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COMPARISON OF PROPHYLACTIC ONDANSETRON ALONE AND DEXAMETHASONE WITH ONDANSETRON TO REDUCE POST-OPERATIVE NAUSEA AND VOMITING (PONV) AFTER LAPAROSCOPIC CHOLECYSTECTOMY.

Anaesthesiology

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ABSTRACT

INTRODUCTION: Laparoscopic Cholesystectomy is removal of Gall Bladder through abdominal ports which is appreciably associated with postoperative nausea & vomiting (PONV) resulting in increased morbidity and discomforts after the surgery in quite a number of patients. Our study was aimed to compare the efficacy of Ondansetron plus Dexamethasone and only Ondansetron as an antiemetic 30 minutes prior to elective laparoscopic Cholecystectomy.

METHODS: In this randomised double blind study, 80 patients of both sexes of ASA I and II aged between 16 to 60 yrs received 4 mg Ondansetron (Group C, n = 40), Ondansetron 4 mg plus Dexamethasone 8 mg (Group T, n=40) intravenously half an hour before induction of general anaesthesia. Peri operative 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 only and 85% of patients receiving Ondansetron plus Dexamethasone (P<0.05). The overall cumulative incidences (0-24 hrs) of PONV were 64% in Ondansetron only group, 36% 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 Ondansetron alone as an antiemetic prophylaxis for PONV following laparoscopic cholecystectomy.

KEYWORDS

Laparoscopic Cholecystectomy, Nausea, Vomiting , Antiemetic, Ondansetron, Dexamethasone.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is superior to traditional treatment for cholelithiasis , open cholecystectomy due to less tissue injury , post operative pain and less side effects1 Though the benefits of this procedure are more but postoperative nausea and vomiting (PONV) is still considered as most common complaint and the reason for prolonged hospitalisation. Prophylactic uses of Ondansetron and Dexamethasone have been found to have reduced nausea and vomiting upto 85 to 90 % after surgery. Ondansetron is a 5-hydroxy tryptamine type 3 receptor (5HT3) antagonist that has provided effective antiemesis in surgical patients4,5,6. Dexamethasone has been found to have a prophylactic antiemetic effects on PONV in patients undergoing laparoscopic cholecystectomy under general anaesthesia7,8,9 .

Some studies4, 10, 11 on the effects of combined use of Ondansetron and Dexamethasone have demonstrated a significantly better outcome against PONV than Ondansetron 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 Ondansetron alone to reduce the occurrence of PONV in patients undergoing Laparoscopic Cholecystectomy.

MATERIALS AND METHODS

This prospective double blind prospective randomized control trial (RCT) was performed after approval of institutional ethical committee and written informed consent in trilingual print from patients were obtained. 80 patients aged 18 to 60 years, ASA I & II of both gender, with body weight between 50 to 70 kgs were scheduled for laparoscopic cholecystectomy under general anaesthesia were recruited in this study and formed our study cohort.

Exclusion criteria for this study were patients with history of motion sickness, gastritis, GERD, peptic ulcer, diabetes mellitus, and recent head injury. Also Pregnant patients, patients on chronic pain therapy, on anti psychotic drugs were not included in this study.

All patients posted for surgery were explained VAS (Visual Analogue Scale) ,consisting of a 10 cm line with various smily faces drawn n it , where 0 means no pain, 10 means worst possible pain at their preoperative visit. Patients were randomly allocated using a random number table. The "C" group received Ondansetron 4 mg plus 2 ml normal saline and the "T" group received Ondansetron 4 mg plus Dexamethasone 8 mg intra venously 30 minutes prior to beginning of surgery. Study medications were prepared by personnel not involved in this study, in identical 5 ml syringe, for each group to ensure blinding of anaesthesiologist. As the provider and the observer both were unaware of drug distributions in the syringes our study remains a doubble binded .

Patients received tablet alprazolam (0.5 mg) per oral 8 hours before operation as per PAC instruction and were fasted for 8 hours before surgery. All subjects were hydrated with 10 ml/kg of Ringer lactate. Premedication was given with Glycopyrrolate 0.2mg , Midazolam 1 mg IV .Anaesthesia was induced with Fentanyl 2µg/kg, followed by propofol 2.5mg/kg. Atracurium (0.6 mg/kg) was given intravenously to facilitate oro-tracheal intubation. Anaesthesia was maintained with Sevoflurane (2-3% dial concentration) along with nitrous oxide 60% in O2 with controlled ventilation adjusted to maintain the end tidal CO2 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 CO2 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 personnel, 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'. Complete response was defined as no PONV and no need for other 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, Morphine 0.1 mg/kg, was administered intravenously. Details of adverse effects during the study period were recorded by the attending anaesthesiologists.

Patient admitted to our tertiary care hospital from December 2018 to November 2019 for undergoing laparoscopic surgery and who conformed to the specified inclusion and exclusion criteria of this study and gave their written consent to undergo this RCT formed the study population. This study population of 80 patients was divided by randomization technique into two equal groups of 40 patients each. Out of these two groups the group that receives the combination drugs (Ondansetron and Dexamethasone) constitutes the study group, while patients receiving only form the control group. All patients received Opioids both intraoperatively and postoperatively, were non-smokers. In this study, each and every patient received a PONV prophylaxis, a placebo group was not included as not only it would be unnecessary for Inter group comparisons, but would have been highly unethical.

STATISTICALANALYSIS

Data obtained from 80 patients were analysed for interpretation. A sample size of 40 patients in each group was required to achieve a power of 0.8 ($\alpha = 0.05$) to detect a large difference.

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. There were no difference between the two groups regarding demographic characteristics (in terms of age, sex height, weight and ASA grade) and duration of surgery (p>0.05) (shown in Table 1).

Table 1. Demographic Charecteristics:

Group D (n = 40)		Group S (n = 40)
Variables	***mean ± SD***	***mean ± SD***
Age (years)	46.4 ± 10	44.8 ± 8
Height (cm)	143.7 ± 4	140.9 ± 5
Weight (kg)	54.2 ± 6	51.6 ± 8
BMI	26.2 ± 0.6	26.4 ± 0.4
ASA I / ASA II	42/8	43/7
Duration of surgery	47.8 ± 26	50.1 ± 30

No significant difference.

The overall cumulative incidences (0-24 hrs) of PONV were 34% in the Ondansetron only group, 3.3% in the Dexamethasone and 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 Ondansetron 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, 32% of patients who received Ondansetron 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 Ondansetron alone (P<0.05) as shown in Table 2.

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

	Ondansetron only (n=40)	**Combination (n=40)**	**P value**
		0-4 h after anaesthesia	
Nausea	9 (18%)	1(1.9%)	**.011**
Vomiting	2(4%)	1(1.9%)	**.019**
Rescue Anti emetic	7	3	**.018**
		4-24 h after anaesthesia	
Nausea	5	1	**.012**
Vomiting	11	2	**.010**
Rescue Anti emetic	8	2	**.014**
Overall cumulative incidences of PONV (0-24h)	22	6	**.016**
Complete response (no PONV, no rescue) in first 24 hours	21	64	**.031**

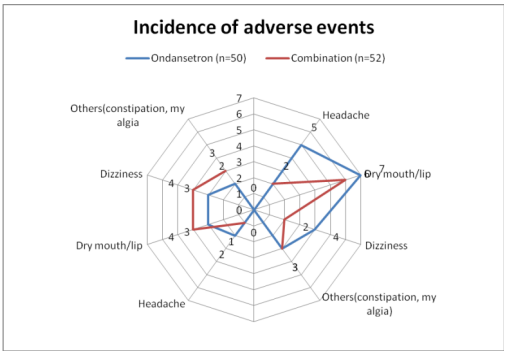
Observed adverse effects were clinically non-serious like dry mouth/lips, headache, dizziness and myalgia, with no difference in incidence between the groups.

Table 3: Incidence of adverse events

Symptoms	**Ondansetron (n=50)**	**Combination (n=52)**
	4-24h after anaesthesia	
Headache	5	2
Dry mouth/lip	7	6
Dizziness	4	2
Others (constipation, myalgia)	3	3
	4-24h after anaesthesia	
Headache	2	1
Dry mouth/lip	3	4
Dizziness	3	4
Others(constipation, myalgia	2	3

The above table has been well reflected in the following Radar diagram.

Graph-1 Showing Incidence of adverse events



DISCUSSION

Our study result revealed that patients receiving Ondansetron plus Dexamethasone had significantly lesser incidence of PONV (62 % vs 34% respectively) as well as more complete response (no nausea & vomiting) after Laparoscopic cholecystectomy , in comparisons with Ondansetron alone in 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 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[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 mostly similar in both groups. In addition patients in both groups also consumed similar amount of opioid 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, Dexamet hasone has been reported to be effective in preventing PONV in LC [6,7,8]. Ondansetron, a 5-HT3 receptor antagonist having antiemetic action in surgical patients [9,11]. Combination of antiemetic drugs proved be an effective method to control severe PONV as there is several stimulus/cause for PONV[18]. The mechanism of action of corticosteroid as antiemetic is unknown; however, it is thought 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 are contributory in this regard[19]. In our study the complete response occurred in 28% of the cases in Ondansetron group and 67% in Ondansetron plus Dexamethasone group. This is comparable to the study conducted by Khalid Ahsan et al[18], Goutam B et and Mohammad Eidey et al[11] Ahmed A et al [20] studied 67 patients undergoing LC receiving combination of Ondansetron and Dexamethasone.

We used the doses of drug i.e. Dexamethasone 8 mg and Ondansetron 4 mg was based on previous studies[4,15,21]. It was shown that Dexamethasone was most effective as anti emetic, when administered just before the induction[19]. As half-life of Ondansetron is approximately 4 -6 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. 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 much in incidence between the groups. Limitations of the study were strength of the study population was not much and not all other 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. However, our study was done on previous studies based on similar protocol.Hence, we conclude that the combination of Ondansetron plus Dexamethasone is better than Ondansetron alone as a prophylactic in preventing PONV following LC.

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