Original Article

Low dose ondansetron with dexamethasone for prophylaxis of postoperative nausea and vomiting following laparoscopic cholecystectomy—A randomized double-blind study

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Abstract

Background and Aims: Ondansetron and dexamethasone combination is effective for prophylaxis against postoperative nausea and vomiting (PONV). Ondansetron, when compared to dexamethasone, is known to cause more adverse effects and is relatively expensive. The present study evaluated the efficacy of standard dose and low dose ondansetron, i.e. 100 μg/kg and 50 μg/kg, respectively, with dexamethasone 8 mg for PONV prophylaxis in laparoscopic cholecystectomy (LC).

Material and Methods: After the approval from the Institutional Ethics Committee-Human Research [IEC-HR] and prospective CTRI registration, this randomized, double-blind interventional study was conducted following informed consent from each participant. Patients aged 18–65 years of either sex, with ASA physical status I or II, undergoing LC under general anesthesia, were included and divided into groups C and L. Patients in groups C and L received 100 μg and 50 μg of ondansetron, respectively, in combination with 8 mg dexamethasone. The incidence of PONV in first 6 hrs, PONV score, rescue antiemetic consumption, rescue analgesia, and hemodynamic parameters were recorded.

Results: A total of 110 patients were included with 55 in each group. Incidence of PONV in the first 6 hours was found to be higher in 1–2 hour- and 2–3-hour time intervals in group L; but was significant only at 1–2-hour time interval ($P < 0.05$). Proportion of patients needing rescue antiemetic in the first 6 hours was higher in group L but was not statistically significant.

Conclusion: We observed that 50 μg/kg combination of ondansetron was associated with higher incidence of post operative nausea in the immediate postoperative period than 100 μg/kg dose; however, no significant difference was observed in incidence of post-operative vomiting between two doses following LC.

Keywords: Dexamethasone, laparoscopic cholecystectomy, ondansetron, postoperative cause vomiting

Introduction

Postoperative nausea and vomiting (PONV) is the common complication following surgery causing patients' and increased postoperative recovery time. Surgeries such as laparoscopic surgeries, middle ear surgeries, and breast surgeries are associated with increased incidence of PONV.[1] The incidence of PONV following laparoscopic cholecystectomy (LC) has been observed to be 53–72%.[2-5]

In numerous investigations, PONV in patients scheduled for LC has been prevented and treated with a variety of antiemetics and among the numerous antiemetic therapies, a combination

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of serotonin receptor antagonists with dexamethasone considered to be highly effective for preventing PONV after LC.[6] Ondansetron is a 5 HT3 antagonist which decreases the incidence of PONV in early postoperative period and dexamethasone, a steroid which is known to decrease the incidence of the PONV in late postoperative period.[7] The use of combination of these drugs for the prophylaxis of PONV against the sole antiemetic drug is always considered superior than monotherapy as it carries lesser side effects, lesser need of rescue antiemetic, and decreased overall incidence of PONV.[7-10] Most of the studies have used a combination of 4 mg ondansetron and 8 mg dexamethasone for PONV prophylaxis and found it to be efficacious.[7-10]

The side effect profile of ondansetron include headache, blurred vision, extrapyramidal side effects, QT prolongation, whereas adverse effects with dexamethasone in single dose are extremely rate and are very minor in nature.[10] Cost-effectiveness is also a major concern as PONV prophylaxis given to almost all patients undergoing surgery under general anesthesia (GA). Here again, the cost of ondansetron is relatively more than dexamethasone. So, it affirms the need of finding the optimal low dose of ondansetron when used in combination with dexamethasone for PONV prophylaxis.

On extensive literature search, no study has evaluated the low dose ondansetron with dexamethasone combination for PONV prophylaxis in patients undergoing laparoscopic cholecystectomy. We hypothesized that the low dose of ondansetron, i.e. 50 μg/kg will be non-inferior or equally efficacious to the standard dose ondansetron, i.e. 100 μg/kg in combination with dexamethasone 8 mg for PONV prophylaxis in patients undergoing LC.

Therefore, the present study compared the efficacy of standard dose and low dose of ondansetron, i.e., 100 μg/kg and 50 μg/kg, respectively, in combination with dexamethasone 8 mg for PONV prophylaxis in patients undergoing laparoscopic cholecystectomy. The primary outcome of the study was to determine the incidence of PONV in the first 6 hours. The secondary outcomes include PONV score at 6–12 hrs and 12–24-hour time intervals, total requirement of rescue antiemetic in the first 24 hrs, postoperative Numerical Rating Score (NRS), and incidence of side effects.

Material and Methods

Following approval from Institutional Ethics Committee-Human Research (IEC-HR), and prospective CTRI registration, this randomized, double-blind interventional study was conducted between January 2021 to August 2022. Written informed consent was taken from all patients. Patients aged 18–65 years of either sex, with American Society of Anesthesiologists (ASA) physical status I or II, undergoing LC under GA were included. Pregnant patients and patients having history of cardiac, hepatic, or renal disease were excluded from the study. Patients were randomly allocated into one of the two groups. Patients in both the groups received dexamethasone 8 mg given at the beginning of the surgery. Patients in the groups C and L received ondansetron 100 μg/kg and 50 μg/kg near the end of the surgery, respectively.

Randomization was done using a computer-generated random number table. The allocation concealment was done using sequentially numbered opaque sealed envelopes. Third person not involved in the study made the study drug, and the patient as well as the investigator was blinded to the study drug used. The dose calculated was diluted with saline to make a volume of 3 ml, and this volume remained same between the two groups so as to ensure double blinding.

Tablet alprazolam 0.5 mg was given as premedication, the night before the surgery. General anesthesia was induced with 0.1 mg/kg morphine IV, 2 mg/kg propofol IV, and 0.1 mg/kg vecuronium IV which was used to facilitate endotracheal intubation. Dexamethasone 8 mg IV was given after induction of anesthesia to all the patients. Anesthesia was maintained with isoflurane 1%–1.5% with nitrous oxide 60% in oxygen. Ventilation was mechanically controlled and adjusted to maintain an end-tidal concentration of CO_2 between 35 and 40 mmHg.

Hemodynamic parameters and minimum alveolar concentration (MAC) had been noted every 15 min during the surgery. Depending on the group allocation, ondansetron 100 μg/kg IV or 50 μg/kg IV was given 30 min before the completion of surgery. The study drug was prepared by the third person not involved in the study. All patients received IV Paracetamol 1 gm infusion toward the end of the surgery. Neuromuscular block had been reversed with 0.05 mg/kg neostigmine and 0.01 mg/kg glycopyrrolate at the end of surgery. After the clinical assessment of adequacy of the reversal of neuromuscular block, trachea had been extubated near the end of surgery.

All patients were kept under observation in the postoperative period for at least 4 hrs. Hemodynamic variables, i.e. heart rate (HR), systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP), were recorded every hour for 4 hours. All the patients received injection paracetamol 1 gm IV 8 hourly for the postoperative pain management. The incidence of nausea and vomiting was

assessed by an investigator who is blinded to the treatment group and was performed hourly till first 6 hrs and then at the following intervals, i.e. 6–12 hrs and 12–24 hrs postoperatively. Nausea had been defined as subjective unpleasant sensation associated with the urge to vomit. Vomiting had been defined as the forceful expulsion of gastric contents.

Postoperative nausea and vomiting were evaluated using numeric scoring system, the PONV score.[10] No nausea or vomiting = 0, nausea but no vomiting = 1, vomiting once in 30 min or more = 2, persistent nausea >30 min, or two or more vomits in 30 min = 3.

The severity of postoperative pain was assessed by using Numeric Rating Pain Scale (NRS pain) score that ranges between 0 (no pain) and 10 (worst pain imaginable). When the patient developed nausea for more than 15 min or vomiting in the postoperative period, then metoclopramide 10 mg was given IV slowly as rescue antiemetic. If the patient's PONV persisted despite administering rescue antiemetic, the physician was allowed to give ondansetron or any other antiemetic as per their discretion.

If NRS pain score is ≥3, injection diclofenac 75 mg IV administered as a rescue analgesic. The patients were enquired about the common side effects of medication, namely headache, dizziness, drowsiness, constipation, and flushing.

Sample size calculation

The sample size was calculated by considering it to be a non-inferiority trial. The reported incidence of PONV following standard dose combination of ondansetron and dexamethasone is 12%.[11] Sample sizing assumes that the expected percentage response in both the comparator and study group to be 82%, and the non-inferiority criteria was set to an absolute value of 20%. To achieve 80% power to demonstrate non-inferiority, it was estimated that 46 subjects per group would be required. With a withdrawal/non-evaluable subject rate of 10%, a total of 51 per group subjects had been recruited leading to a total required sample size of 102 subjects. So, we had included a sample size of 110 patients with 55 in each group.

Statistical analysis

Statistical analyses had been performed using SPSS version 20.0. Data had been presented as mean ± standard deviation or as the number of patients or percentages. Categorical variables had been compared using the Chi-square test or Fisher's exact test. Continuous variables were compared using independent *t*-test. *P* value less than 0.05 was considered statistically significant.

Results

A total of 117 patients were assessed for eligibility, out of which three patients denied consent and 114 patients were enrolled. Out of 114, in four patients LC was turned to open cholecystectomy. Finally, a total of 110 patients with 55 patients in each group were included [Figure 1].

Both the groups were comparable with respect to age, gender distribution, weight, duration of surgery, and total IV fluid infused [Table 1].

The incidence of PONV was observed to be higher in group L at 1–2-hr and 2–3-hr intervals, but was statistically significant only at 1–2-hr interval (*P* value = 0.002*) [Table 2].

In the 0–2-hr interval, only the difference in postoperative nausea was significant (*P* = 0.002); the difference in postoperative vomiting was not significant [Table 3]. There was no significant difference in PONV in 2–6-hr interval and 6–12-hr interval [Table 3]. At 12–24-hr interval, none of the patients in either of the groups had PONV. On intergroup analysis, the need for rescue antiemetic was observed to be comparable between both the groups in the various aforementioned time interval [Table 4].

The mean NRS pain score is comparable between the two groups in the first 24 hr of the postoperative period in various designated time intervals. Out of a total of 110 patients,

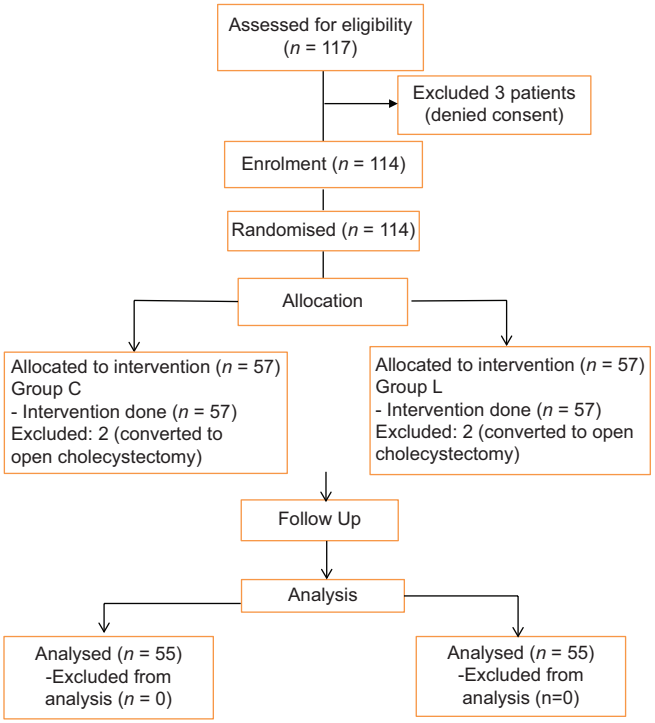

Figure 1: Consort flow diagram

3 patients in each group had received rescue analgesic, and this difference was not statistically significant ($P = 1.0$).

The hemodynamic parameters, i.e. SBP, DBP, MAP, and HR, were recorded in the postoperative period every hourly for first 4 hours. On intergroup analysis, there were no significant difference between the mean SBP, DBP, MAP, and HR at various designated time intervals [Figure 2].

The incidence of side effect was 3.6% (n = 2) in both the groups. One patient each in both the groups developed headache and flushing. The side effects were mild and did not require any intervention. Both the groups were comparable with respect to the side effects.

Table 1: Patients' characteristics

Parameters (mean±SD)	Group C (*n*=55)	Group L (*n*=55)	*P*
Age of the patient (yrs)	36.56 (±11.70)	38.24 (±10.75)	0.437
Gender (F:M)	50:5	47:8	0.376
Weight of the patient (in kgs)	56.40 (±5.25)	58.04 (±5.81)	0.124
Duration of surgery (in mins)	71.73 (±12.48)	71.45 (±11.89)	0.907
Total IV fluid Infused (in ml)	1243.64 (±208.84)	1207.27 (±204.46)	0.358

*Group C: Ondansetron 100 μg/kg + Dexamethasone 8 mg, Group L – Ondansetron 50 μg/kg + Dexamethasone 8 mg. *P<0.05: statistically significant*

Table 2: Patients developing PONV between the two groups at different time intervals

PONV present	Number of cases		*P*
	Group C (*n*=55)	Group L (*n*=55)	
0-1 HR	0	0	-
1-2 HR	1	12	0.002*
2-3 HR	5	10	0.165
3-4 HR	1	1	1.000
4-5 HR	0	0	0.154
5-6 HR	0	0	-
6-12 HR	1	1	1.000
12-24 HR	0	0	-

*Group C: Ondansetron 100 μg/kg + Dexamethasone 8 mg, Group L: Ondansetron 50 μg/kg + Dexamethasone 8 mg. *P<0.05: statistically significant*

Table 3: PONV scores at various time intervals in postoperative period

PONV scores in 0-2 hrs interval			
PONV score	**Group C (n=55)**	**Group L (n=55)**	***P***
0	54 (98.1%)	43 (78%)	0.75
1	1 (1.8%)	11 (20%)	0.002*
2	0	1 (1.8%)	0.9
PONV score between 2-6 hrs			
0	47 (85%)	46 ((83.3%)	1.0
1	8 (14%)	9 (16.3%)	
2	0	0	
PONV score in 6-12 hrs interval			
PONV score	**Group C**	**Group L**	***P***
0	54 (98.1%)	54 (98.1%)	1.0
1	1 (1.8%)	1 (1.8%)	
PONV score in 12-24 hrs interval			
0	55 (100%)	55 (100%)	1.0
1	0	0	

*Group C: Ondansetron 100 μg/kg + Dexamethasone 8 mg, Group L: Ondansetron 50 μg/kg + Dexamethasone 8 mg. *P<0.05: statistically significant*

Discussion

In the present study, the low dose ondansetron (50 μg/kg) in combination with dexamethasone is associated with higher incidence of postoperative nausea in the immediate postoperative period, i.e. within 2 hrs of surgery; however, no significant difference was observed in postoperative vomiting. The requirement of rescue antiemetic, NRS-Pain scores, rescue analgesics, hemodynamic and side effects at various time points in first 24 hrs were comparable between the two groups in patients undergoing LC.

The patients undergoing LC are often scheduled on outpatient basis, and the relatively high incidence of PONV after LC may have negative impact on the recovery of these patients.[12-14] Untreated PONV increases the risk for postoperative bleeding, wound dehiscence, gastric aspiration, and electrolyte imbalance.[15] The etiopathogenic mechanism of PONV after laparoscopic surgery is multifactorial including the central action of carbon dioxide, the influence of the increased intraabdominal pressure, postoperative gastroparesis, etc.[4]

For the prevention of PONV, various antiemetic drugs are used such as 5HT3 antagonist (ondansetron, granisetron), D2 receptor antagonist (droperidol), anticholinergics, corticosteroids, and antihistamines.[7] For PONV prophylaxis, following LC ondansetron 4 mg and dexamethasone 8 mg proves to be an effective combination.[7-10] Various researchers have proposed the need to explore the optimal dose of

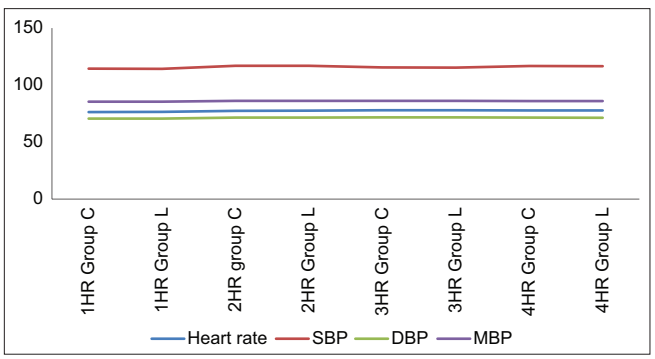

Figure 2: Comparison of hemodynamic parameters between the two groups

Table 4: Patients needing rescue antiemetic between the two groups at various intervals

Need for antiemetic present	Number of cases		*P*
	Group C (*n*=55)	Group L (*n*=55)	
0-1 HR	0	0	-
1-2 HR	0	2	0.154
2-3 HR	2	6	0.142
3-4 HR	2	0	0.154
4-5 HR	0	0	-
5-6 HR	0	0	-
6-12 HR	0	0	-
12-24 HR	0	0	-

*Group C – Ondansetron 100 μg/kg + Dexamethasone 8 mg. Group L – Ondansetron 50 μg/kg + Dexamethasone 8 mg. *P<0.05: statistically significant*

ondansetron when used in combination with dexamethasone for PONV prophylaxis.[16,17] Synergistic action of ondansetron and dexamethasone combination is the reason behind the combination dose. Cost-effectiveness is also a major concern as PONV prophylaxis given to almost all patients undergoing surgery under GA. Here again, the cost of ondansetron is relatively more than dexamethasone, thus affirming the need of finding the optimal low dose of ondansetron when used in combination with dexamethasone for PONV prophylaxis.

On extensive literature search, only two studies have evaluated the low dose ondansetron and dexamethasone combination in patients undergoing strabismus surgery.[17,18]

Splinter *et al*. compared the two doses of ondansetron, i.e. high dose (150 μg/kg) and low dose (50 μg/kg) in combination with 150 μg/kg dexamethasone on the incidence of vomiting after strabismus in children. They concluded the low dose combination to be equally effective for preventing vomiting after strabismus surgery.[17] Same author in a different study concluded that ondansetron (50 μg/kg) plus dexamethasone (150 μg/kg) combination is more efficacious in preventing postoperative vomiting among children undergoing strabismus surgery in comparison to dexamethasone alone.[18] These two studies[16,17] affirmed the efficacy of low dose ondansetron and dexamethasone combination for preventing POV following strabismus surgery. However, no study exploring the optimal dose of ondansetron in combination with dexamethasone for PONV prophylaxis in LC has ever been conducted.

In ondansetron and dexamethasone combination for PONV prophylaxis, the ondansetron is responsible for early PONV prophylaxis, whereas dexamethasone is responsible for late PONV prophylaxis.[7,19] In the present study, since we aimed to evaluate the low dose ondansetron combination with dexamethasone, we considered the PONV incidence and PONV score in the initial 6 hrs as the primary outcome. The overall incidence of PONV was significantly higher in the immediate postoperative period between 1 and 2 hr in the low dose ondansetron group (*P* value = 0.002). As far as PONV scoring is concerned, at 0–2 hr time interval in the postoperative period, 1.8% (n = 1) in group C and 20% (n = 11) in low dose ondansetron group had PONV score of 1, i.e. nausea. No patient in control group and only one patient in low dose ondansetron group had PONV score of 2, i.e. vomiting. In the 0–2-hr interval, this difference between the groups was statistically significant only for postoperative nausea (*P* = 0.002) and not for postoperative vomiting.

Rescue antiemetic consumption, NRS score, and rescue analgesic consumption were comparable between two groups.

The study is dealt with few limitations. Firstly, the study was limited to only 24 hrs following anesthesia. Secondly, the patient satisfaction regarding the overall management and quality of recovery (QoR) could have also been assessed.

Conclusion

We observed that the low dose ondansetron (50 μg/kg) in combination with dexamethasone is associated with higher incidence of postoperative nausea in the immediate postoperative period, i.e. within 2 hrs of surgery; however, no significant difference was observed in postoperative vomiting and the requirement of rescue antiemetic when compared to the standard dose ondansetron (100 μg/kg) and dexamethasone combination in patients undergoing laparoscopic cholecystectomy.

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Conflicts of interest

There are no conflicts of interest.

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