ORIGINAL ARTICLE

Comparison of efficacy of Ondansetron and Dexamethasone combination and Ondansetron alone in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy

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Abstract

Objective: To compare the efficacy of ondansetron alone and combination of ondansetron and dexamethasone in preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

Methods: The randomised control trial was conducted from April 23 to August 22, 2009, at the Liaquat National Hospital, Karachi, and comprised 100 American Society of Anaesthesiology I and II patients undergoing laparoscopic cholecystectomy. Half of the subjects comprised Group A and received ondansetron alone, while Group B received combination of ondansetron and dexamethasone. They were randomised by opaque envelope method. Group A received ondansetron 4mg while Group B received ondansetron 4mg with dexamethasone 8mg, 1 minute before induction. Post-operatively patients were observed for six hours for any episode of nausea or vomiting, or whether the patients required any rescue anti emetic. SPSS 19 was used for statistical analysis.

Results: Patients receiving ondansetron alone showed 14(28%) with incidence of nausea or vomiting while the other group showed 6(12%). This difference was statistically significant ($p<0.046$).

Conclusion: Combination of ondansetron and dexamethasone was more efficacious compared to ondansetron alone in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

Keywords: Anti-emetic, Laparoscopic, Ondansetron, Dexamethasone. (JPMA 64: 242; 2014)

Introduction

Laparoscopic surgery provides enormous benefits to patients, including quick recovery, shorter hospital stay and prompt return to regular activities.[1] Despite the minimally incursive nature of laparoscopy, high incidence (53-70%) of post-operative nausea and vomiting (PONV) is still a significant cause of post-operative morbidity.[2] PONV is highly unacceptable for the patients and may augment uneasiness and unwanted adverse effects that extend recovery time, delay patient discharge, and increase hospital expenses.[3]

PONV may lead to anorexia, dehydration and electrolyte imbalance. Extremely forceful vomiting can lead to wound dehiscence and even rupture of oesophagus.[4] So keeping in view its common occurrence and threatening consequences, PONV must be controlled effectively, especially in high-risk surgical patients.[5] There are certain factors which can pre-dipose a patient to PONV, including the administration of opioids, type of surgical procedure, female patient, history of previous PONV, long duration of operation and depth of anaesthesia, carbon dioxide retention and number of visitors during recovery.[4,6] Laparoscopic cholecystectomy is a procedure that requires necessity of carbon dioxide insufflation resulting in peritoneum distention, and increased pressure in the peritoneal cavity which is a very important risk factor inciting nausea and vomiting.[7]

Prophylaxis and treatment of PONV has been attempted with various drugs over the years, which includes serotonin antagonists, anti-cholinergic, butyrophenones, phenothiazines, steroids and anti-histamines. PONV is multifactorial during laparoscopic cholecystectomy, therefore, combination of different classes of anti-emetics are preferred to control PONV.[8,9] Ondansetron and dexamethasone have well-accepted roles in the prophylaxis of PONV after gynaecological, obstetric, paediatric and general surgery.[10] The chemotactic trigger zone (CTZ) is a region in the brainstem thought to play a significant role in the vomiting reflex. Ondansetron is a 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist that blocks receptors in the CTZ as well as vagal nerve terminals. The exact anti-emetic mechanism of dexamethasone is unknown, but it is thought to enhance the anti-emetic effect of 5-HT3 receptor antagonists[11] that is central/peripheral inhibition of production of 5-HT,

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central inhibition of synthesis of prostaglandins, changes in permeability of the blood brain barrier to plasma proteins, or by releasing endorphins.[12] The optimal dose of dexamethasone ranges from 2-32mg, but most studies show 8mg to be the most effective dose.[3]

Imam SM et al[5] observed no nausea and vomiting in 77.5% of (31/40) patients receiving combination of ondansteron and dexamethasone as compared to 47.5% (19/40) who received ondansteron alone. All their patients underwent elective caesarian sections ($p<0.005$). Bano F et al[13] studied 100 patients undergoing laparoscopic cholecystectomy and compared dexamethasone alone with dexamethosone and ondansetron. In patients receiving combination of dexamethosone and ondansetron, they noticed no nausea and vomiting in 81.6% of patients, while in patients receiving dexamethasone alone, only 60.4% suffered no nausea and vomiting. Significance calculated was less than 0.05. Ahmed N et al[14] studied 67 patients undergoing laparoscopic cholecystectomy receiving combination of ondansetron and dexamethasone. They observed no nausea and vomiting in 85% patients.

Apart from these three studies, to our knowledge there are no studies on this subject in our country. Our study was the first to compare ondansetron alone and ondansetron and dexamethasone combination in preventing nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

Patients and Methods

The randomised control trial was conducted from April 23 to August 22, 2009 in the Department of Anaesthesiology at the Liaquat National Hospital, Karachi. After approval by the institutional ethical committee, 100 patients, American Society of Anaesthesiology (ASA) I and ASA II of age 20 to 70 years undergoing laparoscopic cholecystectomy were included in the study. Patients with ASA III and IV, or suffering from pre-operative emesis or pregnant or taking sedatives, anxiolytics, anti-histamines and anti-emetics or with known history of drug allergy, hypersensitivity to anti-emetics or suffering from ear disease and vertigo or menstruation at the time of surgery (because menstruation can provoke nausea and vomiting which could affect the outcome of the study) or history of post-operative emesis, and history of motion sickness were excluded from the study. They were randomly divided into Group A and Group B with sealed envelope technique of 50 patients in each group. Group A received ondansetron alone and Group B received combination of ondansetron and dexamethasone.

Every patient underwent a pre-anaesthesia assessment before surgery and an informed and written consent was obtained. No pre-medication was given and the patients were kept nil orally (NPO) from midnight. In the operating room, the two groups were formed. Patients belonging to Group A received ondansetron 4mg intravenous (IV), while Group B received ondansetron 4mg with dexamethasone 8mg IV, one minute before induction.

After pre-oxygenation with 100% oxygen, both groups received nalbuphine 10mg IV. Anaesthesia was induced with propofol (2mg/kg), and tracheal intubation was achieved with suxamethonium (1.5-2mg/kg). Intra-operative muscle relaxation was achieved with rocuronium (0.5 mg/kg) initially, then in incremental doses of 0.15 mg/kg as required. Mechanical ventilation was done to maintain end-tidal carbon dioxide (CO_2) of 35 - 40 mmHg. Anaesthesia was maintained with isoflurane and nitrogen oxide (N_2O) (60%) in oxygen (O_2) (40%). At the end of surgery, anaesthesia was discontinued and residual neuromuscular blockage was antagonised by giving neostigmine (0.05mg/kg) mixed with glycopyrrolate (0.01mg/kg). Patients were shifted to the recovery room where they were observed for presence of nausea or vomiting and the requirement of rescue anti-emetics by nurses for the first six hours. In case patient was shifted to a ward, the ward nurses observed presence and absence of nausea and vomiting and noted it on a proforma attached to patient's file. Metoclopramide 10mg IV was used as rescue medication in case of nausea that lasted for more than 15 minutes or an episode of vomiting. The data was collected through structured proforma. Drug or drugs were labelled efficacious if no nausea and vomiting occurred 6 hours post-operatively as per the operative definition and no rescue anti-emetic used.

Statistical analysis was performed using SPSS 19. Frequency and percentage were computed for categorical variables like gender, ASA, PONV and rescue anti-emetic. Mean, standard deviation, median with inter-quartile range (IQR) were computed for quantitative variables like age and weight. Independent sample t test after normality checking was used to apply mean age difference between the groups. Non-parametric test, Mann Whitney test was applied. Due to non-normal data, median weight was compared between the groups. Chi-square test was applied to compare post-operative nausea and vomiting between the groups.

Results

With an overall mean age of 42.90±13.75 years, the 100 patients in the study comprised 16(16%) males and

Table-1: Comparison of characteristics between the groups.

Variables	Group A n=50	Group B n=50	P-values
Mean Age (Years)	41.32±12.9	44.48±14.5	0.25‡
Mean Weight (kg)	60±9.25	60±8.5	0.69†
Gender			
Male	7(14%)	9(18%)	0.58*
Female	43(86%)	41(82%)	
ASA			
I	29(58%)	24(48%)	
II	21(42%)	26(52%)	0.31*

Data are presented as mean ± standard deviation, Median [IQR] and n (%).
†Mann-Whitney test, ‡Independent sample t test and *Chi-Square.
ASA: American Society of Anaesthesiology.

Table-2: Comparison of PONV between groups.

PONV	Group A n=50	Group B n=50	P-values
Nausea	8(16%)	3(6%)	0.11
Vomiting	6(12%)	3(6%)	0.48
Nausea and Vomiting	14(28%)	06(12%)	0.046*

Data are presented as n (%); *significant at $p \leq 0.05$.
PONV: Post-operative Nausea and Vomiting.

84(84%) females. Age, weight, gender and ASA status of the patients were not significant between the two groups (Table-1). Rate of nausea and vomiting separately were also not significant between the groups (Table-2), while during the first 6 hours, the rate of combined nausea and vomiting was significantly high in Group A than Group B [14(28%) vs. 6(12%); p=0.046]. Patients suffering from post-operative nausea and vomiting requiring rescue anti-emetic were 14 (28%) in Group A and 6 in Group B.

Discussion

Numerous anti-emetic regimens, alone or in combination, have been used for treatment and tried for prophylaxis with some degree of effectiveness. Dexamethasone has been used as an anti-emetic for more than 30 years in patients undergoing chemotherapy with limited adverse effects.[15] Dexamethasone lessens the incidence of PONV after abdominal[16] and non- abdominal[17] surgery and is particularly useful for the prophylaxis of late nausea and vomiting.[18]

Ondansetron a 5-HT3 receptor antagonist has provided effective anti-emesis in surgical patients.[19] 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.[20]

Ondansetron has been shown to cause a dose-dependent reduction in PONV with a plateau effect at 4mg, which is the maximum recommended dose by the manufacturers for prophylaxis against PONV.

In patients undergoing laparoscopic cholecystectomy, high incidence of PONV has been reported (50-70%).[21] Dexamethasone in a dose of 8-10mg has been used frequently in the prevention of PONV.[3,22] 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.[23]

Ondansetron has a good effect against vomiting. Dexamethasone also reduces the incidence of vomiting, but appears to be more specific in the prevention of nausea.[24] 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.[25]

The current study compared the efficacy of ondansetron 4mg, with and without dexamethasone 8mg, in the prevention of PONV after laparoscopic cholecystectomy. During the first 6 hours post-operatively nausea and vomiting was not observed in 88% (44/50) in the combination of ondansetron and dexamethasone (Group B) and 72% (36/50) in the ondansetron group (Group A), while nausea and vomiting was observed in 12% (6/50) patients in Group B and 28% (14/50) in group A. Nausea and vomiting was significantly low in group B than group A (p=0.046). Out of 50 patients, nausea was observed in 8 (16%) in Group A, while it was in 3(6%) patients in Group B. Significant difference was not observed between groups (p=0.11). Similarly, vomiting was observed in 6 (12%) cases in Group A and 3 (6%) cases in Group B. Significant difference was also not observed between groups for vomiting (p=0.487).

Imam SM et al.[5] observed no nausea and vomiting in 77.5% of (31/40) patients receiving combination of ondansetron and dexamethasone as compared to 47.5% (19/40) who received ondansetron alone. All these patients underwent elective caesarian sections ($p<0.05$). They found that 22.5% experienced PONV either as nausea and vomiting in the combination group. This result is slightly higher than the current study (22.5% vs 12%). The incidence of PONV was higher in the combination group in that study because all the patients were pregnant, while we had no pregnant patients.

Mckenzie et al[26] conducted a double-blind, randomised study to compare the effectiveness of ondansetron-

dexamethasone (Group I) vs ondansetron (Group II) alone in female patients undergoing major gynaecological surgery with general anaesthesia (GA). A complete response, defined as no emesis and no need for rescue anti-emetic during the 24-h post-operative period, occurred in 52% patients in the combination group vs 38% in ondansetron group (p=0.045). Emesis occurred in 15% in Group I and 34% in Group II (p=0.003). They concluded that the combination anti-emesis of ondansetron plus dexamethasone was more effective than ondansetron alone for prophylaxis against PONV. As far as the percentage analysis is concerned, the results of the current study are better than the results shown by McKenzie et al, when the parameters of vomiting incidence and complete response are compared. A complete response in the ondansetron group was 72% vs. 38% and in the combination group it was 88% vs. 52%. Incidence of vomiting in the ondansetron group was 12% vs. 34% and in the combination group, 6% vs. 15%.

Lopez-olaondo L et al.[27] studied the efficacy of ondansetron 4mg plus dexamethasone 8mg for prophylaxis against PONV in 100 ASA I and II females undergoing major gynaecological surgery with GA. They found that a complete response (no nausea and emetsis episode during the 48-hour post-operative period) occurred in 84% of patients in the ondansetron and dexamethasone group, and in only 20% of patients in the placebo group. In the ondansetron group, it occurred in 52% patients and in 60% patients in the dexamethasone group. The incidence of nausea and emesis episodes in the ondansetron with dexa group was lower than in the placebo ($p<0.01$), ondansetron ($p< 0.05$) and dexamethasone ($p=0.057$) groups. There was no difference between ondansetron and dexamethasone, and both were more effective than placebo ($p<0.05$ and $p<0.01$ respectively). Dexamethasone appreared to be preferable in preventing nausea than emetic episodes. Fewer patients in the combination group needed rescue anti-emetic ($p<0.01$ vs. placebo and $p<0.05$ vs. ondansetron). They concluded that prophylactic combination anti-emesis is effective against PONV. The results of the current study seem statistically comparable. A complete response in the combination group was 88% vs. 84% and in ondansetron group, it was 72% vs. 52%.

Bano F et al[13] studied dexamethasone 8mg plus ondansetron 4mg combination with dexamethasone 8mg alone in patients undergoing laparoscopic cholocystectomy. They found that 81.6% patients didn't have nausea and vomiting post-operatively in the combination group, while 60.4% patients did not complain of either nausea or vomiting in the dexamethasone group. The results of the current study are comparable with respect to the combination group i.e. 88% vs. 81.6%.

Ahmed N[14] et al studied 67 patients undergoing laparoscopic cholecystectomy receiving combination of ondansetron and dexamethasone. They observed no nausea and vomiting in 85% patients. Our results are comparable with respect to ondansetron and dexamethasone combination i.e. 88% vs. 85%.

Bhattarai B et al[28] compared the efficacy and safety of the combination of ondansetron 4mg and dexamethasone 4mg with ondansetron 4mg alone given as prophylaxis for PONV in 100 (50 in each group) ASA I and II adult patients undergoing laparoscopic surgery. They found that a complete response occurred in 92% patients in the combination group, while in the ondansetron group it was 76%. The results of the current study seem statistically comparable. A complete response in the combination group was 88% vs. 92%, and in the ondansetron group, it was 72% vs. 76%.

Dabbous AS et al[29] enrolled 84 (42 in each group) patients and compared the effectiveness of dexamethasone 8mg with either granisetron 1mg or ondansetron 4mg in patients undergoing laparoscopic surgery. They showed no statistically significant difference in anti-emetic efficacy in both groups. Our results are comparable with respect to ondansetron and dexamethasone combination.

Conclusion

The occurrence of PONV was lower in combination (ondansetron + dexamethasone) group than ondansetron alone. Therefore, the need for rescue anti-emetic was lower in the combination group. Hence, the efficacy of combination therapy was found to be superior to ondansetron alone.

References

1. Gupta P, Khanna J, Mitramustafi AK, Bhartia VK. Role of pre-operative dexamethasone as prophylaxis for post-operative nausea and vomiting in laparoscopic surgery. J Min Access Surg 2006; 2: 12-5.
2. Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth 1999; 83: 772-5.
3. Leksowski K, Peryga P, Szyca R. Ondansetron, metoclopramide, dexamethasone, and their combinations compared for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a prospective randomized study. Surg Endosc 2006; 20: 878-82.
4. Ashfaque M. Prevention of postoperative nausea and vomiting: a review of causative factors and management. Med Channel 1998; 4: 43-52.
5. Imam SM, Mufti TM, Bhatti AH, Farida MA. Efficacy of balanced antiemesis for prophylaxis against postoperative nausea and

vomiting: a comparative study of ondansetron and dexamethasone versus ondansetron alone. Pak Armed Forces Med J 2004; 54: 185-90 .
6. Wattwil M, Thorn SE, Lovqvist A, Wattwil L, Gupta A, Liljegren G. Dexamethasone is as effective as ondansetron for the prevention of postoperative nausea and vomiting following breast surgery. Acta Anaesthesiol Scand 2003; 47: 823-7.
7. 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.
8. Scuderi PE, James RL, Harris L, Mims GR. Multimodal antiemtic management prevents early postoperative vomiting after outpatient laparoscopy. Anaesth Analg 2000; 91: 1408-14.
9. Rajeeva V, Bharadwaj N, Batra YK, Dhaliwal LK. Comparison of ondansetron with ondansetron and dexamethasone in prevention of PONV in diagnostic laparoscopy. Can J Anaesth 1999; 46: 40-4.
10. Szarvas S, Chellapuri RS, Harmon DC, Owens J, Murphy D, Shorten GD. A comparison of dexamethasone, ondansetron, and dexamethasone plus ondansetron as prophylactic antiemetic and antipruritic therapy in patients receiving intrathecal morphine for major orthopedic surgery. Anesth Analg 2003; 97: 259-63.
11. Robert S, Donald C, Benjamin C, Kim B. Postoperative nausea and vomiting in the plastic surgery patient. Aesth Plast Surg 2004; 28: 29-32.
12. Harris AL. Cytotoxic-therapy-induced vomiting is mediated via enkephalin pathways. Lancet 1982; 1: 714-6.
13. 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.
14. 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.
15. Aapro MS, Albert DS. Dexamethasone as an antiemetic in patients treated with cisplatin. N Engl J Med 1981; 305: 520.
16. Huang JC, Shieh JP, Tang CS. Tzeng JI, Chu KS, Wang JJ. Low-dose dexamthasone effectively prevents postoperative nausea and vomiting after ambulatory laparoscopic surgery. Can J Anaesth 2001; 48: 973-7.
17. Chen CC, Siddiqui FJ, Chen TL, Chan ES, Tam KW. Dexamethosone for prevention of postoperative nausea and vomiting in patients undergoing thyroidectomy: meta-analysis of randomized control trials. World J Surg 2012; 36: 61-8.
18. Ho CM, Wu HL, Ho ST, Wang JJ. Dexamethasone prevents postoperative nausea and vomiting: benefit versus risk. Acta Anaesthesiol Taiwan 2011; 49: 100-4.
19. Pearman MH. Single dose intravenous ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia 1994; 49: 11-5.
20. Smith DB, Newlands ES, Rustin GJ, Begent RH, Howells N, McQuade B, et al. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin - containing chemotherapy. Lancet 1991; 338: 487-90.
21. 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.
22. Wang JJ, Ho ST, Lee SC, Liu YC, Liu YH, Liao YC. The prophylactic effect of dexamethasone on postoperative nausea and vomiting in women undergoing thyroidectomy: A comparison of droperidol with saline. Anaesth Analg 1999; 89: 200-3.
23. Fujii Y, Uemura A. Dexamethasone for the prevention of nausea and vomiting after dilatation and curettage: a randomized controlled trial. Obstet Gynecol 2002; 99: 58-62.
24. Jones AL, Hill AS, Soukop M, Hutcheon AW, Cassidy J, Kaye SB, et al. Comparison of dexamethasone in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. Lancet 1991; 338: 483-7.
25. Elhakim M, Nafie M, Mahmoud K, Atef A. Dexamethasone 8mg in combination with ondansetron 4mg appears to be the optimal dose for the prevention of nausea and vomiting after laparoscopic cholecystectomy. Can J Anaesth 2002; 49: 922-6.
26. McKenzie R, Tantisira B, Jarambelker DJ, Riley TJ, Abdulhady H. Comprison of Ondansetron with Ondansetron plus Dexamethasone in the prevention of postoperative nausea and vomiting. Anaesth Analg 1994; 79: 961-4.
27. Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N. Comparison of Ondansetron and Dexamethasone in the prophylaxis of pospoperative nausea and vomiting. Br J Anaesth 1996; 76: 835-40.
28. Bhattrai B, Shrestha S, Singh J. Comarison of ondansetron and combination of ondansetron and dexamethasoneas a prophylaxis for postoperative nausea and vomiting in adults undergoing elective laparoscopic surgery. J Emerg Trauma Shock 2011; 4: 168-72.
29. Dabbous AS, Jabbour -Khoury SI, Nasr VG, Moussa AA, Zbeidy RA, Khouzam NE, et al. Dexamethasone with either granisetron or ondansetron for postoperative nausea and vomiting in laparoscopic surgery. Middle East J Anesthesiol.