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Original article:

Comparative Study of Antiemetic Effect of Ramosetron And Combination of Ondansetron With Dexamethasone in Laparoscopic Cholecystectomy Patients

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ABSTRACT:

INTRODUCTION: The newer long acting 5-HT_3 antagonist, ramosetron, has been found to be more effective than ondansetron in the reduction of the early as well as delayed PONV. Otherwise,combination of dexamethasone and 5-HT_3 antagonist is considered to be the optimum choice for the prevention of PONV during general anaesthesia.

METHODOLOGY: This prospective study included 100 female patients planned for laparoscopic cholecystectomy and divided into **c**ontrol group(n=50); receiving ondansetron with dexamethasone,´OD' and the study group(n=50) receiving ramosetron,´R'. Patients were closely monitored for 48 hours for any complaint of nausea, retching, and vomiting or adverse drug. Injection metoclopramide was administered as an additional rescue antiemetic. A complete responsewas defined as theabsence of PONV.

RESULTS: Mann- Whitney test wasapplied in nonparametric measurements like nausea score, pain score. Chi-square test was applied to compare post-operative nausea and vomiting between the groups, ASA grade, nausea gradesand rescue antiemetic requirement. Fisher exact test forearly and late pain scores.

In group 'OD' the PONV response was found in lesser percentage of cases (18%) than in group 'R' with 36% cases. Same proportion ofpatients required rescue antiemetic in the post -operative period in both the groups and no statistically significant difference was seen. The frequency of PONV response in group 'R' was seen higher at different post-operative intervals in comparison to group 'OD'.

CONCLUSION: The conclusion of the study is that**,** combination of dexamethasone with ondansetron is a superior prophylaxis to ramosetron for prevention of PONV ***i***n laparoscopic cholecystectomy patients.

INTRODUCTION:

Postoperative nausea and vomiting (PONV) is a common issue in anaesthesia. Despite several studies for a long time in the past, PONV still remains a significant problem because of its complex mechanism. Nausea andvomiting in thepostoperative periodoccurs in 20% to 30% of patients[1]depending on surgical and patients factors. PONV can be such an unpleasant experience that patients often rate it worse than postoperative pain.[2] PONV may delay a patient's discharge from post-anesthesia care units (PACUs) and can be the leading cause of unexpected hospital admission after ambulatory anesthesia.[3]

Laparoscopic cholecystectomy procedure requires the insufflation of carbon dioxide resulting in, stretch ofintra-abdominalorgans, peritoneal irritation and phrenic nerve excitation by residual CO2 in peritoneal

cavity which are very important risk factors of incidence of nausea and vomiting after laparoscopic cholecystectomy.[4], [5] In patients undergoing laparoscopic cholecystectomy, high incidence of PONV has been reported (50-70%). [6]

Because of the multifactorial etiology of PONV during laparoscopic cholecystectomy, combination of different classes of anti-emetics are preferred to control PONV, [7] [8]including anticholinergics, antihistamines, butyrophenones, benzamide, dexamethasone and 5-HT3 antagonists. Ondansetron, 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist, with limited adverse effects is known to block receptors in the CTZ as well as vagal nerve terminals. Dexamethasone has been used as an anti-emetic for a long time with limited adverse effect. The exact anti-emetic mechanism of dexamethasoneis unknown, but it is thought to act through prostaglandin antagonism, [9] serotonin inhibition in the gut, [10] and by releasing endorphins. [11]

Ramosetron, a new 5-HT3 receptor antagonist, has higher potency and prolonged activity than previously developed 5-HT3 antagonists as an antiemetic after chemotherapy,[12]because of a slower rate ofdissociation from the target receptor and higher binding affinity. So, to assess the comparison of the efficacy and side effects ondansetron with dexamethasone and ramosetron as an antiemetic during laparoscopic cholecystectomy, we designed a randomized double-blind controlled study.

MATERIAL AND METHODS

Following Institutional ethical committee approval, 100 ASA Grade I/II young female patients of 20-40 years undergoing elective laparoscopic cholecystectomy were equally divided into 2 groups (n=50 each) control group ´OD' and study group 'R' using a computer generated sealed envelopes.

It was a prospective double-blind, randomized, clinical study.Exclusion criteria for the study includes patients not giving consent, history of motion sickness, smokers, pregnancy, menstruating females, antiemetic taken within 24 hours before surgery or any long term medication, history of any systemic diseases, cardiovascular, respiratory, hepato-renal, neurological causing delayed gastric emptying,, endocrinal disorders, hematological disorders, history of PONV, prolonged QT interval, study drug sensitivity etc. Control group received ondansetron with dexamethasone and the study group received ramosetron. Based on the previous studies advocating use of the minimum recommended doses, ramosetron in a dose of 0.3 mg and ondansetron in a dose of 4 mg and dexamethasone in a dose of 8mg was administered for prevention of PONV in the present study. Medications was prepared by a blinded paramedic, unaware of the procedure using identical 5-ml syringes and was administered according to the randomization list. Patients were administered alprazolam (0.25 mg) orally on the night before surgery and advised nil per orally from midnight.

In operating room, following securing IV line, the standard non-invasive anesthesia monitoringincludingheart rate, non-invasive blood pressure (NIBP), $ETCO_2$, oxygen saturation, and ECG was initiated. Premedication was done with injection Glycopyrollate (0.004mg/kg), injection Ranitidine (1mg/kg), injection Metoclopramide (0.15mg/kg), injection Butorphanol (0.04mg/kg) ; and induced with injection propofol 2 mg/ kg mixed with 2% xylocard(10mg of xylocard per 10ml propofol) followed by intubation which was facilitated by using injection vecuronium 0.1 mg/kg. A nasogastric tube was inserted after securing theendotracheal tube in place and removed once the surgery is completed. Anesthesia was maintained with nitrous oxide (66%) and

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halothane (0.4-1%) in oxygen. Intra-operative muscle relaxation was maintained with injection vecuronium. At the end of the surgery, injection diclofenac 75 mg IM was given before the reversal of neuromuscular blockade with injection neostigmine (0.04 mg/ kg) and injection Glycopyrollate (0.01 mg/kg). Ondansetron (4 mg) with dexamethasone (8mg) or ramosetron (0.3 mg) was administered intravenously before shifting of the patient from the OT to the post-anaesthesia care unit (PACU). All port sites were infiltrated with injection bupivacaine (0.25%). Additional post-operative analgesia was provided with injection tramadol 2 mg/ kg IM as and when required.

In the PACU, patients were monitored for nausea, vomiting, pain, vital signs and side effects. Pain was assessed by VAS scoring, 0- no pain and 10- worst imaginable pain. Patients were closely monitored for 48h and any complaint of nausea, retching, and vomiting or adverse drug effect were recorded. Injection metoclopramide (10 mg IV) was administered as an additional rescue antiemetic in patients with two or more than two episodes of vomiting and/or significant nausea at any time within 48 h of operation. Exact timing of the administration of the rescue antiemetic was also recorded.

Nausea was measured usinga 10 point numerical visual analogue scale with 0 = no nausea and 10 = nausea as bad as can be. A score of > 5 was considered severe, 5 = moderate and < 5 = minimal. The moderate and severe nausea was considered as major nausea .During the period of monitoring, the vomiting/retching episodes of >2 were considered severe, 2 as moderate, and < 2as mild. Rescue antiemetic consisted of injection metoclopramide 0.15 mg/kg I V and was given for more than two episodes of vomiting. Vomiting occurring up to 24 h after surgery was considered as early vomiting whereas delayed vomiting included vomiting occurring during 24-48 h after surgery. A completeresponse wasdefined as the absence of PONV. Any adverse drug effect occurring during the study period wasdiligently sought and documented.

STATISTICAL ANALYSIS

Assuming an alpha error (α) of 0.05 and a complete response with ondansetron to be 70%, an improvement of 20% was considered clinically significant. A minimum number of 45patients in each group was requiredto achievea powerof 80%. A P-value of< 0.05 was considered as significant. All the data were recorded on standardized case report forms and exported for analysis in SPSS, version 21(SPSS Inc., USA). Parametric values were taken as mean ± SD, and nonparametric values were taken as median (min ± max). For the inter-group comparison of parametric tests, Student's t test was implemented. Unpaired student-t test for age, weight, duration of anaesthesia and surgery, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure. Mann- Whitney test was applied in nonparametric measurements like nausea score, pain score. Chi-square test was applied to compare post-operative nausea and vomiting between the groups, ASA grade, nausea grades, rescue antiemetic requirement. Fisher exact test forearly and late pain scores.

RESULTS:

In terms of demographic parameters, duration of surgery and ASA status and haemodynamic parameters, the two groups were comparable.

In group 'OD' the PONV response was found in lesser percentage of cases(18%; n=9) than in group 'R' with 36%(n=18) cases. The nausea was revealed in all the cases of PONV in both the groups with

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vomiting 2%(n=1) and 8% (n=4) respectively in both the groups;**[Table 1]** which was statistically significant(p=0.04).

Early PONV (<24 hrs.) was observed in 22.2% (n=2) cases in group 'OD' unlike 16.6% (n=3) in group 'R'. We couldn't say that greater proportion of cases was showing early PONV response in group 'OD' as compared to group 'R' as the denominator of patients was different in both the groups, whereas late PONV(>24hrs) was found in all the PONV cases in both the groups.**[Table2]**

The frequency of PONV response in group 'R' was more in comparison to group 'OD' at different post –operative intervals.

As far as the efficacy of the drug in terms of number needed to treat(NNT) is estimated in both the groups, it was found that to have a gain of 1 patient in the decrease of PONV response in group 'OD' versus group 'R', 6 patients had to be administered with intra-operative dexamethasone and ondansetron drugs. Also, lesser the NNT more efficacious was the treatment or drug.**[Table 3]**

Although the frequency of nausea (22 .2%;4/18 in group 'R' vs 22.2% 2/9 in group 'O') and vomiting (88.9%; 8/9 in group 'O' vs 77.8%; 14/18 in group 'R') was relatively in higher percentage in group 'R' , but the difference was insignificant statistically (p=0.32 & p= 0.49 respectively).

When we compared the difference in the frequency of rescue anti-emetic requirement in post-operative period in both the groups, it was found to be statistically insignificant. Amongst the 4 patients in group 'R', the requirement of rescue anti-emetic was observed at 30, 36, 42 hrs. while 2 patients in group 'O' needed rescue anti-emetic at 36 & 48 hrs.**[Table 4]**

The patients in boththe groups experiencedmild pain in the early post-operative period, hence no statistical comparison was made. While this difference in the proportion of female patients experiencing mild pain in the late post -operative period was statistically significant(p0.029***).*** In both the groups, none of the studied patients experienced adverse effects of the drugs.

No statistically significant differences were observed in mean HR, SBP, DBP & MAP at different post-operative periods in both the groups.

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Table 1:Distribution of Post-operative nausea vomiting (PONV) in the two groups

PONV	***Group (O)*** (n=50)	***Group (R)*** (n=50)	P value
Present n(%)	9 (18%)	18 (36%)	0.04*
Absent n(%)	41 (82%)	32 (64%)	
Vomiting	***Group (O)*** (n=50)	***Group (R)*** (n=50)	
Present n(%)	1 (2%)	4 (8%)	0.16
Absent n(%)	49 (98%)	46 (92%)	
Nausea	***Group (O)*** (n=50)	***Group (R)*** (n=50)	
Present n(%)	9 (18%)	18 (36%)	0.04*
Absent n(%)	41 (82%)	32 (64%)	

n- number of patient
* statistically significant

Table no 2: Description of early and late PONV in the 2 groups

PONV	**Group (O) (n=9)**	**Group (R) (n=18)**	**P value**
Early (≤ 24hrs) n(%)	2 (22.2%)	3 (16.6%)	0.64
Late (>24hrs) n(%)	9 (100%)	18(100%)	0.05

Table no.3: Efficacy of the drugs in the 2 groups of female patients in terms of number needed treat (NNT) to prevent PONV response

Groups	**PONV**		**Total**	**Risk difference**	**NNT (95% C.I)**
	Yes	No			
Group (O)	9	41	50	0.18	6 (2.85-9.09)
Group (R)	18	32	50		

Table 4: Comparison of difference in the frequency of rescued antimetic requirement in the post -operative period in the 2 groups

Rescue antiemetic	**Yes**	**No**	**Total**	**P* value**
Group O	2 (22.2%)	7 (77.8%)	9	1.000
Group R	4 (22.2%)	14 (77.8%)	18	
Total	6	21	27	

*chi –square test

DISCUSSION:

The etiology of PONV after general anesthesia is complex, with the involvement of multiple factors related with patient, medical, surgery and anaesthesia.

Apfel [13] proposed four clear risk factors associated with PONV, i.e., female gender, prior history of motion sickness and/ or PONV, non-smoker, and postoperative opioid treatment, and suggested that each factor

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increased risk by 20%. Koivuranta et al. [14] reported five risk factors, i.e., duration of surgery > 1 hour, female gender, prior history of motion sickness, prior history of PONV, and non-smoker. We enrolled only female patients which is an independent risk factor for PONV, hence we didn't include a placebo group which could lead to ethical issues.

Numerous antiemetic regimens, alone or in combination, have been used for treatment and tried for prophylaxis with some degree of effectiveness. [15]Combination of anti-emetic drugs could be an effective method to control severe PONV, perhaps because there is no single stimulus or cause for PONV. [16] Best regimen for the prevention of PONV to be considered so far is a combination of dexamethasone and 5-HT3 antagonist during general anaesthesia.

Dexamethasone in a dose of 8-10mg has been used frequently in the prevention of PONV.[17] Fujii et al found a dose-dependent effect of dexamethasone with a plateau effect at 8mg, which is also the most commonly used dose in many studies, [18] hence, we also accepted for our study.

Dexamethasone is known to reduce the incidence of vomiting, but appears to be more specific in the prevention of nausea. [19] This may explain why the combination of ondansetron and dexamethasone has been shown to reduce the overall incidence of both nausea and vomiting when given for prophylaxis, an effect that is likely to be additive. [20] Studies have shown that ondansetron is more effective in preventing early but not late PONV, whereas dexamethasone was found to have more pronounced action in the late postoperative period. [8], [21],[22] This may be due to the shorter duration of action of ondansetron (4 h) in contrast to the prolonged duration of action of dexamethasone. Thus, the combination of ondansetron and dexamethasone can decrease the incidence of both early and late nausea and vomiting and is commonly practiced in our institute. Many of the recent studies have shown that ramosetron is more effective than ondansetron in preventing PONV for the patients undergoing various other surgeries[23],[24],[25],[26] The elimination half-life of ramosetron is longer than that of ondansetron (9 h vs. 3.5 h).[27]This is clear from the studies that addition of dexamethasone doesn't provide any added advantage to ramosetron, [28] as we can see with the combination of dexamethasone to ondansetron. That' s why, this study was carried out to compare the effects of the combination of ondansetron and dexamethasone with ramosetron alone on early and late PONV up to 48 h after surgery.

In our study, we found that combination of ondansetron and dexamethasone was better than ramosetron for the prevention of PONV. PONV in group 'OD' was seen in 9 patients (18%) and 18 patients (36%) in group 'R'. The result was statistically significant (P= 0.04). Vomiting was seen in 1 patient ofgroup 'OD' and 4 patients of group 'R' (P= 0.16). Early PONV was seen in more number of patients in group 'OD' as compared to group 'R' (22.2% vs 16.6%). This might be attributable to short duration of action of ondansetron as compared to ramosetron.

Sameer Desai et al [29] compared the efficacy of combination of ondansetron and dexamethasone with ramosetron in middle ear surgeries, noted that the incidence of nausea was less with the dexamethasone and ondansetron combination therapy group compared to ramosetron group after the first 2 h. Also, the overall number of patients with no PONV was higher in the combination group than in the

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ramosetron group. It is recommended that the drugs with different mechanisms of action should be used in combination to optimize the efficacy. Same result was seen in our study in laparoscopiccholecystectomy surgeries also.

Sandeep PrithvirajPandharpukaretall [30] compared theefficacyand safety of ramosetron versus ondansetronforpostoperative nausea and vomiting after general anesthesia and found that in ondansetron group, nausea was 42.5% and 10% in ramosetron group all the times till 2 4 hours((<0.005). In ramosetron group, 97.5% ofpatients were emesis free while in ondansetron group 67.5% patients experienced no emesis (0.001). In ondansetron group, 10% patients received rescue antiemetic and in ramosetron group 2.5% of patients received rescue antiemetic, which was statistically significant (0.005). There was no difference in haemodynamic changes, postoperative pain scores and requirement of analgesic between the two groups. In our study, 2% cases in group 'OD' had vomiting and 8% cases in group 'R' had vomiting; rescue antiemetics was given to all patients who experienced vomiting. Post-operative paingrades were lower in group 'OD' as compared to group 'R' (P=0.029). The reason for this could be anti-inflammatory effect of dexamethasone in group 'OD'. In our study also, side effects were comparable in both the groups.

Chengjie Gao et al [31] used 4 mg ondansetron and 0.3 mg ramosetron following general anesthesia to compare PONV between them. Meta-analysis of results showed no statistically significant difference in PON between patients at different time periods during 24 hours after surgery: However, ramosetron had a tendency to be more effective than ondansetron during the 24–48-hour time period after surgery, but this effect did not reach statistical significance (RR 0.60, 95% CI 0.36–1.01; P=0.06).

Sandip Agarkar, Aparna S Chatterjee [32]carried out a study to prevent PONV in high risk patients using ramosetron and ondansetron.The overall incidence of PONV in the first 24 h was found to be 35% in the ramosetron group as opposed to 43.7% in the ondansetron group (P = 0.199). There was no significant difference in the incidence of nausea between ramosetron and ondansetron groups (35% vs. 40.8%) (P = 0.38). Rescue antiemetic requirementwas similar in both groups; 23.3% and 32% in the ramosetronand ondansetron groups, respectively (P = 0.156). None in the ramosetron group required a rescue antiemetic inthe 6–24 h period after surgery. In our study, patients were free of PONV in first 20 hrs. after surgery, nausea started at 24 hours in both the groups. 3 patients in group R and 2 patients in group ' OD' had nausea at 24 hours. Vomiting occurred in 1 patient at 48th hour in group 'OD' and 4 patients in group 'R' at 30, 36 and 2 patients at 42 hour. Overall PONV incidence was statistically lower in group 'OD' as compared to group ' R' (n=9 vs 18).

Ansari MM et al[33] compared PONV in patients, following intravenous administration of ondansetron (4 mg) or ramosetron (0.3 mg) who underwent laparoscopic cholecystectomy. In first 24 hour after surgery, complete response was observed higher in ramosetron group as compared to the ondansetron group but it was insignificant statistically. Complete response in the second24hour aftersurgery was observed again higher in ramosetron groupas compared tothe ondansetrongroup with statisticalsignificance (P<0.05). And, concluded that ramosetron was found tobe safe andmore effective antiemeticthan ondansetron in patients undergoing LC. In our study, early PONV wasseen more in combination group

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(22.2%)as comparedto ramosetrongroup (16.6%) out of total patients, experiencingPONV.

Younghoon Jeon et al [34] compared Ramosetron, Dexamethasone, and a Combination of Ramosetron and Dexamethasone for the Prevention of Postoperative Nausea and Vomiting in Korean Women Undergoing Thyroidectomy in 108 patients. The total PONV rates up to 24 hours post-anesthesia were 35%, 13%, and 10% in the dexamethasone alone, ramosetron alone, and combination groups, respectively. The PONV rate was significantly lower in the combination group compared with the dexamethasone alone group (95% CI, 0.02–0.18vs 0.23–0.47; P = 0.006). PONV was not significantly differentin the combination groupthan that in the ramosetron alone group (95% CI, 0.04–0.22). The incidence of PONV was significantly higher in the dexamethasone alone group than that in the ramosetron alone group (P = 0.03).

As mentioned above, many studies have been conducted comparing different antiemetics with each other and their combination with dexamethasone, proving that combination therapy for PONV with different mechanism of action is better than single drug therapy. Different studies have shown thatcombination ofondansetron with dexamethasone is better than ondansetronalone or dexamethasone alone. In our study where we compared ramosetron with combination of ondansetron and dexamethasone found that the combination therapy is better in terms of incidence of PONV and post-operative pain grades than ramosetron alone in patients undergoing laparoscopic cholecystectomy. The limitation of this study was that we compared the combination of ondansetron and dexamethasone to ramosetron alone. In our study we only included laparoscopic cholecystectomy, female patients of 20-40 years, belonging to ASA I/II category so further studies are required to make it applicable to all other surgeries including male patients with co-morbidities, patients with other risk factors for PONV with expected long duration of nausea and vomiting.

CONCLUSION

In this study, we noted that significantly more patients were free of PONV in the dexamethasone and ondansetron combination group than the patients receiving monotherapy with ramosetron. Hence, combination therapy of ondansetron and dexamethasone is better in efficacy than ramosetron and could be recommended as a superior prophylaxis for PONV in laparoscopic cholecystectomy..

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