

Comparison Between Antiemetic and Long Acting Glucocorticoid in Reducing Nausea and Vomiting after Laparoscopic Procedures

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Abstract

Background: The overall incidence of postoperative nausea and vomiting (PONV) is estimated to be around 20 to 30% and might peak up to 75% in certain high risk patients. Patients who experience postoperative nausea and vomiting consume more time and resources and require additional care. **Objective:** To Compare the role of preoperative corticosteroid and metoclopramide administration in reducing postoperative nausea & vomiting in patients undergoing laparoscopic cholecystectomy **Patients and Methods:** A randomized, double-blind placebo-controlled study included 120 adult patients with gallstone disease scheduled for elective laparoscopic cholecystectomy attended Tikrit Teaching Hospital TTH, during the period from May 2013 to June 2014. The patients were divided into 3 groups, each group with 40 patients. Group (A) was given 8 mg of i.v. dexamethasone at induction of G.A. The 2nd group (B) was given 10 mg of metoclopramide i.v. , while a 2ml of normal saline administered to the control group(C) as placebo. The incidence of nausea and/or vomiting had been reported and compared at 6, and 24 hours postoperatively .

Results: The incidence of PONV were 27.5%, 40 % ,& 70 % in groups A, B and C respectively. The grades of vomiting as following : grade 1 in group A (80%) ,B(58%) and C (53%)., whereas grade 2 in group A(20%), B(42%) & C (47%). Requirements for rescue antiemetics: in group A(40%), while in groups B (58 %)which in not significant ($p=0.130$) and in group C (69%) required rescue antiemetics. **Conclusions:** Dexamethasone is more effective than metoclopramide in reducing postoperative nausea and vomiting following laparoscopic cholecystectomy

Keywords:

Postoperative nausea and vomiting (PONV), Physiology, Grading, Gall stones, Laparoscopic cholecystectomy.

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1. Introduction:

Laparoscopic cholecystectomy (LC) is the most common major surgical procedure performed in Western countries. It offers cure for gallstones with minimally invasive procedure, minor pain and scarring, and early return to full activity¹. Typically, surgeons admit patients to hospital on the day of their operation and discharge them on the same day, after the procedure². Although serious adverse event are uncommon after LC, 50% to 75% of patients experience postoperative nausea or vomiting (PONV)^{3,4}. Despite significant improvements in therapeutics and anaesthesia techniques, PONV is still one of the most common complications of anaesthesia⁵⁻⁸. PONV afflicts around one-third of patients undergoing operation with general anaesthesia, however it is not only GA that predispose to PONV as will be explained below^{6,7,9}.

Physiology of Vomiting:

Nausea is described as the unpleasant sensation associated with the urge to vomit, or awareness of the potential to vomit. while vomiting is the forceful ejection of liquid or semisolid stomach contents through the mouth¹⁰. Central stimulation from the cerebral cortex, CTZ, higher cortical and brainstem centres, nucleus tractus solitarius, vestibular apparatus of the inner ear and the visual centre also affects the vomiting centre¹¹. When stimulated, these receptors relay impulses to the vomiting centre, which then coordinates efferent impulses through the vagus, phrenic, and spinal nerves of the abdominal musculature to initiate the vomiting reflex. Thus, the multifactorial nature of PONV may necessitate combination therapy for prophylaxis and treatment¹¹. (Figure 1).

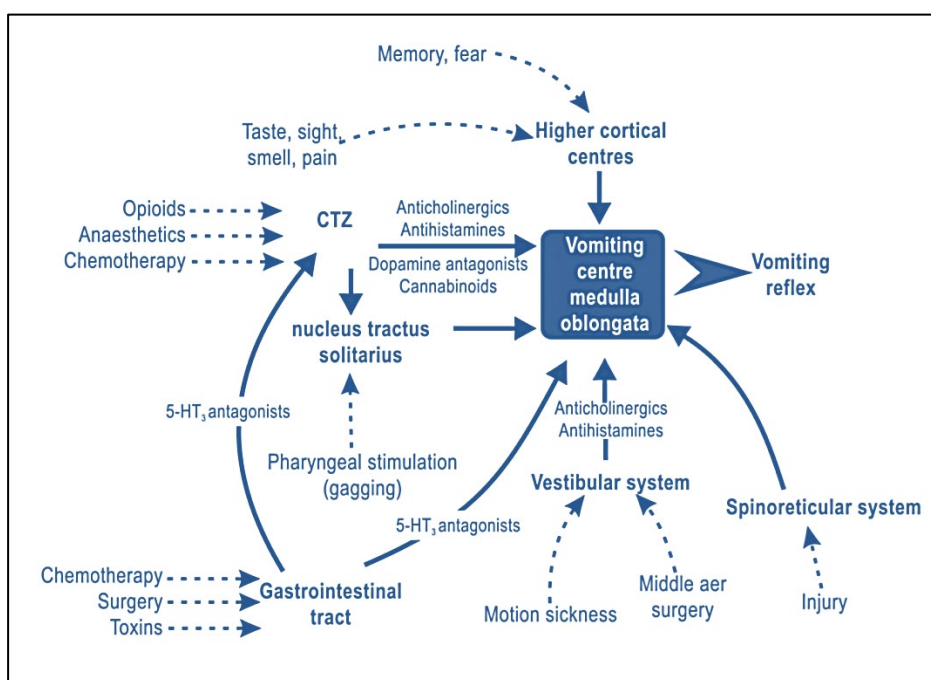


Figure 1. Vomiting pathway¹¹

Grading of vomiting¹²:

Grade 0 : no vomiting

Grade 1 : (1-4) episodes /24 hours.

Grades 2 : > 4 episodes /24 hours.

Etiology of PONV

There are various causes of PONV like laryngeal stimulation, anaesthetic agents, gastro intestinal distension, abdominal pain, opioids, hypoxia, hypotension, vestibular stimulation and psychological factors¹³

Risk Factors for PONV

The etiology of PONV is multifactorial, involving patient, medical, surgery and anaesthesia-related factors.

Patient-related Factors:

Patient-related risk factors are beyond our control and it becomes imperative to identify them during the preoperative anaesthesia evaluation. They include age, gender, history of motion sickness or PONV, and smoking history. Obesity is no longer considered a risk factor for PONV^(13,14).

Medical Factors

Some patients may have coexisting medical problems, such as gastrointestinal diseases (hiatus hernia, gastroesophageal reflux) and metabolic diseases (diabetes mellitus, uraemia, electrolyte abnormalities), that may predispose them to PONV. Pregnancy and preoperative anxiety also increase the risk of PONV. The underlying surgical problem for which the patient is undergoing surgery, such as intracranial stimulation (raised intracranial pressure from tumours) and sensory stimulation from acute abdomen, intestinal obstruction etc., can also

initiate the vomiting reflex. Patients undergoing chemotherapy or radiation therapy are also more prone to emesis^(7,11,13).

Surgery-related factors :

Certain types of surgery are associated with a higher risk of PONV. Otolaryngological surgery, dental surgery, and laparoscopy were found to have a higher incidence of PONV than other procedures. Long operations increase the exposure time to potentially emetogenic anaesthetic drugs and are associated with a higher risk of PONV¹⁰.

Laparoscopic cholecystectomy - along with gynaecological and ophthalmic surgery - is more likely to cause PONV compared to other operations^{10,13}.

Anaesthesia-related factors:

While anaesthetists have little control over surgical factors, they do have control over factors such as premedication, anaesthetic technique, choice of anaesthetic drugs [nitrous oxide, volatile anaesthetics, intravenous (IV) agents, opioids and reversal agents], IV hydration and postoperative pain management. A >35% reduction in systolic blood pressure during anaesthesia, and especially during induction, has been associated with an increased incidence of PONV^{10,13}. Midazolam is frequently used as a sedative for premedication. In addition to its anxiolytic effect, midazolam probably enhances the inhibitory effects of gamma amino butyric acid (GABA) and decreases dopaminergic

neuronal activity and 5-hydroxytryptamine (5-HT) release^{10,11,13}.

Impact of PONV:

PONV usually occurs on the first post-operative day and is most distressing in the early hours of surgery. It is so unpleasant that most patients would prefer to experience postoperative pain rather than nausea and vomiting and it reduces patient's satisfaction with postoperative care¹⁵. It can also lead to wound dehiscence, bleeding, pulmonary aspiration of gastric contents and may trigger cardio-respiratory reflexes, dehydration, water and electrolyte abnormalities, and increased venous pressure¹⁶. Moreover, patients who suffer from PONV require prolonged hospitalization, re-hospitalization, additional healthcare professional time and material resources leading to higher costs. Hence, prophylactic antiemetic therapy is needed for these patients.

, implying that economic consequences are involved^{6,7,10,15}. Antiemetic prophylaxis appears to be cost-effective^{10,11,13,16}.

Glucocorticoids as anti-emetics:

After corticosteroids were found effective in chemotherapy-induced nausea and vomiting, they were used in anaesthesia as prophylaxis against PONV¹⁷. The mechanism of the anti-emetic action of corticosteroids is unknown, but prostaglandin antagonism has been proposed to be the mechanism, and the release of endorphins is another explanation suggested for the action^{4,8,10}. It has also been

speculated that the mechanism of action is related to the anti-inflammatory and membrane-stabilising effect. The glucocorticoids betamethasone and dexamethasone have been studied for the prophylaxis of PONV. The half-life of betamethasone is 5 hrs and that of dexamethasone is 3 hrs. No problems with wound healing, or disturbances of glucose metabolism have been reported after a single prophylactic dose^{17,18}. Dexamethasone has also been found to have a prophylactic effect on PONV in patients undergoing tonsillectomy, thyroidectomy, abdominal hysterectomy, and theoretically in women having ambulatory laparoscopic surgery. It lacks side effects when used as a single injection and has a low cost^{18,19,20}. Data on metoclopramide as an antiemetic after surgery are contradictory. A meta-analysis found that an intravenous dose of 10 mg had only a marginal effect, but because of its complex mode of action (it binds to dopamine, serotonin, and histamine receptors). Yet, metoclopramide still remains an interesting drug for preventing postoperative nausea and vomiting²².

2. Patients and Methods

A randomized, double-blind placebo-controlled study included 120 adult patients with gallstone disease scheduled for elective laparoscopic cholecystectomy. All patients with ASA 1 or 2 were admitted to Tikrit Teaching Hospital, Salah Al-Deen Province, Iraq, during the period from May 2013 to June 2014. An informed consent obtained from each patient before the procedure.

Exclusion criteria :

1. Patient with one or more of gastrointestinal ,neuromuscular, motion sickness, or renal diseases.
2. Nausea and vomiting within 72 hrs before the procedure.
3. Patient taking antiemetics within 72hrs.
4. Pregnancy.
5. Allergy to study medications.
6. Somkers.
7. Conversion to open procedure.

The patients were randomly allocated into 3 groups, each group with 40 patients . At induction of G.A , first group (A) was given 8 mg of i.v. dexamethasone, the 2nd group (B) was given 10 mg of metoclopramide i.v. , while a 2ml of normal saline administered to the control group (C) as placebo. The patients received a single dose of injection (cefotaxime 1g)at the time of induction of anaesthesia. Anaesthetic regimen was standardized for all patients. Sedation: with fentanyl, induction with thiopenton HCl, maintenance with fluthane, relaxation with pancuronium and

reversal with prostigmine. Reverse Trendelenberg with right side up position was made and LC was performed using the standard 4 ports technique with two 10 mm and two 5 mm ports. Pneumoperitoneum was created with the open technique. Nasogastric tube was placed in cases found to have a distended stomach, and removed at the completion of the procedure.

During laparoscopy, intrabdominal pressure (IAP) was maintained at(10-14) mm Hg. Gall bladder was extracted through the epigastric or umbilical ports, and the 10 mm port fascial defect was closed with 1/0 Vicryl. Duration of surgery calculated from induction of anesthesia to extubation. The incidence of nausea and/or vomiting had been recorded in the 3 groups at 6, and 24 hrs postoperatively and compared using a data collection sheet . Patients and investigators who collected postoperative data were blinded to the study drug administered. Postoperative analgesia used diclofenac 75 mg, or paracetamol 600mg ampoules i.m. When patients developed repeated vomiting, they were given Ondansetron 4 mg intravenous injection as anti-emetic, irrespective of the group. *Complete response* : is defined as no PONV and no antiemetic medication during a 24-h postoperative period.

Statistical analysis: Data were analyzed using the statistical package for social sciences (SPSS) software for windows version 20, appropriate statistical tests and procedures were

applied according to the variable type, (P.value) ≤ 0.05 was considered significant.

3. Results

Patients' characteristics :

Age of the patients ranged (18-71) yrs, with mean age (45.38)yrs ,their weights ranged (53–94) kg, mean weight (66.24) kg,. The treatment groups were comparable with regard to patient demographics. Differences among the patient's age, sex, weight and duration of surgery within the 3 study groups are statistically not significant. Thus making no effect on the results among the 3 groups. (P value > 0.05), (Table 1). Out of the 120 patients enrolled in this study, 103 were females (85.8%) and 17 males (14.2%) (Figure 2).

Incidence of PONV :

In dexamethasone sodium phosphate group (A), 6 patients (15%) reported nausea and 5 patients (12.5%) had episodes of vomiting. So total incidence of PONV was 11 (27.5%) and the remaining 72.5% of patients were free of PONV. It was highly significant when compared to control group (P < 0.001). In Metoclopramide group (B), total incidence of PONV occurred in 16 patients (40%). Nine patients(22.5%) reported nausea and 7 patients(17.5%) developed vomiting that is 60% had no PONV and it was significant compared to control group (P= 0.007). In Placebo control group (C) , PONV had been reported in 28 patients (70%); nausea in 15 cases (37.5 %), and vomiting in 13 patients (32.5 %),

These findings are summarized in (Table 2 and Figure 3).

Frequency and grades of vomiting :

Grade 1 (1- 4)episodes /24 hrs:

It occurred in 4 (80%) out of the 5 patients who developed vomiting in group A, in group B occurred in 4 out of the 7 patients (57.1%), and in group C reported in 7 out of 13 patients (53.8%).

Grade 2(>4)episodes/24 hrs:

It had been reported in 1 patient (20 %) ,3 patients (42.9%), and 6 patients (46.2%) in the groups A, B, and C respectively. So, most of patients (80%) who developed vomiting in group A are of low grade (grade 1), in contrast to groups B and C. The result is just significant (P= 0.048), (Table 3)

Time onset of vomiting :

Regarding the time onset ,we found that group A reported the least percentage of late onset of vomiting, i.e. among the 5 patients who developed vomiting ,3 (60%) had developed vomiting within the first 6 hours, and 2 patients(40%) had late onset vomiting (6-24 hrs). In group B, 3 out of 7 (42.9%) had late onset vomiting. In group C , 7 out of 13 (53.8%) reported vomiting after 6 hours. Statistical analysis revealed no significant difference between groups A and B, P>0.05, (Table 4).

Requirements for rescue antiemetics :

Two patients (40 %) in group A, 4 patients (57.1%) in groups B and 9 patients (69.2%) in group C required rescue antiemetics (**Table 5**).

Complete response:

It was 72.5 % ,60 %, and 30 % in groups A, B, and C respectively .We did not observe

any incidents or adverse events attributable to either drug, nor did groups differ in the time taken for discharge or in the quality of recovery when compared with the use of saline , (**Figure 4**).

Table 1. Baseline characteristics of patients in the studied groups.

Variable	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	P. value
Age (years) mean $\pm$ SD	48 $\pm$ 13	45 $\pm$ 14	44 $\pm$ 13	NS
Weight (kg) mean $\pm$ SD	66 $\pm$ 10	65 $\pm$ 10	68 $\pm$ 10	NS
Sex (Female/Male)	34/6	36/4	33/7	NS
Duration of surgery (min) mean $\pm$ SD	52 $\pm$ 5	55 $\pm$ 5	62 $\pm$ 5	NS

SD: standard deviation, NS: not significant; > 0.05

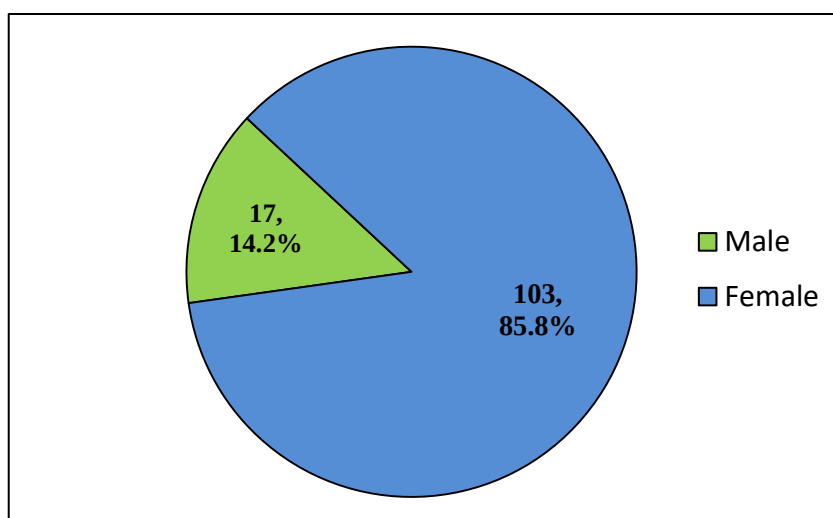


Figure 2. Gender distribution of total 120 patients .

Table 2. Comparisons of the three studied groups in PONV incidence rates

Finding	Group A (n = 40)		Group B (n = 40)		Group C (n = 40)	
	No.	%	No.	%	No.	%
Nausea	6	15.0	9	22.5	15	37.5
Vomitting	5	12.5	7	17.5	13	32.5
None	29	72.5	24	60.0	12	30.0
P. value (vs. Placebo group)	< 0.001		0.007		1.0	

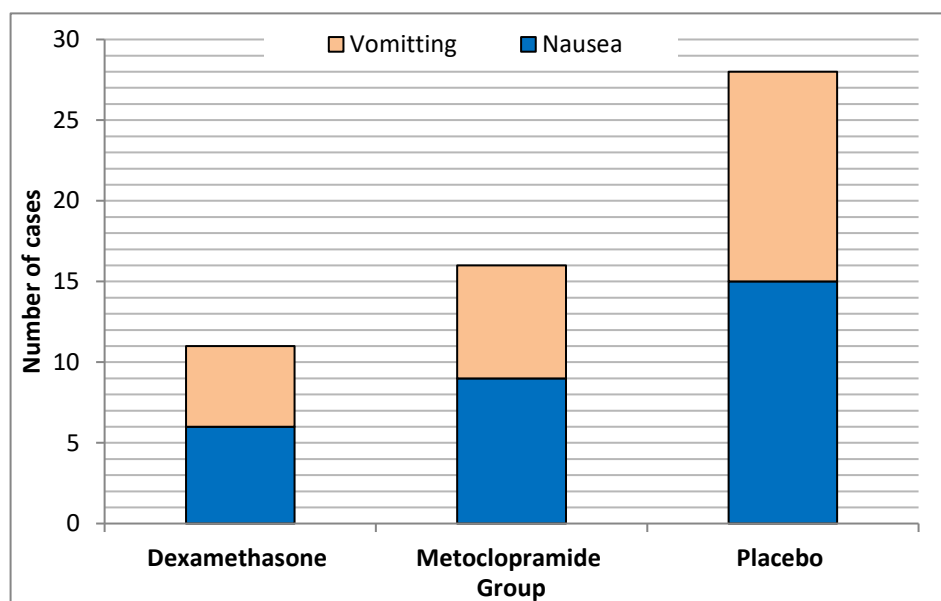


Figure 3. Incidence of PONV among different groups.

Table 3. Grades of vomiting in study groups.

Grade	Group A (n = 5)		Group B (n = 7)		Group C (n = 13)	
	No.	%	No.	%	No.	%
Grade 1	4	80.0	4	57.1	7	53.8
Grade 2	1	20.0	3	42.9	6	46.2
P. value = 0.048 significat						

Table 4. Time onset of vomiting among study groups.

Time onset	Group A (n = 5)		Group B (n = 7)		Group C (n = 13)	
	No.	%	No.	%	No.	%
Within 6 hrs	3	60.0	4	57.1	6	46.2
(6 - 24) hrs	2	40.0	3	42.9	7	53.8

Table 5 . Number and percentage of patients had vomiting and required rescue antiemetics.

Required Rescue	Dexamethasone (n = 5)		Metoclopramide (n = 7)		Placebo (n = 13)	
	No.	%	No.	%	No.	%
Yes	2	40.0	4	57.1	9	69.2
No	3	60.0	3	42.9	4	30.8

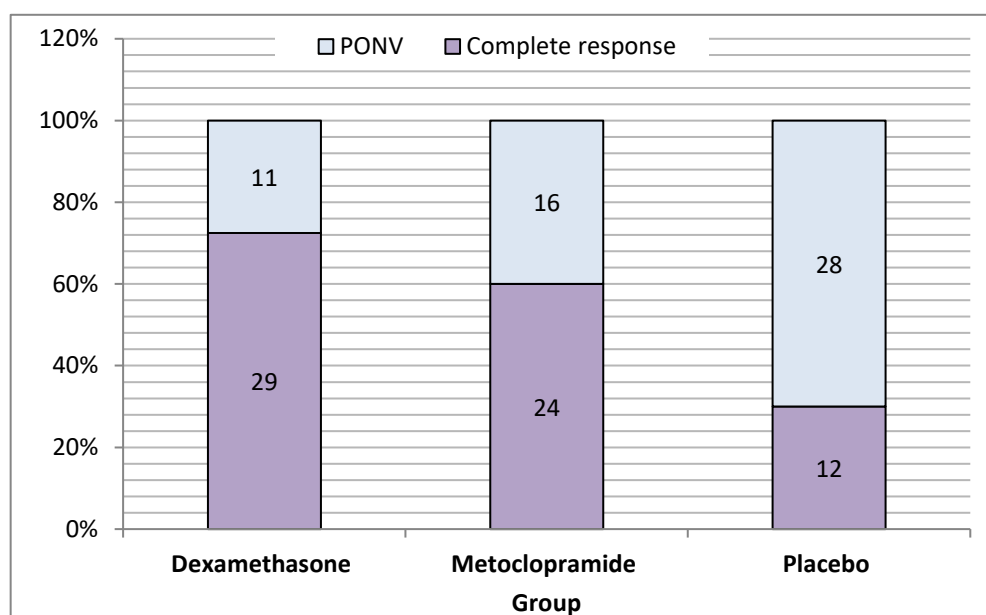


Figure 4. Complete response and PONV among study groups.

4. Discussion

In the present study, it had been found that the total incidence of PONV was (70%) in 24 hours after patients undergoing LC when no antiemetic was given prophylactically. This percentage is within the range reported in the previous literatures, and reflects how common PONV is in cases of LC. The results of the present study have been supported by other studies as well. PONV incidence was 64% in a study established by Jhi-Joung Wang⁸. K Ivanov found that 60 % in the control group, which was the same to result of Paech et al.^{5,9}

Wang in accordance with Biswas⁷ and colleagues found that incidence of PONV was 63 % in a similar study of a saline control group. According to Rudra the incidence was less (54 %). However, a higher percentage was recorded by Mohamed A. as (77%)¹⁴. Hospitals have different routines and regimens in their anaesthesia practice. The doses of opioids used during the anaesthesia can vary, as well as the dosage of volatile and IV anaesthetics. The routine use of neuromuscular relaxation and its reversal may differ among the hospitals. The regimen of postoperative pain medication, the use of NSAIDs and opioids may also diverge and this reflects variation in PONV incidence among different centres¹⁰.

PONV in dexamethasone group:

In the present study, the incidence of PONV in patients who had received

dexamethasone or metoclopramide was 27.5 % , and 40 % respectively. A wide range of doses of dexamethasone (5-32) mg has been used in the management of PONV and emesis associated with chemotherapy⁸. Among these doses (8-10mg) has been most frequently used in the prevention of PONV^(4,8). So A 8 mg dose was chosen for the present study, and significantly decreased PONV.

Dexamethasone had been shown to be effective in reducing the incidence of PONV in numerous studies. These results are in agreement with the result of a study by Jhi-Joung Wang who recorded PONV in dexamethasone group as 26%.⁸

Wang et al. Ivanov et al., and Ahmad et al all reported PONV in dexamethasone given sample was 23 %, ^{4,5,16} while both Rudra A, and Gupta P^{7,12} results were relatively higher as 24%. Mohamed A recorded that 40% had PONV¹⁴. Elhakim et al. , Aouad et al. and Pappas et al.²³ in their studies reported that patients who received intravenous dexamethasone preoperatively had significantly lower episodes of vomiting in the 24-hours following surgery compared with those who received the placebo dose of normal saline. Biswas and colleagues⁷ reported the incidence of PONV with placebo up to 63% compared to 37 % with dexamethasone (P<0.05). In another study by Feo et al⁷. on laparoscopic surgery patients, the incidence of nausea and vomiting was 46% in the

placebo group and 14% in the dexamethasone group. P.-E. Sa´nchez-Rodrı´guez²⁰ found that PONV was 28% and concluded that preoperative dexamethasone can significantly reduce the incidence of PONV, pain and fatigue after elective LC. Above observation contradicts with that of Jan Wallenborn who stated that dexamethasone (8mg) alone is ineffective prophylactic antiemetic, but becomes so once combined with metoclopramide (25mg) ²². In contrast, *Chekman et al.*, comparing the effect of dexamethasone and metoclopramide (injected 10 minutes before anaesthesia) in 45 patients divided into 3 groups, showed that PONV incidence was not significantly different

between the dexamethasone and metoclopramide groups. The difference between our results and theirs was probably due to the time of drug injection, since its effect on PONV might be diminished. The small sample of patients in Chekman's study is also a main limitation²². Dosage of dexamethasone used by those authors is different ranging from(5, 8 to 10 mg) and this may account to the differences in effectiveness of the drug. ^{1,7,15,18}. In summary, (Table 6) shows the comparison of incidence of PONV in the present study compared to previous studies that compared dexamethasone vs. controls

Table 6. Comparison of PONV in 2 groups among other studies.

Study	PONV in control group	PONV in dexamethasone group
The present study	70 %	27.5%
Wang et al (Taiwan 2002) ⁸	64 %	26%
Ivanov et al (Bulgaria 2007) ⁵	60%	23%
Michael et al (Australia2007) ⁹	60%	25 %
Rudra et al (India 2005) ⁷	54 %	24%
Mohamed A (KSA2008) ¹⁴	77%	40%
Sa´nchez-Rodrı´guez et al (Mexico 2010)	67%	28%
Ahmad J et al (Pakistan 2010) ¹⁶	63.3%	23%
Farhat (Pakistan 2009) ¹⁹	76.7%	30%
Gupta(India 2006) ¹²	Not included	24%
Gautam(Nepal 2008) ¹⁶ .	Not included	34%

Regarding frequency of vomiting, i found that dexamethasone besides reducing the total incidence of PONV, it also lowered the frequency of vomiting in group A patients . In a study by Gupta P. et al ,¹² comparative rates reported in dexamethasone group, as 11 %(grade 1) and 1% (grade 2). These observations will be reflected in less antiemetic requirements ,hence cost , and nursing care. About time onset of vomiting ,though it has been found to reduce overall incidence of PONV, we did not observe a significant virtue of dexamethasone over metoclopramide against late onset vomiting (after 6 hrs), this may be explained as that the majority of vomiting cases were early onset i.e. within the 1st six hrs postoperatively.¹⁹ Dexamethasone probably has a delayed onset time of at least 2 hours and a prophylactic IV dose is best given at the time of induction rather than at the end of surgery to prevent early PONV 17. The late onset and prolonged antiemetic efficacy of dexamethasone may be attributed to its prolonged biological half-life (36-72 hr). Ivanov⁵ found that dexamethasone is more effective than metoclopramide in reducing both early (0-12hrs), and late (12-24hrs). After a thorough literature search I was unable to find a report of side effects associated with the use of a single dose of dexamethasone.

Requirements for rescue antiemetics :

In the present study 40 % in group A, 58 % in groups B and 69% in group C , required

rescue antiemetics. Mohamed A¹⁴ gave antiemetics to 23% of dexamethasone group, and 47% of control group. These numbers are both more than ours, and this may be attributed to individual variation in tolerating nausea and/or vomiting. Comparable ,slightly less results found by Jhi-Joung Wang as 13 % for dexamethasone and 41% for the control groups⁸. However , Gautam reported 31.9% of dexamethasone received patients required rescue antiemetics¹⁵. Michael et al.⁹ used a 4 mg dexamethasone and 2 mg ondansetron combination , and reported that 16 % of them required antiemetics. This outlines the cost-efficacy of using dexamethasone , avoiding the unnecessary expenses on antiemetics with their unwanted effects and saving the nursing care efforts.

Complete response :

The highest percentage of complete response was in group A (72.5 %), as compared to B (60 %), and C (30%). In dexamethasone group a slightly higher success rates achieved by Jhi-Joung Wang (74 %),¹ and by Mohamed A (77%).¹⁴ However, a lower result (66 %) recorded by Gautam and his colleagues¹⁵. A study conducted by Michael et al. ,he used a combination of 4 mg dexamethasone with 2 mg ondansetron even higher percentage of patients (83%) had complete response⁹. This may be explained as being due to the additional effect of ondansetron.

5. Conclusions

In light of the findings of the current study a single prophylactic dose of dexamethasone is safe, and effective in the prevention of PONV of laparoscopic cholecystectomy. The Dexamethasone is more effective than metoclopramide in reducing PONV following LC, with no observed adverse effects however, Dexamethasone is not particularly effective in preventing late onset (i.e. after 6 hrs) vomiting after LC. Further studies with larger sample size and multi-center are still needed for further assessment.

Ethical Issues:

This study was ethically approved and signed written consent obtained from each patient before enrollment, additionally, all official agreements were obtained.

Conflict of Interest : None

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