ml).

Group C –Patients received 6 ml of 0.9% saline I.V. as placebo (control group).

Patients with a history of motion sickness, previous history of PONV, vestibular disease and those who had received anti-emetics 24 hours prior to surgery were excluded from the study. The patients were prepared by overnight fasting and no pre-medication was given to any patient.

In the operating room intravenous line (I.V) was secured and patient monitoring included continuous record of ECG, SPO2, blood pressure, heart rate and ETCO2. All the patients were pre-oxygenated for 3 minutes and the study drugs were administered intravenously immediately before induction. The Anesthetic technique was standardized. Anesthesia was induced with propofol 2 mg/kg, morphine 0.1 mg/kg and vecuronium 0.1 mg/kg (to facilitate intubation) and maintained with 66% nitrous oxide in oxygen, and incremental doses of vecuronium and supplemented with 0.5-1% of halothane. After tracheal intubation, a nasogastric tube was inserted to clear stomach of any air or secretions present. Intermittent positive pressure ventilation was controlled mechanically and ETCO2 maintained between 30-35 mm Hg.

During the surgery the patients were positioned in reverse Trendelenberg position with the right side of the table elevated. The abdomen was insufflated with carbon dioxide and intra-abdominal pressure of 10-12 mm of mercury was maintained with flow rate ranging from 1.8-2 liters/minute. Duration of anaesthesia, duration of surgery and duration of carbon dioxide insufflations were recorded in each patient. Paracetamol 15mg/kg i/v was given towards the end of surgery. At the end of surgery neuromuscular blockade was antagonized by 10 mcg/kg of glycopyrrolate and neostigmine 50mcg/kg intravenous. The trachea was extubated when patient was fully awake.

All the episodes of PONV (nausea, retching and vomiting) were recorded during the first 24 hours after anaesthesia by direct questioning the patients or their attendants. The patient was asked whether he felt nauseated and if retching or vomiting had occurred with only two possible answers (yes/no). The rescue medication was given in the form of metoclopramide 0.2 mg/kg. Pain relief in post-operative period was provided with 1.5 mg/kg of Diclofenac sodium intramuscular as and when needed. Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the labored, spasmodic, rhythmic contractions of respiratory muscles and vomiting was defined as forceful expulsion of gastric contents from the mouth. Complete response was defined as no nausea or retching or vomiting and no need of rescue medication in the post-operative period. The details of any adverse effects if present were also recorded throughout the study.

Data collected was statistically evaluated and analyzed. Parametric data was expressed as mean±SD, thereby the intergroup comparison were made by student's t-test. The test was two sided and referred for p-value for its significance. P-value less than 0.05 ($p<0.05$) was taken to be statistically significant. The analysis was performed on SPSS version 11.3, statistical software for social sciences, Chicago U.S.A for windows.

III. Results

There was no statistical difference between the groups with regards to age, weight, duration of surgery and anesthesia, duration of CO2 insufflation (Table 1)

Table 1: Comparison of demographic data and other characteristics in two groups

Characteristics	Group A mean±SD	Group B mean±SD	Group C mean±SD	P value	Remarks
Age (years)	32.5±11.4	30.1±11.0	29.2±10.3	0.134	NS
Weight (Kgs)	55.2±8.4	54.6±9.4	55.1±8.5	0.754	NS
Duration of Anaesthesia in minutes	70.2±10.6	68±8.8	69.1±7.4	0.22	NS
Duration of Surgery In minutes	61.5±8.4	63.9±10.2	62.4±9.3	0.216	NS
Duration of CO2 insufflation in minutes	51.5±9.1	56.7±8.1	59.3±10.7	0.19	NS

The cumulative incidences of post-operative nausea and vomiting in our study during 0-24h were 26.66% in granisetron plus dexamethasone group and 20% in ondansetron plus dexamethasone groups. (Table 2)

Table 2: Comparison of nausea, retching and vomiting in the study period of 3 groups.

PONV episode	Group A	Group B	Group C	P value	Remarks
Nausea	08(26.66%)	06(20%)	17(56.66%)	0.005	HS
Retching	07(23.33%)	04(13.33%)	12(40%)	0.05	S
Vomiting	06(20%)	04(13.33%)	12(40%)	0.03	S

HS: Highly significant. S: Significant.

On comparing the postoperative nausea and vomiting among the groups we found out that during the 0-3hr post-anesthesia 7 (23.33%) patients in group A as compared to 12 (40%) patients in group C had post-operative nausea and vomiting and the difference was statistically insignificant. During next 3-24hr study period the PONV was observed in 6 (20%) patients in group A and 17 (56.66%) patients in group C. The difference was statistically significant when group C was compared to group A . (Table 3)

Table 3: Comparison of PONV between Group A and Group C during 24 hours study period.

Time Interval (24 hours)	Group A No. (%)	Group C No.(%)	P value	Remarks
0-3 h	7(23.33%)	12(40%)	0.15	NS
3-24 h	6(20%)	17(56.6%)	0.015	S

Comparing group B versus the placebo group C, during 0-3hr post anesthesia we found that 6(20%) patients in group B as compared to 12(40%) patients in group C had post-operative nausea and vomiting. Being statistically significant during this early period ($p<0.05$), but during next 3-24hr study period post-operative nausea and vomiting was observed in 5(16.66%) patients in group B and 17(56.66%) patients in group C. Statistically it was found to be highly significant ($p=0.001$). (Table 4)

Table 4: Comparison of PONV between Group B & Group C during 24 hours study period.

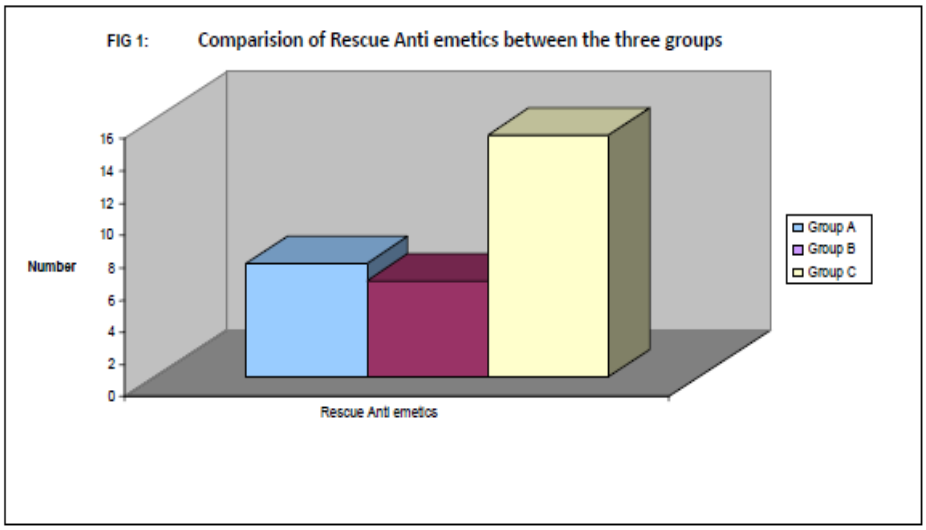
Time Interval (24 hours)	Group B No. (%)	Group C No.(%)	P value	Remarks
0-3 h	6 (20%)	12(40%)	<0.05	S
3-24 h	5(16.66%)	17(56.66%)	0.001	HS

Comparing Group A versus Group B, we observed that during 0-3hr study period 7(23.33%) patients in group A as compared to 6(20%) patients in group B had nausea and vomiting post operatively. The difference was found to be statistically insignificant ($p=0.67$). During next 3-24hr study period 6(20%) patients in group A as compared to 5(16.66%) in group B had nausea and vomiting .The statistical result was again insignificant ($p=0.68$). Complete response observed in group A was 80% and group B was 83.33% (Table 5)

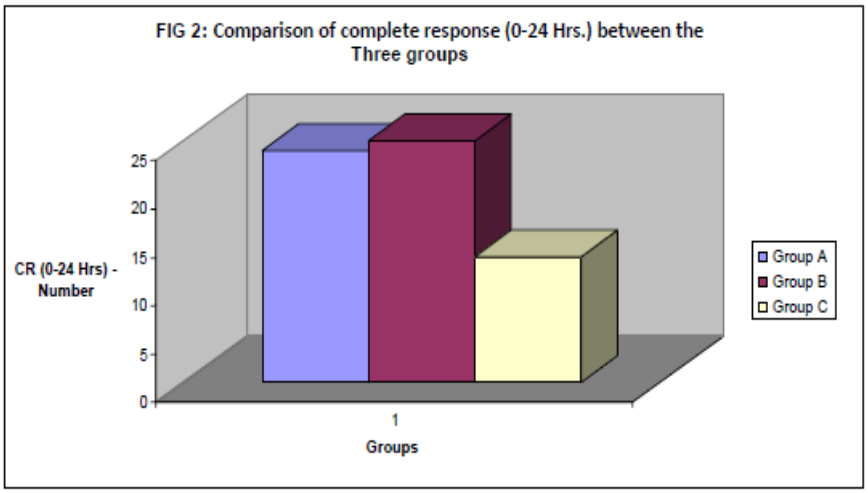
Table 5: Comparison of PONV between Group A and Group B during 24 hours study period.

Time Interval (24 hours)	Group A No. (%)	Group B No. (%)	P value	Remarks
0-3 h	7(23.33%)	6(20%)	0.67	NS
3-24 h	6(20%)	5(16.66%)	0.68	NS

Out of thirty patients in each group only 7(23.33%) patients in granisetron-dexamethasone group and 6(20%) patients in ondansetron-dexamethasone group required rescue antiemetics as compared to 15(50%) patients in placebo group.Fig1



Complete response (no Nausea, no retching and no vomiting) was observed in 24 patients (80%) in group A, 25 patients (83.33%) in group B and 13 patients (43.33%) in group C (Fig: 2)



Minimal adverse effects were reported and were common in all the three groups. Headache and dizziness were the most common adverse effects observed in all the three groups.

IV. Discussion

Postoperative Nausea and vomiting is not simply an unpleasant and distressing experience, but may be a major factor in upsetting post-operative convalescence. PONV is the most frequent side effect during the first 24 hours after emergence from anesthesia. It can cause significant morbidity[10] Availability of large number of drugs in use, and continued research for newer drugs to treat emesis indicates the magnitude of the problems and lack of efficacy of different drugs[11]. The overall incidence of post-operative nausea and vomiting during the first 24hours following surgery ranges from 20%-30%.After laparoscopic cholecystectomy it is reported to be as high as 40%-70% [12]. Because the causes of PONV are multifactorial, no single antiemetic medication has been 100% effective for its prevention. Anti-emetics are the main stay of therapy for PONV. The main groups of drugs used in the treatment are phenothiazines, butyrophenones, anticholinergic, antihistamines, serotonin antagonists, benzamides and steroids. [2]

Most of the anti-emetics are known to cause drowsiness and extrapyramidal side effects. As a result of continuous search for better anti-emetics, 5HT3 receptor antagonists were introduced with a greater margin of safety. The introduction of this class of drugs in the 90s represented a major improvement in the prevention and treatment of PONV. The 5HT3 receptor antagonists are highly selective and potent antagonists of these receptors in the brain and gastro intestinal tract and possess a good efficacy, are free of significant side effects and have negligible drug interaction [13]. Dexamethasone was traditionally used in chemotherapy related emesis but has also been found to be effective in PONV .It has anti emetic effects that are comparable with

conventional anti emetic agents. Anti- emetic efficacy is better when it is used in combination with another anti emetic drug than when it is used alone[16] .

In our study post-operative nausea and vomiting was observed in 17(56.66%) patients who did not receive any anti emetic prophylaxis (group C) and in a study conducted by Fujii Y et al (1997) the incidence of post operative nausea and vomiting after laparoscopic cholecystectomy was reported to be 46%.**[14]** The cumulative incidences of post-operative nausea and vomiting in our study during 0-24h were 26.66% in granisetron plus dexamethasone group and 20% in ondansetron plus dexamethasone group. This is comparable with a study conducted by Sriraman R et al (2007)[16] where incidence of postoperative nausea was 30% in granisetron plus dexamethasone group and 20% in ondansetron plus dexamethasone.

On comparing the postoperative nausea and vomiting profile amongst the three groups we found that during the 0-3 hour study period the variance in PONV amongst groups A & C was non-significant but in the next 3-24 hour study period PONV was observed in 6 (20%) patients in group A and 17 (56.66%) patients in group C ($p = 0.015$), hence complete response was observed in 24 (80%) patients who received granisetron (40mcg/kg) plus dexamethasone (8mg) as compared to 43.33% in placebo group. In a study carried by Sriraman R et al (2007)**[16]** complete response was observed in 68% patients when same drug combination was given as prophylaxis in gynaecological laparoscopy, whereas in a different study conducted by Biswas B.N and Rudra A (2003)**[14]**complete response was observed in 95% of the patients with the same combination of the drugs used for emetic prophylaxis in laparoscopic cholecystectomy. Our observation of 80% complete response is slightly higher than the 68% response of Sriraman et al but is slightly lower than the 95% response of Biswas and Rudra (2003)**[11]**. These mild differences could have been due to some differences in the selection of patients and differences in response of different populations comprising the studies concerned and surgical procedure involved.

Similarly on comparing groups B & C, in the 0-3 hour period PONV variance was insignificant but during next 3-24hr study period post-operative nausea and vomiting was observed in 5(16.66%) patients in group B and 17(56.66%) patients in group C being statistically highly significant ($p=0.001$). Also a complete response was observed in 25(83.33%) patients who received ondansetron (0.1mg/kg) plus dexamethasone (8mg) as compared to 43.33% in placebo group, similar to the study by Sriraman R et al (2007). **[16]**

Finally on comparing the granisetron plus dexamethasone v/s ondansetron plus dexamethasone) groups, non significant difference was found between the groups in the 0-3 hr. Period ($p=0.67$) and during next 3-24hr study period 6(20%) patients in group A as compared to 5(16.66%) in group B had nausea and vomiting .The statistical result was again insignificant ($P=0.68$).Complete response observed in group A was 80% and group B was 83.33%. Sriraman R et al (2007) showed complete response in 68% patients given granisetron plus dexamethasone and in 78% patients given ondansetron plus dexamethasone in patients undergoing gynaecological laparoscopy. The results were statistically insignificant and comparable to our study. A study conducted by Tong J G et al (2005) **[10]** showed statistical insignificant variations in complete response when similar drug combinations were used in patients undergoing abdominal hysterectomy. The study is again comparable with our study. Both the combinations are equally effective in the prevention of early and late PONV.

In our study rescue anti emetics were only used in 7 patients (23.33%) in granisetron plus dexamethasone group as compared to 6 patients (20%) in ondansetron plus dexamethasone group and 15 patients (50%) in placebo group. This shows that requirement of rescue anti emetics was considerably less in combination groups of our study as compared to the placebo group. In a study conducted by Sriraman R et al in (2007)[16] showed that the requirement of rescue anti emetics was 20% in granisetron-dexamethasone group and 14% in ondansetron-dexamethasone group. These observations are again comparable to our study

Headache and dizziness were the most common adverse effects observed in all the three groups. High doses and prolonged use of dexamethasone is known to cause side effects such as infection, glucose intolerance, adrenal suppression, delayed healing in surgical settings but a single dose of dexamethasone is not known to cause any such complications (Wang W et al 2000)**[17].**As such there is no harm in using dexamethasone in prophylaxis of PONV in combination with other anti emetics.

V. Conclusion

We conclude that a high incidence of PONV exists following general anesthesia for laparoscopic cholecystectomies (56.66%). It is also concluded that the incidence of PONV is significantly reduced by the prophylactic use of ondansetron-dexamethasone and granisetron-dexamethasone. There is no statistically significant difference in the efficacy of the two drug combinations in lowering the incidence of post-operative nausea and vomiting after laparoscopic cholecystectomies in ASA I and ASA II adults of either sex.

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