Prophylactic Antiemetic Therapy With Ondansetron, Granisetron And Metoclopramide In Patients Undergoing Laparoscopic Cholecystectomy Under General Anaesthesia

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Citation

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Abstract

Nausea and vomiting is a common and distressing complication for patients with virtually all types of surgical procedures, its consequences being physical (like sweating, tachycardia, electrolyte imbalance) surgical (disruption of vascular anastamosis) and anaesthetic (aspiration pneumonitis).
The aim of the present study was to compare the antiemetic effect of intravenous granisetron 3mg, ondansetron 4mg & metoclopramide 10mg in a randomized double blind study for prophylaxis of post operative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy under general anaesthesia.
60 patients (ASA I & II) undergoing laparoscopic cholecystectomy under general anaesthesia were randomly allocated into three equal groups. Group A (n=20) received 4mg ondansetron, Group B (n=20) 3mg granisetron and group C (n=20) metoclopramide 10mg. The drugs were diluted in 50ml normal saline and given intravenous slowly over 10mins before induction of anaesthesia. Anaesthesia procedure was common to all the patients. Emetic episodes in first 24 hours were recorded and compared in different study groups. Results were analyzed using chi square test. A value of $p < 0.05$ was considered to be significant.
Emetic episodes were observed in 45% patients in group B, 70% patients in Group-A and 95% patients in group C.
To conclude, minimal emetic episodes were observed in early post-operative period (1-12hrs) in patients who had received intravenous granisetron in comparison to ondansetron and metoclopramide. However, after 12 hours emesis free periods were statistically insignificant between group A and B while patients in group C had no antiemetic effect.

INTRODUCTION

The most common and distressing symptoms, which follow anaesthesia and surgery, are pain and emesis. The syndrome of nausea, retching and vomiting is known as ‘sickness' and each part of it can be distinguished as a separate entity[1]. PONV (post operative nausea and vomiting) has been characterized as big ‘little problem[2] and has been a common complication for both in patients and out patients undergoing virtually all types of surgical procedures.

The consequences of PONV are physical, surgical and anaesthetic complications for patients as well as financial implications for the hospitals or institutions[3]. Physical consequences include sweating, pallor, tachycardia, stomach ache, increased chances of oesophageal tear, wound dehiscence and electrolyte imbalance. Surgical consequences include disruption of vascular anastomoses and increased intracranial pressure[4]. The anaesthetic consequences are aspiration pneumonitis and discomfort in recovery. For institutions there is increased financial burden because of increased nursing care, delayed discharge from Phase I and II recovery units and unexpected admissions. Hence, prophylactic antiemetic therapy is needed for all these patients.

Sometimes nausea and vomiting may be more distressing especially after minor and ambulatory surgery, delaying the hospital discharge[5]. There are a number of factors influencing the occurrence of PONV which includes patient factors (age, gender, obesity, anxiety, history of motion sickness or previous PONV and gastro paresis), operative procedures, anesthetic techniques (drugs for general

anesthesia, regional anesthesia and monitored anesthesia care) and post-operative factors (pain, dizziness, ambulation, oral in-take and opioids). Laparoscopic surgery is one condition, where risk of PONV is particularly pronounced. This increased risk of PONV is due to pneumo-peritoneum causing stimulation of mechanoreceptors in the gut[6].

Plenty of antiemetic drugs are available these days which include anticholinergic drugs (scopolamine, atropine), dopamine antagonist drugs (promethazine, prochlorperazine and metoclopramide), antihistaminic drugs (diphenhydramine hydroxzine), $5HT_3$ receptor antagonists (ondansetron, granisetron, dolasetron) and steroids (dexamethasone). In spite of plenty of anti-emetic drugs available no single drug is 100% effective in prevention of PONV and combination therapy has got a lot of side effects. So the present study was undertaking to compare the antiemetic effects of IV granisetron, ondanisetron and metoclopromide for prophylaxis of post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

MATERIAL AND METHODS

After approval from institutional ethical committee 60 female patients aged between 20-60 years who were classified as ASA grade I and II were included in the study. An informed consent from each patient was obtained. Patients with history of previous exposure to general anaesthesia, gastrointestinal disease, motion sickness, PONV, pregnancy and menstruation or those who had taken antiemetic drugs within 24 hours of operation were excluded from the study.

On arrival to the operation theatre routine monitoring devices were attached. SpO2, heart rate, ECG, blood pressure and $ETCO_2$ were observed throughout study period. All patients received 0.2mg of glycopyrrolate i/m ½ hour before operation. Using double blind randomization technique these patients were given either granisetron 3mg, ondansetron 4mg or metoclopramide 10mg. All the drugs were diluted in 50ml normal saline and given slowly 10 minutes before induction. Analgesia was provided with injection tramadol 1-2mg/Kg. Induction of anaesthesia was done with injection. sodium thiopentone 5mg/kg and intubation was facilitated with injection succinylcholine 2mg/kg body weight. Maintenance of anaesthesia was done with nitrous oxide (67%), oxygen (33%), isoflurane and muscle relaxation maintained with Inj. pancuronium 0.05-0.1 mg/ kg body weight with intermittent positive pressure ventilation to maintain $ETCO_2$ between 4.6-5.2 Kpa. An orogastric tube was introduced and suction was applied to empty the stomach of air and other contents, the orogastric tube was removed at the completion of surgery before tracheal extubation.

Abdominal insufflation for laparoscopic procedure was achieved with CO_2 and intrabdominal pressure was maintained between 1.3 to 1.8Kpa. At the end of the surgery residual neuromuscular blockage was antagonized by injection glycopyrrolate 10µg/kg and neostigmine 0.05 mg/kg and the patient was extubated. Post operative pain relief was provided with injection diclofenac sodium-75 mg intramuscular when pain score was > 4(VAS). All patients received supplementations and investigator who collected post-operative data was blinded to study drug administered while in the recovery ward.

Episodes of PONV were determined and noted in first 24 hours after operation at different time interval of 1, 4, 9, 12, 18 and 24 hours. At the end of each interval the anaesthesiologist registered whether vomiting has occurred and asked the patients whether they felt nauseated. The result was scored as Nausea =1, Retching=2 and vomiting=3.

Nausea was defined as subjective unpleasant sensation associated with the urge to vomiting. Retching was defined as spasmodic, rhythmic contraction of the respiratory muscles without expulsion of gastric contents and vomiting was defined as forceful expulsion of gastric contents. Patients who experienced any episode of nausea, retching and vomiting were given injection metoclopramide 10mg intravenous slowly as rescue treatment. Patient who received antiemetic were classified as treatment failure and were considered to experience both nausea and vomiting.

Side effects were registered during initial 6 hours in recovery ward. For example headache, dizziness, dry mouth, extra pyramidal symptoms, restlessness or any other abnormal movement.

Data was analyzed using Chi square test and analysis of variance. Differences were considered significant when $P<0.05$.

RESULTS

The treatment groups were comparable with regards to patient demographics (Table I). Complete control of PONV (no emesis, no rescue treatment for 24 hours after

administration of study agent) was achieved in 30% of cases in group A, in 55% of cases in group B and in 5% of cases in group C. During 0-12 hours emesis free period was 40%, 75% and 10% in groups A, B and C respectively. Stating it the other way 60% patients in group A, 25% patients in group B and 90% patients in Group-C experienced episodes of nausea and vomiting (Graph I) in first 12 hours. The difference was statistically significant between groups A and B in the first 12 hours but not beyond that (Table II). The difference in emetic sequaly was significant between group A and C throughout 24 hours (Table III). The incidence of emesis was also statistically significant between B and C during entire 24 hrs period (Table IV). However from 12-24 hours the difference between group A and B was not much significant.

Thus granisetron was definitely found to be superior to the other too agents for suppression of PONV.

Figure 1

Table I: Demographic data with regards to age and weight of study groups.

DEMOGRAPHIC DATA			
Age (Years)	Group A	Group B	Group C
	38±7.7	39.5 ± 11	38.75± 7.85
Weight (K.g)	50.1 ±5.5	50.6±7.15	52.2±6.3
p>0.05 NS			

Figure 2

Table II: Comparative evaluation of emetic sequelae in groups A and B.

Duration	Sickness	Result
0 – 1 Hrs	x^2 4.8 p <0.05	significant
1 – 4 Hrs	x^2 7.4 P < 0.005	significant
4 – 9 Hrs	x^2 5.56 p < 0.02	significant
9 – 12 Hrs	x^2 5.0 p < 0.05	significant
12 – 18 Hrs	x^2 2.4 p > 0.05	insignificant
18 – 24 Hrs	x^2 2.4 p > 0.05	insignificant

Statistical difference between group A and B was significant at 0 -12 hours ($p < 0.05$) and insignificant ($p > 0.05$) at 12 -24 hours

Figure 3

Table III: Comparative evaluation of emetic sequelae between groups A and C

Duration	Sickness	Result
0 – 1 Hrs	x^2 0 p > 0.10	insignificant
1 – 4 Hrs	x^2 3.94 p < 0.05	significant
4 – 9 Hrs	x^2 5.56 p < 0.05	significant
9 – 12 Hrs	x^2 4.8 p < 0.05	significant
12 – 18 Hrs	x^2 4.20 p < 0.05	significant
18 – 24 Hrs	x^2 4.20 p < 0.05	significant

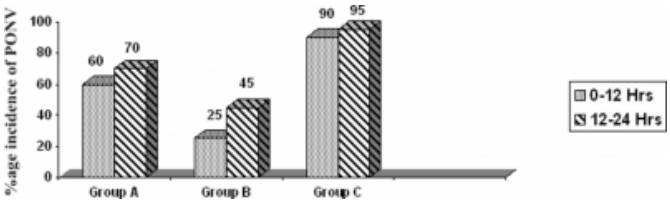
Figure 4

Table IV: Comparative evaluation of emetic sequelae between groups B and C

Duration	Sickness	Result
0 – 1 Hrs	x^2 8.4 p > 0.005	significant
1 – 4 Hrs	x^2 19.8 p < 0.001	significant
4 – 9 Hrs	x^2 19.6 p < 0.02	significant
9 – 12 Hrs	x^2 17.0 p < 0.001	significant
12 – 18 Hrs	x^2 11.6 p < 0.001	significant
18 – 24 Hrs	x^2 11.6 p < 0.001	significant

Figure 5

Graph I: emetic sequelae in the three groups during 0-12 and 12 – 24 hours post operatively.



DISCUSSION

PONV is amongst the most common complications following anaesthesia and surgery with a selectively high incidence after laparoscopic cholecystectomy. The etiology behind the PONV following laparoscopic cholecystectomy is

complex and multifactorial and is dependent on variety of factors including patient demographics, type of surgery, anaesthetic technique and postoperative care. Patient related factors are age, sex, obesity, a history of motion sickness, menstruation and history of PONV[6]. In this clinical trial however, the treatment groups were similar with respect to patient demographics, operative management and patient related factors. If such factors had not been controlled the number of patients who were observed to be emesis free in the present study would have changed. All patients were anaesthetized and operated by the same team of anaesthesiologists and surgeons. Duration of surgery and agents used for anaesthesia were also similar.

The introduction of $5HT_3$ (serotonin) receptor antagonists in 1991[7] has heralded a major advance in treatment of PONV because of absence of adverse effects that were observed with commonly used antiemetic drugs. The $5HT_3$ receptor antagonists produce no sedation, no extra pyramidal symptoms or adverse effects on vital signs and do not interact with other anaesthetic agents. Current $5HT_3$ receptor antagonists are granisetron, tropisetron, ondansetron, alosetron, cilansetron, palonosetron, tropisetron and dolasetron. All the $5HT_3$ receptors antagonists have the basic double nitrogen ring back-bone for their chemical structure. This may be the chemical site of action of $5HT_3$ receptor antagonist on serotonin[8]. $5HT_3$ receptors analogues are routinely used now a day to prevent PONV.

Y. Fuji et al in 2000[9] reported that granisetron is statistically superior to droperidol and metoclopramide for prevention of PONV. Results showed the incidence of PONV to be 13%, 30%, 33% and 37% after administration of granisetron, droperidol, metoclopramide and placebo respectively ($P<0.05$). These findings are in agreement with our study where incidence of PONV was 30% with granisetron 95% with metoclopramide ($P<0.001$).

Comparison of single dose granisetron to prevent PONV induced by moderately emetogenic chemotherapy has been done which concluded that single oral dose of granisetron 2mg results in equivalent level of protection against nausea and vomiting as intravenous Ondansetron 8 – 16 mg[10].

Bhattacharaya D et al [11] in 2001, reported lower incidence of emesis sickness ($P<0.05$) in early post operative period (Ist six hours) in patients who received intravenous granisetron in comparison to those who received ondansetron and placebo. In this study emetic episodes were 7% with granisetron as compared to 20% seen with ondansetron. This is in agreement with our study where emetic episodes were observed in 60% patients receiving ondansetron compared to 25% receiving granisetron and 90% in metoclopramide group. Statistically granisetron was superior to ondansetron in our study too.

Kushwaha et al in 2007[12] in their study concluded that PONV was controlled better with granisetron (incidence of PONV=16%) than with ondansetron (incidence of PONV=28%). This result is also in accordance with our study.

CONCLUSION

From the results of the study it can be safely concluded that granisetron is much more effective than ondansetron in first 12 post operative hours and also that granisetron and ondansetron both are superior to metoclopramide for prophylactic therapy for PONV.

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