

A randomized, placebo controlled study evaluating preventive role of ondansetron, dexamethasone and ondansetron plus dexamethasone for postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy.

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Abstract: A prospective, randomized placebo controlled study was undertaken to compare efficacy and safety of ondansetron-dexamethasone combination with each drug alone as a prophylaxis against post-operative nausea and vomiting (PONV) in patients after elective laparoscopic cholecystectomy done under general anaesthesia. This study was conducted on total of 320 patients of both sexes undergoing laparoscopic cholecystectomy. Patients were divided into four groups of 80 patients each depending upon the antiemetic agent given. Group I patients received placebo (distilled water 2ml). Group II patients received intravenous ondansetron (4mg). Group III patients received intravenous dexamethasone (8mg). Group IV patients received intravenous ondansetron (4mg) plus dexamethasone (8mg). In the postoperative period all the patients were closely monitored upto 24 hours for PONV and any other specific complaints. The combination of ondansetron and dexamethasone significantly decreased PONV to 10% from 85% in placebo group, 35% in ondansetron and 30% in dexamethasone group. On statistical analysis combination was found to be highly significant than placebo and significant from ondansetron or dexamethasone alone. **Conclusion:** The study revealed that combination of ondansetron and dexamethasone is safe and effective combination than each drug alone for prevention of postoperative nausea and vomiting. In recent years interest has been focused on combination therapy because no single agent is effective against PONV. Further studies on prophylactic combination of drugs should be done to make PONV a rare occurrence.

INTRODUCTION

Postoperative nausea and vomiting are common complications of all type of abdominal surgeries which invariably prove disturbing to the patient, the surgeon and anaesthetist. Many patients find it more troublesome than the postoperative pain itself. It results in significant morbidity and longer stays in the hospital, especially in patients undergoing laparoscopic cholecystectomy. The incidence of PONV in laparoscopic cholecystectomy ranges from 25 to 42% when antiemetic treatment is not considered prophylactically².

The consequences of PONV are physical, surgical and anaesthetic complications for patients as well as financial implications for the hospitals or institutions³. Persistent vomiting leads poor patient satisfaction, electrolyte disturbances, delayed wound healing and wound dehiscence and sometimes life threatening aspiration. A return to status quo in all surgical patients may be delayed and hospital stay may be prolonged. Plenty of antiemetic drugs are available these days which include anticholinergic drugs (scopolamine, atropine), dopamine antagonist drugs (promethazine, prochlorperazine and metoclopramide), antihistaminic drugs (diphenhydramine hydroxizine), 5HT₃ receptor antagonists (ondansetron, granisetron, dolasetron) and steroids (dexamethasone).

In spite of plenty of antiemetic drugs available, no single agent is 100% effective against PONV. This may be because PONV is multifocal in origin and there is no single stimulus for PONV. In recent years interest has been focused on combination therapy. Ondansetron plus dexamethasone has been used successfully to treat emesis refractory to ondansetron alone⁴. Hence the present study was carried to find the role and safety of ondansetron, dexamethasone and ondansetron plus dexamethasone in preventing PONV in patients undergoing laparoscopic cholecystectomy.

MATERIAL AND METHODS

This prospective randomized placebo controlled study was conducted in the Department of Surgery of Government Medical College, Patiala from July 2007 to June 2010 after seeking clearance from ethical committee. In this study 320 patients of both sexes scheduled for elective laparoscopic cholecystectomy were selected. Patients older than 60 years and younger than 18 years, smokers, alcoholics, those with history of hypersensitivity to any drug, patients with impaired liver and kidney functions, history of previous

PONV, patients on antidepressants or calcium channel blockers and patients converted to open cholecystectomy were excluded from the study. The patients were randomly allocated to four groups of 80 patients each. The patients enrolled in placebo group (Group I) received 2ml of distilled water. Patients in group II were given intravenous ondansetron (4mg). Patients enrolled in group III received intravenous dexamethasone (8mg). Group IV patients were given combination of intravenous ondansetron (4mg) and dexamethasone (8mg). The study drugs were given intravenously before administering the general anaesthesia. All the patients were asked to empty their urinary bladder just before the operation. Standard balanced general anaesthesia was given to all the patients. All operations were performed using four port standard laparoscopic cholecystectomy technique. In the postoperative period all the patients were closely monitored up to 24 hours for PONV and the amount of rescue antiemetic requirement. The PONV was defined as the subjective unpleasant sensation associated with awareness of urge to vomit (nausea, retching or vomiting were grouped together). The incidence of PONV was recorded 1 hourly up to 6 hours, every 3 hourly up to 12 hours and every 6 hourly up to 24 hours.

The severity of PONV was graded as follows⁵

1. No PONV: Absence of any emesis or nausea.
2. Mild PONV: Patients having only mild nausea, or one emetic episode or nausea lasting for less than 10 minutes and where no antiemetic is required.
3. Moderate PONV: Patient has 1-2 emetic episodes or moderate to severe nausea and antiemetic therapy is required.
4. Severe PONV: Patient has more than 2 emetic episodes or is nauseated more than twice and more than one antiemetic required.

Patients received ondansetron (4mg), intravenous as rescue antiemetic.

Statistical Analysis: Statistical analysis was done using Student 'T-test'. P-value less than 0.05 was considered significant.

RESULTS

Physical status: Four groups had comparable number of patients in all groups and showed insignificant variations. Mean age of our patients was 38.85 (17-62) and 264 of them (82.5%) were females.

Postoperative Nausea and Vomiting (PONV): A complete response (no nausea and vomiting) was observed in 90% of patients in combination group compared to 15% in placebo group, 65% in ondansetron and 70% in dexamethasone group which is a statistical significant difference (Table 1 and 2). Rescue antiemetic medication was used in 44(55%) patients in placebo group compared to 28(35%) in ondansetron group and 24(30%) in dexamethasone group. No patient in combination group required rescue antiemetic medication. (Table 1&2)

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Table 1: Incidence of postoperative nausea and vomiting (PONV) in all four groups

Group	Total no. of Patients	No. of Patients with PONV	%age of PONV	Rescue antiemetic
I	80	68	85	44(55%)
II	80	28	35	28(35%)
III	80	24	30	24(30%)
IV	80	8	10	0

Table 2: Statistical analysis of all groups

Groups	Chi sq	P	Significance
I vs II	15.91	0.0012	Highly significant
I vs III	14.8	0.002	Highly significant
I vs IV	23.71	0.0001	Highly significant
II vs III	3.84	0.2793	Not significant
II vs IV	9.81	0.0203	Significant
III vs IV	8.5	0.0367	Significant

DISCUSSION

Postoperative nausea and vomiting is area of concern as nearly 53-72% of patients require antiemetic therapy after laparoscopic cholecystectomy⁶. We conducted a study on 320 patients who underwent laparoscopic cholecystectomy under general anaesthesia. They were divided into four groups of 80 each depending upon the antiemetic agent given. It is interesting to note that 90% of patients had no nausea and vomiting in combination group compared to 15% in placebo group, 65% in ondansetron and 70% in dexamethasone group. Rescue antiemetic in postoperative period was required in 44 (55%) patients in placebo group compared to 28 (35%) in ondansetron group and 24 (30%) in dexamethasone group. However, no patient in combination group required rescue antiemetic medication. In recent years interest has been focused on combination therapy because no single agent is effective against PONV. This may be because it is multifactorial in origin and there is no single stimulus for PONV. The idea of combination therapy for prevention and treatment of postoperative nausea vomiting came from various studies where Ondansetron plus dexamethasone have been used successfully to treat emesis refractory to Ondansetron alone⁸.

Dexamethasone was reported as an effective anti-emetic in patients receiving cancer chemotherapy in 1981⁷. Glucocorticoids have been recognised as an important modifier of postoperative physiology, inflammatory, humoral and immunological response, by regulation of trauma induced humoral factors. The exact mechanism by which glucocorticoids decrease the incidence of nausea and vomiting is not fully understood, but probably can be explained by centrally mediated anti-emetic action via inhibition of prostaglandin synthesis, or inhibition of release of endogenous opioids⁸.

The major concern regarding the use of dexamethasone is infection, delayed wound healing and other side effects. But various studies in the literature have shown that a single-dose dexamethasone does not increase complications⁹⁻¹¹. A metanalysis on perioperative administration of high dose of methylprednisolone (30-35 mg/kg), was not associated with significant side effects¹². We did not have any postoperative complications which could be attributed to dexamethasone prophylaxis.

The introduction of serotonin (5HT₃) receptor antagonists in 1991 has heralded a major advance in treatment of PONV because of absence of adverse effects that were observed with commonly used antiemetic drugs¹³. Ondansetron produces no sedation, no extra pyramidal symptoms and adverse effects on vital signs. Serotonin (5HT₃) receptor antagonists affect the chemoreceptor trigger zone and act at vagal afferents in the gastrointestinal tract. Ondansetron has been shown to be effective in the prevention and treatment of PONV in many studies.

No single drug has proved to be universal solution to PONV. It is not feasible to give very high doses of such drugs because of saturation effects and safety, so combination of antiemetic and corticosteroid drugs are a possibility.

The real benefit to patients will be realised if effective prophylactic combination of drugs make postoperative nausea and vomiting a rare occurrence. Our results should significant decrease in incidence of postoperative nausea and vomiting and also the statistically significant reduction in the use of rescue antiemetic in combination group complement previous studies. Lopez-Olando et al¹⁴ concluded that prophylactic administration of a combination of dexamethasone

and ondansetron is effective in preventing PONV in patients undergoing gynaecological surgery with fewer patients requiring rescue antiemetic compared to other regimens of placebo, ondansetron or dexamethasone¹⁴. Biswas et al¹⁵ also found that combination of dexamethasone and ondansetron provided adequate control of PONV in patients undergoing laparoscopic tubal ligation with overall complete response in 78% of patients.

Gautam et al¹⁶ compared efficacy of ondansetron – dexamethasone combination with each drug alone as a prophylaxis against PONV in patients after elective laparoscopic cholecystectomy. They concluded that the combination of ondansetron and dexamethasone was better than each drug alone in preventing PONV. Dexamethasone alone was significantly less effective in preventing early vomiting compared to its combination with ondansetron whereas ondansetron alone was less effective against late PONV as compared to combination therapy. This result is also in accordance with our study.

Long-term corticosteroid therapy may have significant morbidity. However, side effects from small, or even high dose, corticosteroid treatment have been rare. Neff and colleagues¹⁸ reported excruciating peri-anal pain immediately after dexamethasone administration¹⁷. The mechanism responsible for this phenomenon was not well understood but slow intravenous infusion of diluted dexamethasone can prevent this side effect. In our study no adverse related to dexamethasone or ondansetron were observed.

CONCLUSION

None of the available agents is entirely effective for preventing PONV. As there are different major receptor systems involved in the aetiology of PONV, a combination of agents that act on different receptors results in better prophylaxis. Prophylactic administration of combination of ondansetron with dexamethasone is safe and more effective than ondansetron and dexamethasone when used alone in reducing incidence of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Further studies on prophylactic combination of drugs should be done to make PONV a rare occurrence.

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