Comparison of Ondansetron, Dexamethasone and Ondansetron Plus Dexamethasone For The Prevention of Post-operative Nausea and Vomiting after Laparoscopic Cholecystectomy

Suman Chattopadhyay[1,*], Ananya Biswas[2], SK Samim Ferdows[3], Dilip Kumar Bhowmik[4], Swagata Dey[5], Biswanath Biswas[6]

[1]Associate Professor, Midnapore Medical College, Paschim Midnapur, [2]Assistant Professor, Dept. of Anatomy, Malda Medical College, Malda, [3]Assistant Professor, Dept. of Community Medicine, [4]Assistant Professor, [5]Senior Resident, [6]Professor & HOD, Dept. of Anaesthesia, IQ City Medical College, Durgapur

***Corresponding Author:**
Email: sumanc24@gmail.com

Abstract

Introduction: Laparoscopic cholecystectomy is associated with an appreciably high rate of postoperative nausea & vomiting (PONV) which is considered as a reason of patient's delay in discharge and disability aggravation. This study was designed to compare the effectiveness of Ondansetron, Dexamethason and Ondansetron plus Dexamethasone as an antiemetic prophylaxis for preventing PONV in patients after laparoscopic cholecystectomy.

Methods: In this randomised double blind study, 153 patients of both sexes of ASA I and II aged between 16 to 60 yrs received 4 mg Ondansetron (Group O, n = 50), 8 mg Dexamethason (Group D, n =51) or Ondansetron 4 mg plus Dexamethasone 8 mg (Group OD, n=52) intravenously immediately before induction of anaesthesia. Perioperative care was standardised in all patients. Patient was then observed for 24 hours postoperatively for any episode of PONV and any adverse effects of the study drugs.

Results: A complete response (defined as no PONV and no need for another antiemetic) was achieved in 62% of the patients receiving Ondansetron, 64.7% of the patient receiving Dexamethasone and in 84.6% of patients receiving Ondansetron plus Dexamethasone (P<0.05). The overall cumulative incidences (0-24 hrs) of PONV were 40% in Ondansetron group, 37.3% in the Dexamethasone group and 15.4% in combination group (P<0.05). No difference in adverse events was observed in between group.

Conclusion: We concluded that combination of Ondansetron plus Dexamethasone is better than each drug alone as an antiemetic prophylaxis against PONV following laparoscopic cholecystectomy.

Keyword: Laparoscopic cholecystectomy, Prophylactic, Antiemetic, Ondansetron, Dexamethasone, Nausea, Vomiting.

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-4994.2016.00078.0

Introduction

Laparoscopic cholecystectomy (LC) is a standard treatment for cholelithiasis, due to decreased post operative trauma and less side effects[1]. Though the benefits of this procedure are more but postoperative nausea and vomiting (PONV) is still considered as most common complaint and the reason of prolonged hospitalisation, more morbidity and delayed functional recovery[2]. The incidences of PONV range from 25 to 42% when antiemetic treatment is not considered prophylactically[3].

Ondansetron is a 5-hydroxy tryptamine type 3 receptor ($5HT_3$) antagonist that has provided effective antiemesis in surgical patients[4,5,6]. Dexamethasone has been found to have a prophylactic antiemetic effects on PONV in patients undergoing laparoscopic cholecystectomy under general anaesthesia[7,8,9] .

Some studies[4,10,11] on the combination of Ondansetron plus Dexamethasone have demonstrated a significantly better clinical efficacy against PONV than Ondansetron or Dexamethasone alone.

So far, there is limited data on this type of study in Indian scenario, therefore this study was designed to compare Ondansetron - Dexamethasone combination with either Ondansetron or Dexamethasone in preventing PONV in patients undergoing laparoscopic cholecystectomy.

Material and Method

This prospective double blind prospective randomized control trial (RCT) was performed after approval of institutional ethics committee and written informed consent from patients were obtained. 165 patients aged 16 to 60 years, ASA I & II of both sex, body weight between 50 to 75 kg, scheduled for laparoscopic cholecystectomy under general anaesthesia were recruited in this study and formed our study cohort. We excluded patients with history of motion sickness and/ or previous history of PONV, pregnancy, menstruating, taken anti- emetic drugs and opioids within 3 days before surgery. Patients with

history of corticosteroid hypersensitivity, previous peptic ulcer, diabetes mellitus, and smoking were also excluded from the study. VAS (Visual Analogue Scale) consisting of 10 cm line, where 0 means no pain, 10 means worst possible pain were explained to all patients at their preoperative visit. Patients were randomly allocated using a random number table, to receive intravenously one of the three treatment regimes: Ondansetron 4 mg plus 2 ml normal saline, Dexamethasone 8 mg plus 2 ml normal saline or Ondansetron 4 mg plus Dexamethasone 8 mg (n = 55 each) just before induction of anaesthesia. Study medications were prepared by personal not involved in this study, in identical 5 ml syringe, for each group to ensure blinding of anaesthesiologist. As patients and anaesthesiologists were both blinded this RCT was a double blind study. These drugs were administered intravenously just before induction of anaesthesia. Patients and investigators who collected postoperative data were blinded to the study drug administered.

Patient admitted to our tertiary care hospital from September 2014 to August 2015 for undergoing laparoscopic surgery and who conformed to the specified inclusion and exclusion criteria of this study and gave their written consented to undergo this RCT formed the study population. This study population of 165 patients was divided by randomization technique into three equal groups of 55 patients each. Out of these three groups the group that receives the combination drugs (Ondansetron and Dexamethasone) constitutes the study group, while patients receiving either Ondansetron or Dexamethasone alone form the control group. All patients received opioids both intraoperatively and postoperatively, were nonsmokers and underwent laparoscopic surgery; all known factors for causing PONV. Hence each and every patient received a PONV prophylaxis, a placebo group was not included as not only it would be unnecessary for intergroup comparisons, but would have been highly unethical.

Patients received tablet alprazolam (0.5 mg) orally, night before operation and were fasted at least 6 hours before surgery. All subjects were hydrated with 10 ml/kg of ringer lactate. Anaesthesia was induced with fentanyl 2µg/kg, followed by propofol 2mg/kg. Atracurium (0.6 mg/kg) was given intravenously to facilitate oro-tracheal intubation. Anaesthesia was maintained with isoflurane (1% inspired concentration) along with nitrous oxide 60% in O_2 with controlled ventilation adjusted to maintain the end tidal CO_2 at around 35-45 mm of Hg. Muscle relaxation for pneumo-peritonium and surgical procedures were provided with additional doses of atracurium.

A nasogastric tube was passed to empty the stomach which was suctioned and removed before extubation. During laparoscopy intra-abdominal pressure was maintained at 8-12 mm/Hg by CO_2 insufflation and patients were placed in 15 – 20 degree head up position with little left lateral tilt. Patients were monitored during general anaesthesia by continuous ECG, NIBP, pulse oxymetry and capnometry. At the completion of surgery residual neuromuscular blockade was antagonised with intravenous neostigmine 0.05 mg/kg and glycopyrrolate 0.01mg/kg. Trachea was extubated once the patient was awake. All patients received supplementation of oxygen (3L/min) by a face mask in post operative period for 3 hours and were monitored continuously in the recovery room. The incidence of nausea and vomiting were recorded for first 24 hours post operatively (0-4 hrs at recovery room, and 4-24 hours in ward).

The episode of PONV was recorded by an anaesthesiologist, blinded to which treatment the patient has received. Episodes were identified by spontaneous complaint by the patients or by direct questioning. Nausea was defined as a subjective unpleasant sensation associated with awareness of urge to vomit; retching was defined as a laboured, spasmodic, rhythmic contraction of respiratory muscles without the expulsion of gastric contents from the mouth[12]. Complete response was defined as no PONV and no need for another antiemetic medications. If two or more episodes of emesis occurred in each observation period, another rescue antiemetic (10 mg Metoclopramide) was given intravenously. We made no distinction between retching and vomiting (i.e. a retching event was considered as vomiting event).

Pain was classified as mild, moderate and severe depending on the VAS score of the patients. If VAS score was ≥ 3, mepiridine 0.5 mg/kg, was administered intravenously, total consumed Mepiridine during the first 24 hrs postoperative period was recorded. Details of adverse effects during the study period were recorded by the attending anaesthesiologists.

Statistical Analysis

Out of 165 patients enrolled, 12 patients required conversion to open chocystectomy for surgical reasons, and were excluded from the study. Data obtained from 153 patients were analysed for interpretation. A sample size of 45 patients per group was required to achieve a power of 0.8 ($\alpha = 0.05$) to detect a large difference. Here we initially selected 55 patient per group for better result and compensation for any drop-out during the study. A P-value of less than 0.05 was considered as significant. Statistical difference between the two groups in discrete and continuous variables was tested using Chi square and Student t-test. All values were expressed as mean ± SD range or number (%).

Results

Patients profile and information on the surgery and anaesthesia are summarised in Table 1. The treatment groups were comparable with regard to patient's demographics and types of operation.

Table 1: Patient demographic profile (mean ± SD) or range or number

	Ondansetron (n=50)	Dexamethasone (n=51)	Combination (n=52)
Age (years)	42.3±10.8	41.6±11.l	43.2±10.6
Weight (kg)	56±8.6	54.9±8.2	55.2±7.8
Sex (female/male)	40/10	38/11	38/12
Duration of surgery (min)	72.4±7	73.8±6	73.7±6
Duration of anaesthesia (min)	90.1±6	88.8±5	88.1±8
Postoperative (24 hour) meperidine consumption (in mg)	113.5 (90-130)	111.6(75-120)	111.6 (75-120)

No significant difference

The overall cumulative incidence (0-24 hrs) of PONV were 40% in the Ondansetron group, 37.3% in the Dexamethasone group, 15.4% in Ondansetron group respectively. Thus during the first 24 hours postoperative period patients who had received Ondansetron plus Dexamethasone demonstrated significant lesser incidences of PONV than those who received either Ondansetron or Dexamethasone alone ($P<0.05$) as shown in Table 2.

The complete response (no nausea & vomiting) occurred in 84.6% of the patients who had received Ondansetron plus Dexamethasone, 62% of patients who received Ondansetron and 64.7% of the patient received dexamethasone alone. Thus a complete response during the first 24 hours postoperative period was significantly more common in the patients who had received Ondansetron plus Dexamethasone than those who received either Ondansetron or Dexamethasone alone ($P<0.05$) as shown in Table 2.

Table 2: Number (%) of patients with complete response (no PONV, no rescue antiemetic), nausea, vomiting, requiring rescue antiemetic during initial 4h (0-4h) and the next 20h (4-24 h) after anaesthesia

	Ondansetron (n=50)	Dexamethasone (n=51)	Combination (n=52)	P value
0-4h after anaesthesia				
Nausea	9 (18%)	9(17.65%)	1(1.9%)	
Vomiting	2(4%)	5(9.8%)	3(5.7%)	
Rescue antiemetic	7	6	1	
4-24h after anaesthesia				
Nausea	7(14%)	1(1.9%)	1(1.9%)	
Vomiting	1 (2%)	3(5.9%)	3(5.8%)	
Rescue antiemetic	5	2	1	
Overall cumulative incidences of PONV (0-24h)	20(40%)	19(37.3%)	8(15.4%)	<0.05*
Complete response (no PONV, no rescue) in first 24 hours	31(62%)	33(64.7%)	44(84.6%)	<0.05*

*statistically significant chi-square values

Observed adverse effects were clinically non-serious like dry mouth/lips, headache, dizziness and myalgia, with no difference in incidence between the groups.

Table 3: Incidence of adverse events

	Ondansetron (n=50)	Dexamethasone (n=51)	Combination (n=52)
4-24h after anaesthesia			
Headache	5(10%)	4 (8%)	5(10%)
Dry mouth/lip	4(8%)	4 (8%)	4(8%)
Dizziness	4(8%)	3 (6%)	4(8%)
Others(constipation, myalgia)	3(6%)	3 (6%)	5(10%)
Total	16(32%)	14 (27%)	18(35%)
4-24h after anaesthesia			
Headache	4(8%)	4 (8%)	4(8%)
Dry mouth/lip	4(8%)	3 (6%)	4(8%)

Dizziness	4(8%)	3 (6%)	5(10%)
Others(constipation, myalgia)	3(6%)	4 (8%)	3(6%)
Total	15(30%)	14 (27%)	16(32%)

Values are in number (%)

Discussion

Our study result revealed that patients receiving Ondansetron plus Dexamethasone had significantly lesser incidence of PONV (15.4% vs 40% and 37.3%) as well as more complete response (no nausea & vomiting) after laparoscopic cholecystectomy (84.6% vs 62% and 64.7%), in comparisons with either Ondansetron or Dexamethasone alone during the first 24 hours postoperative period.

Etiology behind the PONV after LC is complex and multi-factorial. Stretch of intra abdominal organs, peritoneal irritation and phrenic nerve excitation by residual CO2 in peritoneal cavity which are very important risk factors of incidence of nausea vomiting after LC[13-14]. A number of factors including anaesthetic techniques, sex, pain, care in post operative period, and patient demographics are considered to influence the incidence of PONV[12]. In this clinical study, however, the treatment group were similar with respect to patient demographics and operative management, and patients with a history of motion sickness and previous history of PONV were excluded because they had a high incidence of emetic symptoms[15]. Otherwise, the number of patients who were observed to be emesis free in the present study would have been changed if such patient related factors had not been controlled. All patients were anaesthetized and operated by same team of surgeon and anaesthesiologists. Duration of surgery and anaesthesia were similar in both groups. In addition patients in both groups also consumed similar amount of mepiridine as analgesic in post operative period. Therefore, the difference in incidence of PONV among the groups can be attributed to the study drugs.

Dexamethasone was first reported to be an effective antiemetic agent in patients receiving chemotherapy in 1981[7]. Recently, Dexamethasone has been reported to be effective in preventing PONV in laparoscopic cholecystectomy[16,7,8]. Ondansetron, a 5HT3 receptor antagonist having antiemetic action in surgical patients[17,4]. Combination of antiemetic drugs could be an effective method to control severe PONV as there is no single stimulus/cause for PONV[18]. The mechanism of action of corticosteroid as antiemetic is unknown; however, there have been some suggestions that central/peripheral inhibition of production of 5HT, central inhibition of synthesis of prostaglandin, or change in permeability of blood brain barrier to serum proteins[19]. In our study the complete response occurred in 62% of the cases in Ondansetron group, 64.7% in Dexamethasone group and 84.6% in Ondansetron plus Dexamethasone group. This is comparable to the study conducted by Khalid Ahsan et al[18], Goutam B et al[4] and Mohammad Eidey et al[11]. Ahmed A et al[20] studied 67 patients undergoing LC receiving combination of Ondansetron and Dexamethasone. They observed no nausea and vomiting in 85% patients. Our results are comparable with respect to Ondansetron plus Dexamethasone combination.

We used the doses of drug i.e. Dexamethasone 8 mg and Ondansetron 4mg was based on previous studies[4, 15,21]. It was shown that dexamethasone was most effective as antiemetic, when administered just before the induction[19]. As half-life of Ondansetron is approximately 3.5 – 4 hours in adults[19], and the mean duration of the procedure in our study was about 1 hour, we assumed that timing of antiemetic combination before induction would not affect the outcome. The study drugs are not known to be incompatible when mixed together[4,22].

In our study we didn't find any complications related to use of Dexamethasone[23]. Adverse effects observed in this study were not clinically serious in both the groups and did not differ in incidence between the groups.

Limitations of the study were that, not all laparoscopic studies were included in this study. The high incidence of PONV after LC may justify the use of prophylactic antiemetic so we did not include a placebo group. Also we did not mention expense for treatment of established PONV and sequel of PONV. Another limitation is the timing of the antiemetic prophylaxis at the beginning of induction rather than towards the end of the operation. However our study was done on studies based on similar protocol[11,13].

We conclude that the combination of Ondansetron plus Dexamethasone is better than either Ondansetron or Dexamethasone alone as a prophylactic in preventing PONV following laparoscopic cholecystectomy.

Acknowledgements: Nil declared

References

1. Mealy K, Gallagher H, Bany M et al. Physiological and metabolic response to open and laparoscopic cholecystectomy. Br J Surg 1992;79:1061-4.
2. Hessami MA, Yari M. Granisetron versus dexamethasone in prophylaxis of nausea and vomiting after laparoscopic cholecystectomy. Anesth Pain Med 2012;2(2):81–4.
3. FujiiY, SaitohY, Tanaka H et al. Granisetron/Dexamethasone combination for prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Eur J Anaesthesiol 2000;17:64-8.
4. Gautam B, Shrestha BR, Lama P, Rai S. Antiemetic prophylaxis against postoperative nausea and vomiting with ondansetron-dexamethasone combination compared to ondansetron or dexamethasone alone for patients undergoing laparoscopic cholecystectomy, Kathmandu University Medical Journal 2008;6(3):319-28.

5. Liberman MA, Howe S, Lane M. Ondansetron versus placebo for prophylaxis of PONV in patients undergoing ambulatory laparoscopic cholecystectomy. Am J Surg 2000;179:60–2.
6. Koivuranta MK, Laara E, Ryhanen PT. Antiemetic efficacy of prophylactic ondansetron in laparoscopic cholecystectomy. A randomized, double-blind, placebo-controlled trial. Anaesthesia 1996;51:52-5.
7. Wang JJ, Ho ST, Liu YH, et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth 1999;83:772-5.
8. Wang JJ, Ho ST, Uen YH et al. Small dose Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy Anesth Analg 2002;95:229-32.
9. Fukami Y, Terasaki M, Okamoto Y, Sakaguchi K, Murata T, Ohkubo M, et al. Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy: a prospective randomized double-blind study. J Hepatobiliary Pancreat Surg 2009;16(3):367–71.
10. Lopez-Olando L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth 1996;76:835-40.
11. Eidy M, Vafaei HR, Rajabi M, Mohammadzadeh M, Pazouki AR. Effect of Ondansetron and Dexamethasone on post operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Journal of Minimally Invasive Surgical Science 2013;2(2):138-43.
12. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162-84.
13. Argiriadou H, Papaziogas B, Parlidas T, Parlapani A, Georgiu M. Tropisetron versus ondansetron for prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomized double blind, placebo - controlled study. Surg Endosc 2002;16:1087-90.
14. Bano F, Zafar S, Aftab S, Haider S. Dexamethasone plus ondansetron for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a comparison with dexamethasone alone. J Coll Physicians Surg Pak 2008;18:265-9.
15. Apfel CC, Laara E, Koivuranta M, Greim CA. A simplified risk score for predicting PONV: conclusions from cross-validations between two centers. Anesthesiology. 1999;91:693–700.
16. Kashmiri ZA, Sheikh Z, Haider S. Injection dexamethasone in preventing postoperative nausea and vomiting: a comparison with placebo in the patients undergoing laparoscopic cholecystectomy. J Coll Physicians Surg Pak 2006;16:689-92.
17. Pearman MH. Single dose intravenous ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia 1994; 49(Suppl.):11-5.
18. Ahsan K, Abbas N, Naqvi SMN et al. Comparison of efficacy of Ondansetron and Dexamethasone combination and Ondansetron alone in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy. J Pak Med Assoc 2014;64(3):242-6.
19. Bhattarai B, Shreshta S, Singh J. Comparison of ondansetron and combination of ondansetron and dexamethasone as a prophylaxis for postoperative nausea and vomiting in adults undergoing elective laparoscopic surgery. J Emerg Trauma Shock 2011;4(2):168-72.
20. Ahmed N, Muslim M, Aurangzeb M, Zarin M. Prevention of post operative nausea and vomiting in laparoscopic cholecystectomy. J Med Sci 2012;20:33-6.
21. Elhakim M, Nafie M, Mahmoud K, Atef A. Dexamethasone 8 mg in combination with ondansetron 4 mg appears to be optimal dose for the prevention of nausea and vomiting after laparoscopic cholecystectomy. Can J Anaesth 2002;49:922-6.
22. Trissel LA. Handbook of Injectable Drugs,11th ed. Special Publishing Department of the American Society of Health-System Pharmacists, Bethesda, Maryland; 2001.
23. Lim SH, Jang EH, Kim MH et al; Analgesic effect of preoperative versus intraoperative Dexamethasone in laparoscopic cholecystectomy with multimodal analgesia. Korean J Anesthesiol 2011:61(4):315-9.