The Impact of Prophylactic Dexamethasone, Metoclopramide or both on Nausea and Vomiting After Laparoscopic Cholecystectomy

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) are one of the most common complaints following laparoscopic cholecystectomy.

Objective: This study was designed to compare the effects of dexamethasone, metoclopramide, and their combination on preventing PONV in patients undergoing laparoscopic cholecystectomy.

Methods: A total of 135 patients enrolled in the study. American Society of Anesthesiologists (ASA) physical status I and II patients were included in this randomized, double blind, placebo-controlled study. Patients were randomly assigned to group A administered 8mg iv dexamethasone, group B received metoclopramide 10 mg, group C received combination of 8mg dexamethasone and 10 mg metoclopramide and group D received 10 cc normal saline.The incidence of PONV, mean visual analog pain scores, request for analgesia, side effects , and well-being score were recorded during the first 24 h postoperatively.

Results: Total incidence of PONV during 24 hr was 24% in the dexamethasone group (group A), 47% in the metoclopramide group (group B), 15% in the dexamethasone plus metoclopramide group (group C) and 61% in the placebo group (group D).

None of the dexamethasone plus metoclopramide group patients required other antiemetic (B6 ample iv.), as compared with one patient in dexamethasone group, three patients in the metoclopramide group and five patients in the placebo group. Pain scores, the time to the first request for analgesia, and side effects were similar across the study groups.

Conclusions: Dexamethasone and the combination of dexamethasone plus metoclopramide were more effective in preventing PONV than metoclopramide and placebo.

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INTRODUCTION

Laparoscopic cholecystectomy (LC) has been regarded the gold standard procedure for the surgical treatment of cholelithiasis and for some cases of cholecystitis and cholecystic polyps. Although the operative procedure was perfect and the surgical outcome is satisfactory, postoperative nausea and vomiting (PONV) are distressing side effects and high incidences have been reported mainly after (LC) (46–72%) [1-5]

Numerous antiemetics have been studied for the prevention and treatment of PONV in patients scheduled for laparoscopic cholecystectomy [1]. Traditional antiemetics, including anticho-linergics (e.g., scopolamine), antihistamines (e.g., dimenhydrinate), phenothiazine (e.g., promethazine), butyrophenones (e.g., drop-eridol), and benzamide (e.g., metoclopramide) are used for the control of PONV. The available and cost effective nontraditional antiemetics for the prophylaxis against PONV are dexamethasone and propofol. Serotonin receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron, and ramosetron), compared with traditional antiemetics, are highly efficacious for PONV. None of the available antiemetics is entirely effective, perhaps because most of them act through the blockade of one type of receptors [5,6,]. Among the effective antiemetics currently prescribed for PONV,serotonin subtype3antagonists(e.g. ondansetron and granisetron) are expensive [7].

At present, when antiemetics of different pharmacological classes are available, it is possible to combine them and provide better control of PONV without producing additional side effects, but it increases the cost of treatment [7,8]. Other currently used, lower-cost antiemetics (e.g., anticholinergics, antihistamines, and dopamine receptor antagonists) have side effects, such as sedation, dry mouth, restlessness, changes in arterial blood pressure, and extrapyramidal symptoms [6,9].

Dexamethasone, a corticosteroid, is cost-effective and effective antiemetic drug, with minimal side effects after a single-dose administration. It was first reported in 1981 as an effective antiemetic in patients receiving cancer chemotherapy [6,10]. since then dexamethasone has been reported to reduce the episodes of emesis in patients undergoing chemotherapy [10-12], surgical operations [13,14] and laparoscopic cholecystectomy [4,15,16] examethasone is as effective as ondansetron, it provides simple, safe, inexpensive, and effective prevention method for PONV [17]. The antiemetic's effect of glucocorticoids acts centrally by increase production of endogenous prostaglandin and opioid. [18] Furthermore, peri operative corticosteroid administration may decrease

postoperative pain because of its anti-inflammatory effect [18]

Recently, a combination of ondansetron and dexamethasone has been shown to be a highly effective prophylactic measure in patients undergoing laparoscopic cholecystectomy [19]. However, the higher cost of ondansetron has been a significant factor limiting its routine prophylactic use [20].

The aim of this randomized, double-blind, placebo controlled trial was to evaluate the impact of prophylactic dexamethasone, metoclopramide or combination on PONV, requirement to analgesia, antiemetics and possible side effects in patients undergoing laparoscopic cholecystectomy.

METHODS

Between March 2016 and October 2018, a total of 142 patients, a randomized double-blinded placebo-controlled study design of an elective laparoscopic cholecystectomy (LC) under general anesthesia were included in this study. A written consent was considered. The study was approved by the Medical University ethical committee.

The exclusion criteria include, according to American Society of Anesthesiology (ASA) physical class III and IV; age over 60 years; body mass index above 35; pregnancy; signs of gastrointestinal, endocrine, renal, hepatic or immunological disease; use of opioids or tranquilizers less than 1 week before the operation; treatment with steroids; a history of alcohol or drug abuse; preoperative diagnosis of gallbladder empyema and previous endoscopic sphincterotomy for common bile duct stones and conversion to open cholecystectomy.

Seven patients (5 %) were excluded from the study, because of preoperative treatment with steroids (two patients), previous endoscopic sphincterotomy (one patient), conversion to open cholecystectomy (two patient), and age over 60 years (two patients).

Data collection:

A total of 135 patients (95 per cent) were randomized to receive either 8 mg of dexamethasone, 10 mg metoclopramide, combination of dexamethasone and metoclopramide or saline (control group) intravenously, 90 min before skin incision for dexamethasone and after recovery from anesthesia for metoclopromid. Both the patients and the data collectors were blinded with respect to the study group. thirty-four patients (group A) were randomized to receive intravenous dexamethasone (table 1), thirty-four patients (group B) were randomized to receive (group C) were randomized to receive intravenous combination of dexamethasone and

metoclopramide (table3) and thirty-three patients (group D) were received intravenous saline (control group) (table4). There were no statistical differences in gender distribution, age, body mass index, ASA score, pathology, surgeon, or median operation and anesthesia time between the groups.

All patients completely investigated after full history and physical examination include biliary, hepatic and renal profile.

The degree of (PONV) was evaluated at (1^{st} 6hr, 2^{nd} 6hr and 3^{rd} 12hr) after operation.

- ➢ Requirement for antiemetics.
- ➢ Requirement for analgesics.

Nausea and pain were rated using a visual analogue scale score system (VAS) (no nausea, 0; severe nausea, 10), and the number of vomiting episodes was also recorded

Assessment of nausea (VAS) 1-10, Assessment of vomiting (no. of vomiting episodes).

Assessment of pain (VAS)1-10 i.e. detection of pain (visceral, incisional and shoulder pain).

The length of Hospital stay was defined as the number of postoperative days (including the day of operation) before hospital discharge.

The study end points were degree of postoperative nausea, vomiting, pain, analgesics and antiemetics medication required. Vomiting was defined as forceful expulsion of gastric content through the mouth, whereas nausea was defined as unpleasant sensation associated with awareness of urge to vomit. The details of any adverse effects (headache, dizziness, anxiety, perineal itching, etc.) throughout the study is recorded

Data presented as mean ± standard deviation (SD), ASA: American Society of Anesthesiologists classification; BMI: body mass index, PNP: pneumoperitoneum N: number, NS: normal saline, both: mean combination of dexamethasone and metoclopramide

RESULTS

Postoperative analgesia with 75 mg IM diclofenac showed no significant difference among the four groups in terms of pain intensity and number of patients receiving postoperative analgesia (Table 6). The intensity of postoperative pain was relatively minor. At 24 hr. after surgery all four patient's groups reported a similar low VAS pain score (median; group A, 2; group B, 3; groups C, 2 and 3 in group D). Analgesic with 75 mg IM diclofenac was only requested by two (group D)

patients and one (group B) patient, and none of the group A and C patients. The potential side effects include headache, sedation, anxiety, dizziness, sleep problems, and perineal itching. In our study, the most frequently reported side effects were sleep disturbances, sedation, and headache, with no
significant difference between the groups (Table 7). Perineal itching was not observed in any of our patients. The patients postoperative general state is summarized in (Table 8). Two patients from the control group (group D) and none of the patients from other groups described their postoperative state as poor and very poor. The patients administered dexamethasone (group A) and dexamethasone plus metoclopramide (group C) reported a significantly higher rate ($p < 0.007$) of

very good postoperative state than those receiving NS. Also, the patients administered NS reported a significantly higher rate of alternating postoperative state than those receiving dexamethasone and the combination of dexamethasone plus metoclopramide ($p = 0.01$).

Table 1: Patients characteristics according to groups

	Dexamethasone group (group A, N=34)	Metoclopramide group (group B, N=34)	Dexamethasone and metoclopramide group (group C, N=34)	Controlled group (group D, N=33)
ASA I/II	15/19	13 / 21	14 / 20	15 /18
Age (years)	38.235 ± 8.58	37.735 ± 11.25	37.647 ± 8.40	39.06 ± 10.14
Sex (M /F)	12 / 22	10 /24	9 / 25	11 / 22
Weight (kg)	75.3 ± 10.9	77.1 ± 11.2	74.3 ± 12.1	76.3 ± 12.4
Height (cm)	170.4 ± 11.2	172.4 ± 11.9	168.4 ± 10.6	171.7 ± 10.7
BMI	25.93	25.94	26.2	25.88
Duration of anesthesia (min)	65 ± 20	66 ± 19	63 ± 18	66 ± 21
Duration of surgery (min)	49 ± 18	51 ± 17	47 ± 17	52 ± 17
Duration of PNP (min)	42 ± 21	44 ± 20	41 ± 20	43 ± 23
Fentanyl administered (µg)	198 ± 53	199 ± 52	188 ± 58	188 ± 53

* ($p < 0.05$) compared with control group (N.S).
** ($p < 0.05$) compared with metoclopramide group

Table 2: Incidence of nausea and vomiting during 24 h postoperatively according to medication groups

	Group A Dexamethasone N.34	Group B Metoclopramide N.34	Group C Both N.34	Group D (NS) N.33
Nausea	3 (9%)	6 (18%)	2 (6%)*	8 (24%)
vomiting	2 (6%)	4 (12%)	2 (6%)	6 (18%)
Total PONV	5 (15%)*	10 (29%)	4 (12%)*	14 (41%)
antiemitics	1 (3%)	3 (9%)	0 (0%)	2 (6%)
analgesic	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Nausea	5 (15%)	9 (26%)	3 (9%)*.**	11 (33%)
Vomiting	3 (9%)*	6 (18%)	2 (6%)	8 (24%)
Total PONV	8 (24%)*	15 (44%)	5 (15%)*.**	19 (5^%)
antiemitics	1 (3%)	3 (9%)	0 (0%)	4 (12%)
analgesic	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Nausea	5 (15%)*	10 (29%)	3 (9%)*.**	12 (36%)
vomiting	3 (9%)	6 (18%)	2 (6%)*	8 (24%)
Total PONV	8 (24%)*	16 (47%)	5 (15%)*.**	20 (6١%)
antiemitics	1 (3%)	3 (9%)	0 (0%)*	5 (15%)
analgesic	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Complete response	26 (76%)*	18 (53%)	29 (85%)*.**	13 (39%)

Table 3: Postoperative visual analog scale (VAS) pain score

	VAS (mean)	Analgesic requirement
GROUP A		
0-6 hr.	3	
6-12 hr.	2	
12-24 hr.	2	
Total (0-24hr) median	2	0 (0%)
GROUP B		
0-6 hr.	3	
6-12 hr.	3	
12-24 hr.	2	
Total (0-24hr) median	3	1 (3%)
GROUP C		
0-6 hr.	3	
6-12 hr.	2	
12-24 hr.	2	
Total (0-24hr) median	2	0 (0%)
GROUP D		
0-6 hr.	3	
6-12 hr.	3	
12-24 hr.	3	
Total (0-24hr) median	3	2 (6%)

Table 4: Incidence of side effects

	Group A (Dexamethasone) N.34	Group B (Metoclopramide) N.34	Group C (Both) N.34	Group D (NS) N.33
Headache	1 (3%)	2 (6%)	2 (6%)	3 (9%)
sedation	3 (9%)	2 (6%)	2 (6%)	2 (6%)
anxiety	1 (3%)	3 (9%)	1 (3%)	2 (6%)
dizziness	0 (0%)	0 (0%)	1 (3%)	1 (3%)
Sleep problems	2 (6%)	3 (9%)	2 (6%)	4 (12%)
Perineal itching	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 5: Postoperative well-being scores

	Very good No. (%)	Good No. (%)	Alternative No. (%)	Poor No. (%)	Very poor No. (%)
Group A (N.34)	17 (50%)	16 (47%)	1 (3%)	0 (0%)	0 (0%)
Group B (N.34)	15 (44%)	15 (44%)	4 (12%)	0 (0%)	0 (0%)
Group C (N.34)	19 (55%)	14 (42%)	1 (3%)	0 (0%)	0 (0%)
Group D (N.33)	8 (25%)	15 (44%)	8 (25%)	1 (3%)	1 (3%)

DISCUSSION

The present study had emerged several important findings which highlights the efficacy of combination dexamethasone and metoclopramide, with antiemetic alone in preventing PONV in patients undergoing laparoscopic cholecystectomy. Although laparoscopic cholecystectomy decreased surgical morbidity and had become by now the standard treatment of cholelithiasis [21], the high incidence of PONV remains a major clinical problem. The high incidence of PONV after laparoscopic surgery is not fully understood, but it is probably multifactorial [22], several factors, including age, sex, pregnancy, steroid use, smoking, history of motion sickness, intraoperative use of fentanyl and isoflurane, residual pneumoperitoneum after CO2 insufflation [23], peritoneum distention, diaphragm irritation, and visceral organ irritation

with manipulation [24] have been considered to influence the incidence of PONV. In the present study, however, treatment groups were similar with respect to demographic data and duration of anesthesia, surgery and CO2 insufflation, whereas those with a history of steroid use and previous endoscopic sphinecterotomy were excluded from the study. therefore, the difference in the incidence of PONV among the study groups could be attributed to the variation in the drugs administered.

As mentioned before, Dexamethasone, a corticosteroid, is cost-effective antiemetic drug, with minimal side effects after a single-dose administration. the mechanism of the antiemetic action of dexamethasone and the precise site of action remain unclear. A previous study has suggested that dexamethasone may antagonize prostaglandin [25] or release endorphins [26], resulting in mood relieve , a sense of well-being, and stimulate appetite. Dexamethasone was found to be effective when used alone in the prevention of PONV in several studies [4]. Henzi et al. [3] analyzed 17 trials involving 1,946 patients, which compared prophylactic dexamethasone with placebo to prevent PONV, and found it to be superior to placebo without evidence of any clinically relevant toxicity.

In the present study, the total incidence of PONV was (61%) in the control group and significantly reduced to (24%) with dexamethasone group and (15 %) with combination of dexamethasone and metoclopramide. Metoclopramide is a central dopaminergic D2 receptor antagonist and a pro kinetic drug that increases gastric emptying and shortens bowel transit time. Henzi et al. [27] also performed a meta-analysis of metoclopramide and found the dose of 10 mg to have no significant anti-nausea effect, our results with metoclopramide group comparable with the study results of Henzi et al. [27]. In the present study metoclopramide proved to be a poor antiemetic agent in a dose of 10 mg, associated with a high incidence of PONV (47%), we found no significant reduction of PONV on comparing metoclopramide with placebo. Several studies compared a single dose of dexamethasone with a single dose of Metoclopramide in the prophylaxis and treatment of PONV and found dexamethasone to be superior in the control of nausea and vomiting [9, 28]. The present study comparable to this observation with an incidence of complete response of (76%) with dexamethasone group. However, current opinion questions the role of mono-therapy, and combinations of dexamethasone with some other antiemetics have been found to be more effective than any drug alone [29, 14,30]. Biswas et al. [29] demonstrated that granisetron plus dexamethasone reduced the incidence of PONV after laparoscopic cholecystectomy more effectively than granisetron alone. McKenzie et al. [30] studied ondansetron and ondansetron plus dexamethasone in women undergoing general anesthesia for major gynecologic surgery, and the results showed the combination to be more effective than ondansetron alone. Because of the high cost of these agents, we prefer to use the less expensive metoclopramide in our study.

Although some studies describe the combination of metoclopramide and dexamethasone was inefficient combination for the prevention of PONV ([31, 32]. Present study approves this combination to be effective when compared to placebo (15% versus 61% resp.). Furthermore, none of the patients from the dexamethasone and metoclopramide group required a rescue antiemetic, pointing to the high efficacy of this drug combination in the prevention of PONV, this difference possibly due to the timing of the combination drugs or to the different sample size.

Pain after laparoscopic cholecystectomy is relatively minor and is most intense during the first 4 h after surgery [33]. In present study, all study groups experienced sufficient pain relief with paracetamol vial (500 mg/8 hr.), and reported low VAS pain scores (0–3).

The most common side effects observed in this study were headache, sedation, and sleep disturbances. these were relatively mild, and there were no significant difference in the incidence of side effects among the treatment groups.

CONCLUSION

The combination of dexamethasone plus metoclopramide and dexamethasone alone was superior to metoclopramide and placebo in preventing PONV after laparoscopic cholecystectomy.

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