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EDUCATION

A comparative study of intravenous ondansetron with intravenous ondansetron and dexamethasone combination in prevention of postoperative nausea and vomitting in patients undergoing elective laparoscop

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A B S T R A C T

Laparoscopic cholecystectomy is associated with an appreciably high rate of postoperative nausea & vomiting (PONV). It is prudent to know if addition of Dexamethasone to Ondansetron have better prevention of PONV or not. Aims: To compare the efficacy of intravenous ondansetron against intravenous ondansetron and dexamethasone combination in prevention of PONV in laparoscopic cholecystectomy and to study the side effects of drug if any. Settings and Design: A double blind randomized controlled trial was conducted in a tertiary care hospital in 100 patients undergoing laparoscopic cholecystectomy divided in 2 groups of 50 each. Methods and Material: Group A patients received Inj. Ondansetron in the dose of 0.08 mg/kg with Inj. Dexamethasone in the dose of 0.15 mg/kg and Group B patients received Inj. Ondansetron in the dose of 0.08 mg/kg. The occurrence of PONV was recorded using the PONV SCORE based on the definition at durations between 0-6 hrs, between 6-12 hrs and between 12-24 hrs post operatively. Statistical analysis used: Student’s t tests were used to compare continuous variables and Chi-Square tests to assess differences in proportions. p-value less than 0·05 considered to be significant.

K E Y W O R D S

Title: - A comparative study of intravenous ondansetron with intravenous ondansetron and dexamethasone combination in prevention of post-operative nausea and vomiting in patients undergoing elective laparoscopic cholecystectomy.

Abstract:

Context: Laparoscopic cholecystectomy is associated with an appreciably high rate of postoperative nausea & vomiting (PONV). It is prudent to know if addition of Dexamethasone to Ondansetron have better prevention of PONV or not.

Aims: To compare the efficacy of intravenous ondansetron against intravenous ondansetron and dexamethasone combination in prevention of PONV in laparoscopic cholecystectomy and to study the side effects of drug if any.

Settings and Design: A double blind randomized controlled trial was conducted in a tertiary care hospital in 100 patients undergoing laparoscopic cholecystectomy divided in 2 groups of 50 each.

Methods and Material: Group A patients received Inj. Ondansetron in the dose of 0.08 mg/kg with Inj. Dexamethasone in the dose of 0.15 mg/kg and Group B patients received Inj. Ondansetron in the dose of 0.08 mg/kg. The occurrence of PONV was recorded using the

PONV SCORE based on the definition at durations between 0-6 hrs, between 6-12 hrs and between 12-24 hrs post operatively.

Statistical analysis used: Student's t tests were used to compare continuous variables and Chi-Square tests to assess differences in proportions. p-value less than 0·05 considered to be significant.

Results: Post-operative Nausea and Vomiting (PONV) observed between 6 hrs to12 hrs in postop period was 2% in group A and 14 % in group B (p< 0.027) and between 12 hrs to 24 hrs it was 4% in group A and 16 % in group B. (p< 0.027).

Conclusions: Treatment of PONV is more effective by the combination of ondansetron and dexamethasone than single use of ondansetron in laparoscopic cholecystectomy.

Keywords: PONV, Ondansetron, Dexamethasone, Laparoscopic Cholecystectomy

INTRODUCTION:

Postoperative nausea and vomiting (PONV) is a common distressing symptom in patients undergoing laparoscopic surgery and can contribute to anxiety, dehydration, metabolic abnormality, wound disruption and delayed recovery. (1,2) The incidence of PONV varies from 20 to 80 %. (3-6) 5HT3 antagonists e.g. Ondansetron, are effective in PONV. (7-9) Dexamethasone has a prophylactic antiemetic effects on PONV. Previous studies have established the efficacy of ondansetron and dexamethasone in prevention of PONV independently. Therefore, this study was initiated to compare the effectiveness of combination of preoperative dexamethasone and ondansetron on PONV in patient undergoing laparoscopic cholecystectomy and to compare the adverse events if any.

Material and methods:

A double blind randomized controlled trial was conducted in a tertiary care hospital after obtaining institutional ethical committee approval. Hundred patients undergoing laparoscopic cholecystectomy were enrolled in this study after obtaining written informed consent. Inclusion criteria were age between 18-65 years, ASA grading I and II, Either sex male or female. Exclusion criteria were patient refusal, patients with known allergy to Ondansetron and pregnancy.

Sample size was calculated by using computerized software winpepi (Version 11.65 copyright J. H. Abramson Aug.23,2016). Required sample size was 100 (50 in each group).

Block randomization was used to allocate the patients in two groups as follows. Randomisation was done using computer program.

1. Group A – Inj. Ondansetron in the dose of 0.08 mg/kg with Inj. Dexamethasone in the dose of 0.15 mg/kg
2. Group B – Inj. Ondansetron in the dose of 0.08 mg/kg

Student's t tests were used to compare continuous variables and Chi-Square tests to assess differences in proportions and to measure the linear trend as appropriate. p-value less than 0·05 considered to be significant. Microsoft Excel 2016 was used for data compilation and SAS version 20.0 for all statistical analyses.

Patients were premedicated with Inj. Glycopyrrolate 2 µg/kg IM 30 min before induction. On arrival in the Operation Theatre, Systolic Blood Pressure(SBP), Diastolic Blood Pressure (DBP), Heart rate (HR), Electrocardiogram (ECG) and oxygen saturation (SpO2) was observed and recorded prior to induction and throughout the procedure.

Patients were pre-oxygenated with 100% oxygen for 3 min. Inj. Midazolam 0.03 mg/kg and Inj. Pentazocin 0.3 mg/kg was administered. Patients were induced with Inj. Propofol 2 mg/kg. Iv Inj. Succinylcholine was administered in the dose of 2 mg/kg. Patients were intubated with proper sized cuffed endotracheal tube. Patients were ventilated with O2, N2O, Isoflurane and Inj. Vecuronium as muscle relaxant.

At the end of surgery, patients were reversed with iv Inj. Glycopyrrolate and Inj. Neostigmine and extubated.

The incidence of nausea and vomiting were recorded for first 24 hrs post operatively (04 hrs at recovery room, and 4-24 hrs in ward). The occurrence of PONV was recorded using the PONV SCORE based on the definition at durations between 0-6 hrs, between 6-12 hrs and between 12-24 hrs post operatively.

Rescue Antiemetic (Inj. Metoclopramide 10 mg) was given if necessary. The frequency and total Antiemetic doses in first 24 hrs was recorded.

Monitoring chart included duration of surgery, time of first rescue antiemetic, total antiemetic required in first 24 hrs, side effects (nausea, vomiting, hypotension, bradycardia, dry mouth, Skin rash, or any other clinically relevant sign / symptom), haemodynamic parameters (SBP, DBP, HR, SPO2) at baseline and after 15, 30, 60 mins, at the end of surgery and after 24 hrs.

OBSERVATIONS AND RESULTS:

Patients in both the groups were comparable in age, gender, BMI and ASA grading. (figure 1)

Average Systolic blood pressure tapered steadily in both groups over the period of surgery. The difference between the average systolic blood pressure at baseline, and after 15, 30, 60 minutes and at the end of the surgery were not statistically significant between two groups. (figure 2)

Average diastolic Blood pressure tapered steadily in both groups over the period of surgery. The difference between the average diastolic blood pressure at

baseline, and after 15, 30, 60 minutes and at the end of the surgery were not statistically significant between two groups. (figure 3)

Average heart rate tapered steadily in both groups over the period of surgery. The difference between the average heart rate at baseline, and after 15, 30, 60 minutes and at the end of the surgery were not statistically significant between two groups. (figure 4)

Post-operative Nausea and Vomiting (PONV) observed between 6 hrs to12 hrs in postop period was 2% in group A and 14 % in group B ($p < 0.027$) and between 12 hrs to 24 hrs it was 4% in group A and 16 % in group B. ($p < 0.027$) The difference was statistically significant. (table 1)

Hypotension and bradycardia was recorded in 4 % cases of group B and none in group A.

Mean dose of Metoclopramide required for management of PONV in 24 hrs. in group A was 10 mg and in group B was 14.3 ± 4.95 mg. More than one doses of Metoclopramide were required in group B in 24 hrs. (table 2)

DISCUSSION:

Laparoscopic cholecystectomy (LC) is a standard treatment for cholelithiasis, due to decreased postoperative trauma and less side effects. Though the benefits of this procedure are more but postoperative nausea and vomiting (PONV) is still considered as most common complaint. (10) Laparoscopic surgeries stand second in terms of incidence of PONV. The incidence of PONV varies from 20 to 80 %, and it is an economic and social burden. (3,4) PONV after laparoscopic surgery contributes to anxiety, dehydration, metabolic abnormality, wound disruption, delayed recovery and other issues. (1) It can cause tension on suture lines, venous hypertension, and increased bleeding under skin flaps.

It exposes the subject to increased risk of pulmonary aspiration of vomitus. (2) Esophageal rupture, subcutaneous emphysema, and bilateral pneumothorax are additional complications. The patients frequently list pain, nausea, and vomiting as their most important perioperative concern. (11) With the change in the emphasis from an inpatient to outpatient hospital and office-based medical / surgical enhancement, there has been increased interest in the “big little problem” of PONV. (12)

The etiology and consequences of PONV are complex and multifactorial with patients’ medical and surgery-related factors. A thorough understanding of these factors, as well as the neuropharmacology of multiple emetic receptors (dopaminergic, muscarinic, cholinergic, opioid, histamine, and serotonin) and physiology (cranial nerves VIII, IX, X, and gastrointestinal reflex) relating to PONV is necessary to manage PONV. (11) Stretch of intra-abdominal organs, peritoneal irritation and phrenic nerve excitation by residual CO_2 in peritoneal cavity which are very important risk factors of incidence of nausea vomiting after LC. A number of factors including anaesthetic techniques, sex, pain, and care in post-operative period, and patient demographics are considered to influence the incidence of PONV. (13)

There are at least 3 kinds of vomiting, the first of which is attributed to anesthetics, such as ether, the second to reflex responses, such as pain or ovarian surgery, and the last to opioids.

Early studies reported incidence of PONV as high as 75%–80% after opioid premedication and prolonged ether anesthesia. (5)

Although the actual morbidity associated with nausea is relatively low in healthy outpatients, it should not be considered an unavoidable part of the perioperative experience. The availability of an emesis basin for every patient in the postanesthesia recovery unit is a reflection of the limited success with the available therapeutic techniques.

The newest class of antiemetics used for prevention and treatment of PONV are serotonin (5HT3) receptor antagonists—ondansetron, granisetron, tropisetron, and dolasetron.

These antiemetics do not have the adverse effects of the older, traditional antiemetics. The available antiemetics, such as 5HT3 antagonists, are effective in very low doses. Thus, cost could be lowered and drug side effects prevented when given as prophylaxis, lowering the economic burden imposed due to complications and increased medical care resulting from PONV. (14) Ondansetron, a 5-HT3 receptor antagonist has antiemetic action in surgical patients. Combination of antiemetic drugs proved be an effective method to control severe PONV as there is several stimuli / causes for PONV. (8)

Dexamethasone was first reported to be an effective antiemetic agent in patients receiving chemotherapy in 1981. Recently, Dexamethasone has been reported to be effective in preventing PONV in LC as a mono drug or in combination. (15) Many previous studies where dexamethasone was administered in various other surgeries in the doses of 8 mg orally, 0.15 mg/kg up to 8 mg and 1 mg/kg up to 25 mg IV have reported favourable results for postoperative antiemesis. (16-18) Glucocorticoids bind to intracellular glucocorticoid receptors, and exert their effects via gene transcription. (19) As changes to both gene expression and protein synthesis take time, most effects of corticosteroids are not instantaneous, rather, they only become apparent after several hrs. Therefore, glucocorticoids usually take 1–2 h to have biologic effects, and this also depends on the route of administration. (20)

In this study approximately matching cases were chosen in each group in order to maintain the parity in the groups. The findings of age and gender distribution are in line with the reported incidence of acute calculous cholecystitis which is three times more common in women than in men up to the age of 50 years. (21) The average BMI in present study was comparable to Har et

al who reported average BMI in the range of 26 to 27 kg/m2. (21) Yoon JH et al suggested that BMI can be used as one of the predictive factors of steatocholecystitis for obese patients. (22) Largely, it was observed that all the demographic parameters as well as risk factors in both the groups were comparable at the baseline.

Average Systolic and diastolic blood pressure tapered steadily in both groups over the period of surgery. The stable ranges of the blood pressure and heart rate in both the groups indicates proper hemodynamic stability during the surgeries.

Present study result revealed that patients receiving Ondansetron plus Dexamethasone had significantly lesser incidence of PONV as well as more complete response (no nausea & vomiting) after Laparoscopic cholecystectomy, in comparisons with Ondansetron alone in 24 hrs.' postoperative period. The complete response occurred in 62% of the cases in Ondansetron group and 88% in Ondansetron plus Dexamethasone group. This is comparable to the study conducted by Fukami et al and Ahmed A et al. (23,24) Some studies on the combination of Ondansetron plus Dexamethasone have demonstrated a significantly better clinical efficacy against PONV than Ondansetron or Dexamethasone alone. (23,25,26)

Ondansetron was effective at decreasing PONV in the early postoperative stage (0–6 h), while dexamethasone was more effective at decreasing PONV in the late postoperative stage (6–24 h). This may be because glucocorticoids act through both gene expression and protein synthesis which takes time. (20) Interestingly, Thomas and Jones found a failure of prophylaxis during the first three hrs after laparoscopic surgery in 28.3 % of patients who had received dexamethasone compared to with 22 % of patients who had received ondansetron. (27) The late onset and prolonged antiemetic efficacy of dexamethasone may be attributed to its prolonged biological half-life (36–72 h). (28) Accordingly, the timing of dexamethasone administration is important. Wang et al confirmed that dexamethasone is most effective when it is administered at the induction rather than at the termination of anaesthesia. (29)

Mean doses of Metoclopramide required for management of PONV in 24 hrs. in group B was higher than group A. Also, it was observed that mean doses of Metoclopramide were higher as more than one dose was given in 24 hrs in group B.

In present study, Inj. ondansetron in the dose of 0.08 mg/kg body weight and Inj. dexamethasone iv in the dose of 0.15 mg/kg body weight was used. The study drugs are not known to be incompatible when mixed together. (7)

Adverse effects observed in this study were not clinically serious in both the groups and did not differ in incidence between the groups.

The limitations of present study included not counting the frequency, severity, length and duration of nausea and vomiting in addition to follow-up. Today, cost-benefit analyses have become an important factor when considering what drugs to use as prophylactic antiemetics. The cost-benefit analysis could not be performed in present study as it was conducted in government hospital set up and getting access to all direct and indirect costs was not feasible.

So, we conclude that the treatment of PONV is more effective by the combination of ondansetron and dexamethasone than the use of either one of these two in laparoscopic cholecystectomy. More specifically, ondansetron alone is effective to prevent the premature PONV. However, using ondansetron alone is less effective in preventing late onset PONV compared to the combination of ondansetron and dexamethasone.

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