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A Comparasion of Perioperative Ramosetron and Ramosetron with Dexamethasone Prophylaxis for the Prevention of Postoperative Nausea and Vomiting Following Laparoscopic Cholecystectomy under General Anaesthesia

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Abstract

Introduction: *Post Operative Nausea and Vomiting (PONV) is a well known complication following laparoscopic cholecystectomy under general anaesthesia ranges from 53-72 %. A reduction in the incidence of PONV following laparoscopic cholecystectomy will be highly beneficial for the patients to avoid patient dissatisfaction and peri-operative morbidity. This study have been undertaken to find out the efficacy of combination therapy of ramosetron with dexamethasone for the prevention of PONV following laparoscopic cholecystectomy under general anaesthesia.*

Methods: *30 patients in each study group, age 18-65 years of either sex with ASA class I and II, scheduled for elective laparoscopic cholecystectomy under standardized general anaesthesia were enrolled in this randomized, double blind prospective study. Medication was given intravenously immediately before administration of induction agent. Enrolled patients were divided into two groups as RD group (ramosetron 0.3 mg with dexamethasone 6 mg and R group (ramosetron 0.3 mg). The incidence of nausea, and vomiting, severity of nausea and need of rescue antiemetic were studied for the first 24 hours postoperatively at 0-6 hours and 6-24 hours and 0-24 hours.*

Results: *The incidence of nausea, PONV, rescue antiemetic were reduced in the RD group during 0-6 hours post operative periods while the incidence of vomiting was significantly reduced in RD group during 0-6 hours post operative (P = 0.003). The severity of nausea which measured by VRS was also significantly lesser in the RD group (P = 0.00). There were no clinically significant adverse effects during the study which required intervention. Following the study, patients were reported to have experienced satisfactory postoperative period.*

Conclusions: *Perioperative prophylaxis of ramosetron with dexamethasone combination given before the induction of anaesthesia is more effective regimen than ramosetron alone in preventing the incidence of PONV after elective laparoscopic cholecystectomy under general anaesthesia.*

Keywords: *Ramosetron, Dexamethasone, Postoperative nausea and vomiting, Verbal Rating Scale, Laparoscopic Cholecystectomy, General Anaesthesia.*

Introduction

Laparoscopic surgery decreases the morbidity associated with cholecystectomy and has become the most common treatment modality for symptomatic cholelithiasis.[1,2] Post Operative Nausea and Vomiting (PONV) is a well known

complication following laparoscopic cholecystectomy under general anaesthesia ranging from 53-72%.[3,4,5,6,7] A reduction in the incidence of PONV following laparoscopic cholecystectomy will be highly beneficial for the patients to avoid patient dissatisfaction and peri-operative morbidity.

Modalities like acupressure, transcutaneous electrical nerve stimulation (TENS), herbs, scopolamine, diphenhydramine, droperidol, promethazine, and metoclopramide have been used with limited efficacy. Often their uses have been associated with adverse effects ranging from dizziness, dry mouth, to severe cardiac arrhythmias and death.[8]

Serotonin (5-HT3 receptor antagonist) class of drugs are the new agents which are most commonly used as anti-emetics because of their rapid onset without sedative side effects. Among the various 5-HT3 receptor antagonists, ondansetron, the first of this category, was approved by Food and Drug administration in 1991 to be used in the treatment of PONV.[9] Granisetron, the most recently approved of the group for the indication of PONV, lags significantly behind in the number of published trials to prove its efficacy.[10] Ramosetron is a recently developed serotonin (5HT3 receptor) antagonist with potent antiemetic action and longer elimination half life (9 hours) than ondansetron (3.5 hours) and granisetron (4.9 hours).[11,12] This highlights the scope for ramosetron to be effective for a longer duration, whereas, the commonly prescribed ondansetron's action lasts about 6 hours. Combination therapy has been shown to be superior to single agent as the cause of PONV is multifactorial and involves multiple pathways and receptors. Moreover, if an agent is ineffective against PONV, repeating a second dose of the same agent is unlikely to increase efficacy.[13]

There are many studies which have used the concept of multi-modal therapy for prevention of PONV showing excellent results in various categories of surgeries involving gastrointestinal, oto-rhinolaryngeal and gynaecological specialties.[13] However, there are few studies involving ramosetron as part of the combination medication. Ramosetron alone has been found to be superior to granisetron and ondansetron for the management of PONV following laparoscopic cholecystectomy.[14,15]

In the study, we would like to test the hypothesis that combination of a long acting 5-HT3 receptor antagonist with dexamethasone which has a different mechanism of action will yield superior results compared to ramosetron administered alone for the prevention of PONV following laparoscopic cholecystectomy under standardized general anaesthesia.

Materials and Methods

This randomized, double blind prospective study was conducted at a teaching hospital in Meghalaya. After obtaining approval for the study from Institutional Ethical Review Board, a written informed consent was taken from each patient. In the present study, 30 patients in each study group, age 18-65 years of either sex with ASA class I and II, scheduled for elective laparoscopic cholecystectomy under standardized general anaesthesia were enrolled.

Pregnant patients, vomiting or retching within 24 hours before the operation, administration of antiemetics or steroids or psycho-active medications within 24 hours of operation, having cardiovascular, renal, hepatic, endocrine, gastrointestinal or neurological diseases were excluded in the study. In the study, patients were asked to provide their detailed medical history and their characteristic informations: - age, weight, history of previous PONV, motion sickness and smoking. Enrolled patients were randomly divided into R group (n=30) and RD group (n=30) and receive one of the two medications according to a computer generated randomized number table. The study drug was given intravenously, immediately before administration of induction agent. Patients in R group received ramosetron 0.3 mg and RD group ramosetron 0.3 mg with dexamethasone 6 mg.

According to randomization, the study drug was drawn by the principal investigator in a 5 ml

syringe and was diluted upto 5 ml with the sterile normal saline. For RD group, both the medications were drawn in a same syringe and diluted upto 5 ml with the sterile normal saline to avoid visual bias. They were labelled with secret codes. The codes with secret keys were kept by the principal investigator to avoid evaluation bias by the follow-up investigator. The administrations of the medications as well as follow up evaluation were done by the investigator. All patients along with the investigator collecting the post operative data as well as the nurses involved in the post operative care of patients were blinded to the treatment received.

Night before the surgery, patients were given tab alprazolam (0.5 mg), cap ranitidine (50 mg) and nil per oral (NPO) after dinner. At morning, on the day of surgery, patients were given cap ranitidine (150 mg) with a sip of water. A standardized anaesthesia regimen was given during the study. Patients were premedicated with inj midazolam intravenously (0.03 mg/kg) and induced with inj thiopentone sodium (5 mg/kg), inj fentanyl (2 µg/kg) and inj vecuronium bromide (0.1 mg/kg) to facilitate endotracheal intubation. Anaesthesia was maintained with oxygen, intermittent inj vecuronium bromide (0.02 mg/kg) and isoflurane. At the end of the operation, muscle relaxant was reversed with inj neostigmine (0.05 mg/kg) and inj glycopyrolate (0.01 mg/kg). The incidence of post operative nausea and vomiting, severity of nausea, and the need for rescue antiemetic were studied for the first 24 hours after operation at 0-6 hours and 6-24 hours and 0-24 hours.

Patients were monitored for every 15 minutes in the post anaesthetic care unit (PACU) and every 2 hours in the ward except when asleep.

An episode of nausea was defined as a sensation of uneasiness and discomfort in the stomach with an urge to vomit. The intensity of nausea was assessed by using Verbal Rating Scale (VRS).[8] Patients were asked to rate their degree of nausea during the assessment as none, mild, moderate, severe. Vomiting was either defined as a clinical symptom, the forceful expulsion of gastric contents through the mouth or nose, or retching (similar to vomiting with the exception that no gastric contents enter the pharynx, dry heaves).

Rescue medication for post operative nausea and vomiting (inj metoclopramide 10 mg as initial rescue drug and inj promethazine 12.5 mg as a second rescue drug) was given on patient's request or complaint of nausea (VRS-moderate) or vomiting. In order to minimize suffering from post operative nausea and vomiting, patients were educated to inform and request treatment when nausea and vomiting occur, during the post operative period.

In the study, we also evaluated adverse events and records during the entire overall observation periods. Lastly, patients were asked to rate their overall satisfaction with the anaesthetic experience on 5 points scale as: 1. Very good, 2. Good, 3. Fair, 4. Poor, 5. Very poor, at the completion of observation.

Sample size was calculated using the incidence of PONV following laparoscopic abdominal surgeries. For power calculation, we have taken the average incidence as 50%. We aim to reduce the incidence to at least 15% so as to make the monotherapy an effective one. This was because, despite various modalities of intervention, PONV ranges between 10-30% following various surgical procedures under general anaesthesia. We hypothesize that combination therapy may bring the incidence further down making it a superior modality of treatment. With a 35% improvement in the risk (one-tailed), 26 patients patient would be required but we enrolled 30 patients in each group to be investigated to find out statistically comparable results between the two groups at alpha power of 0.05% and beta power of 80%. Data collected from the study were analysed using SPSS version 11.0 for windows (SPSS, Chicago, II, USA). Categorical data and proportional comparison were analyzed with Chi-square test with appropriate correction, if required. Significance of difference between mean values would be done with Student's t test. A P value of < 0.05 was taken as level of significance.

Table 1. Demographic profiles and preoperative co-morbidities of patients

	R group (n=30)	RD group (n=30)	Statistical test and value	P value	inference
Age (years) Mean ± SD	39.93 ± 12.23	36.63 ± 11.87	0.41 #	0.67	NS
Weight (kg) Mean ± SD	55.23 ± 10.27	55.63 ± 9.25	0.15 #	0.87	NS
Sex (M:F)	1:29	3:27	1.07 ##	0.30	NS
BMI Mean ± SD	23.67 ± 4.11	24.47 ± 4.42	0.72 #	0.72	NS
ASA (I:II)	30:0	30:0	-	-	-
H/O motion sickness (%)	2 (0.6%)	0	2.07 ##	0.15	NS
H/O Smoking (%)	5 (1.5%)	5 (1.5%)	0. 00 ##	1.00	NS
H/O PONV (%)	0	0	-	-	-

(NS = not significant, # = Ind t-test, ## = Chi square)

Demographic profiles were comparable between two study groups and found statistically not significant. (Table 1)

Table 2. Intraoperative parameters during the study.

	R group Mean ± SD (n=30)	RD group Mean ± SD (n=30)	Statistical test* and value	P-value	Inference
Thiopentone (mg)	245.83 ± 6.61	240.50 ± 59.60	0.34	0.73	NS
Duration of anaesthesia (mins)	82.16 ± 25.07	75.33 ± 22.51	1.11	0.27	NS
Intraoperative fentanyl (µg)	85.33 ± 25.96	87.66 ± 23.58	0.36	0.71	NS
Duration of surgery (mins)	73.66 ± 23.85	75.36 ± 27.17	0.25	0.80	NS
Duration of pneumo-peritoneum(mins)	65.33 ± 21.89	61.16 ± 20.41	0.76	0.44	NS
Intra-abdominal pressure (cm of water)	12.63 ± 0.49	12.53 ± 0.50	0.77	0.44	NS

(NS = Not significant, * = Ind t-test)

The total thiopentone, fentanyl dose consumed during induction, duration of anaesthesia, duration of surgery, duration of pneumo peritoneum and intra operative abdominal pressure fixed during pneumo peritoneum were comparable in both groups during the study. (Table 2)

Table: 3 Incidence of Nausea, Vomiting, PONV, VRS (Severity of nausea).

	R group (n=30)	RD group (n=30)	Statistical test * and value	P value	Inference
0-6 Hours					
Nausea	17(56%)	12(40.60%)	1.66	0.20	NS
Vomiting	10(33.33%)	1 (3.33%)	9.02	0.003	**S**
PONV	18(59.40%)	12 (40.60%)	2.4	0.12	NS
Rescue - antiemetic	11(37.30%)	5 (17.50%)	3.06	0.08	NS
VRS	4 (13.33%)				
None	14(46.67%)	9 (30%)			
Mild	9 (30 %)	17 (56.67%)	5.97	0.00	**S**
Moderate	3 (10%)	4 (13.33%)			
Severe		0			
6-12 Hours					
Nausea	10(33%)	8(27.40%)	0.32	0.57	NS
Vomiting	3(10%)	0	3.16	0.07	NS
PONV	10(33%)	8(27.40%)	0.32	0.57	NS
Rescue -antiemetic	7(24.10%)	3(10.90%)	1.92	0.16	NS
VRS					
None	5(16.67%)	9(30%)			
Mild	18(60%)	20(66.67%)	5.82	0.12	NS
Moderate	6(20%)	1(3.33%)			
Severe	1(3.33%)	0			
0-24 Hours					
Nausea	19(62.70%)	16(52.80%)	0.62	0.43	NS
Vomiting	10(33.33%)	1(3.33%)	9.02	0.003	S
PONV	19(62.70%)	16(52.80%)	0.62	0.43	NS
Rescue antiemetic	12(40.60%)	7(24.10%0	1.93	0.17	NS
VRS					
None	13(43.33%)	16(53.33%)			
Mild	13(43.33%)	14(46.67%)	4.34	0.11	NS
Moderate	4(13.33%)	0			
Severe	0	0			

(***** = Chi Square, S = Significant, NS = Not Significant, VRS = Verbal Rating Scale)

The incidence of vomiting was significantly reduced in the RD group (P=0.003) during the 0-6 hours post operative period. There were decrease incidence of nausea and PONV during the entire study periods though not statistically significant. Patients in the RD group sought lesser rescue anti emetic during the study period than in the R group. The severity of nausea which is measured by VRS was significantly decreased in the RD group, particularly during 0-6 hours post operative period. (Table 3)

Table: 4 Incidence of adverse effects and patient satisfaction score

	R group (n=30)	RD group (n=30)	Statistical test * and value	P-value	Inference
Dizziness	5(16.67%)	3(10%)			
Headache	10(33.33%)	8(26.67%)	2.00	0.57	NS
Diarrhoea/constipation	0	1(3.33%)			
Others	15(50%)	18(60%)			
Patient satisfaction score					
Very good	8(26.67%)	14(46.67%)			
Good	17(56.67%)	14(46.67%)	3.21	0.20	NS
Fair	5(16.67%)	2(6.67%)			
Poor	0	0			
Very poor	0	0			

(* = Chi square test, NS = Not significant)

During the entire study periods, there were no serious adverse effects in the patients which required clinical intervention. Study was conducted and completed smoothly. All the participating patients in the both the group were satisfactory with anaesthetic techniques. (Table 4)

Discussion

Post operative nausea and vomiting is a common, undesirable complication after laparoscopic cholecystectomy under general anaesthesia. The exact aetiology of PONV is complex which is considered to involve multifactorial pathway with the vomiting centre receiving afferents from cerebral cortex, viscera and chemo receptor trigger zone (CTZ). There are certain independent perioperative risk factors considered to contribute to the causes of PONV.[16] History of migraine, history of PONV or motion sickness in a child's parent or sibling, better ASA physical status, intense preoperative anxiety, certain ethnicities or surgery types, decreased perioperative fluids, crystalloid versus colloid administration, increasing duration of anaesthesia, general versus regional anaesthesia or sedation, balanced versus total intravenous anaesthesia, and use of longer-acting versus shorter-acting opioids are some of the possible risk factors to PONV. It may be mentioned that the knowledge of risk factors and causative pathway of PONV are necessary for the satisfactory management of PONV.

Pharmacological therapy consists of anticholin-ergics (e.g. scopolamine), butyrophenone (e.g. droperidol), benzamide (e.g metoclopramide) and antiserotonin (e.g. ondansetron) were able to control PONV to certain limited extend. Non traditional antiemetics, e.g. propofol, dexamethasone and midazolam, have also been used in the prophylaxis of PONV. However, antiemetics in the group of anticholinergic, antihistaminic, butyrophenone and benzamide group of drugs are associated with significant undesirable side effects e.g. sedation, hypotension, dry mouth, restlessness and extrapyramidal symptoms. Antiserotonins (5-HT3 receptor antagonists) are one of the most effective treatment remedy available for the prevention of PONV. Various studies were conducted comparing antiserotonins (ondansetron, granisetron, ramosetron) and other drugs like dexamethasone, droperidol, metoclopramide and saline showing highly variable results in various emetogenic surgeries.[12,15,17,18,19]

Ramosetron hydrochloride was first developed in Japan and its antiemetic utility was demonstrated in the chemotherapy induced nausea and

vomiting.[20] It is also reported that ramosetron is more effective among the available 5-HT3 receptor antogonist agents for preventing PONV in the highly emetogenic surgeries [21,22,23,24,25] and chemotherapy induced PONV when ramosetron was given prior to administration of anti cancer drugs such as 5-fluro uracil.[26]

Dexamethasone, a long acting glucocorticoid and a potent synthetic analogs of cortisol which has powerful anti-inflammatory and immunosup-pressive effects, was reported to use as an effective emetic agent in the chemotherapy induced nausea and vomiting,[27] elective tonsillectomy[28,29] and major gynaecological surgeries.[30] It is also further reported that dexamethasone has decreased the post operative pain and fatigue therefore enabling the faster resumption of recreational activities in the postoperative periods.[31]

Multi-modal emetic prophylaxis has shown a better management strategy in the prevention of PONV in high risk population thereby increasing the patient satisfaction.[32] Combination of 5-HT3 receptor antagonists and dexamethasone has shown effectiveness in preventing PONV in chemotherapy induced nausea and vomiting,[33] major gynaecological surgeries[34,35] and laparoscopic cholecystectomy.[36,37,38]

Ramosetron with dexamethasone combination prophylaxis was reported to provide an effective modality for the prevention of chemotherapy induced acute and delayed emesis with no side effects,[39,40] laparoscopic cholecystectomy[41] and thyroidectomy.[42]

During the study, preoperative history of motion sickness, previous PONV, total anaesthetic drugs consumed, duration of anaesthesia, duration of surgery, duration of carbon dioxide insufflations (pneumo-peritoneum) and intra-abdominal pressure maintained during pneumo-peritoneum were comparable in both study groups. Patients in both groups also consumed approximately similar amounts of intravenous fentanyl for providing adequate analgesia. None of the enrolled patients left during the study period.

In the present study, the total incidences of nausea, vomiting and PONV were found decreased in the RD group than R group where the incidence of vomiting was decreased among the RD group significantly (P = 0.003) during the first 0-6 hours postoperative peroid. This finding is found better than the studies reported by Rajeeva V et al.[35] and Fujii Y et al. [43] in term of duration of PONV free periods, rescue antiemetic requirements and side effects profiles of the anti emetics used. These might be attributed to the prolonged half life (9 hrs), high affinity for 5-HT3 receptor and minimum sides effect of ramosetron[8,44,24,45] and the contribution by dexamethasone (mechanism may be decreased production/secretion of serotonin and anti-prostaglandin action)[14,30] to the anti emetic effect of ramosetron as a part of multi modal therapy.[13,46,32] During the study, few patients from both groups complained of non specific symptoms which were tolerable. Among the undesirables side effects, headache was the most common followed by dizziness which was in conformity with other anti serotonins.

There were two other studies[41,42] which have already published using similiar combination regime for the prevention of PONV following surgical procedures. However there were certain differences from these published studies during the conduct of the study in term of the timing and doses of study drugs administration and anaesthetic agents used which might influence the results. The incidence of nausea, vomiting, PONV, nausea severity (measured by VRS in the present study and NRS[41]) and rescue antiemetic in all the three study were decreased. However, the decreased incidence of vomiting and nausea severity scale (VRS) could be reported (statistically) significantly only during the first 0-6 hours post operatively in the present study, whereas the decreased incidence of PONV, nausea severity, rescue antiemetic during 0-24 hour postoperatively[42] and the decreased incidence of rescue anti emetic during 0-24 hours postoperatively with decreased nausea severity

scale (NRS) during the entire 0-48 hours study periods.[41]

During the study, though there is some debate regarding the actual dose of ramosetron[23] and dexamethasone[47] for the prophylaxis of PONV, we used 0.3 mg of ramosetron (6 µg/kg) and 6 mg dexamethasone though in the other published study 8 mg dexamethasone was used.

There are side effects of study drugs viz:- dizziness, headache which are common in all group. Clnically serious adverse events did not occur during the study period. Recently, several investigators have reported the effectiveness of ramosetron on the treatment of irritable bowel syndromes with diarrhoea.[48]

Satisfaction with antiemetic prophylaxis was better in ramosetron with dexamethasone combination prophylaxis (though not statistically not significant, P = 0.20).

There were certain limitations during the study which includes: - devoid of control group, subjectivity on part of patients while reporting nausea, vomiting and smaller in sample size. The study does not includes control group for the fear that patients devoids of appropriate antiemetic following highly emetogenic surgeries may exposed to risk of PONV which is unpleasant therefore considered unethical.

The absence of complete prevention of PONV in the study could be attributed to the multifactorial pathways of PONV and various independents risk factors like preoperative history of PONV, motion sickness, female gender[7,49] (more so during menstrual periods) and use of inhalational anaesthesia (isolflurane), opioids (inj fentanyl), hydration status and even with inj neostigmine and inj glycopyrolate.[18,49] Further studies with minimum preoperative risks and larger sample size will still necessary in order to demonstrate complete absence of PONV following such highly emetogenic surgeries.

Conclusion

Perioperative prophylaxis of ramosetron with dexamethasone is more effective than ramosetron alone in preventing the incidence of PONV after laparoscopic cholecystectomy under general anaesthesia.

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