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Prophylactic Anti-Emetic Effect of Dexamethasone and Metoclopramide on the Nausea and Vomiting Induced by Laparoscopic Cholecystectomy: A Randomized, Double Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is an unpleasant, distressing and frequent adverse effect after general anesthesia and surgery which has a high incidence in patients undergoing laparoscopic cholecystectomy. While none of the currently available antiemetic drugs are fully effective in all patients, it has been reported that dexamethasone is effective against emesis in patients undergoing general anesthesia.

Objectives: This study evaluates the prophylactic anti-emetic effect of dexamethasone in comparison with metoclopramide and placebo for the prevention of post-operative nausea and vomiting in patients undergoing elective laparoscopic cholecystectomy.

Patients and Methods: In Mostafa Khomeini hospital, a teaching hospital of Shahed University, Tehran, Iran, a randomized, double-blind and placebo-controlled study on 161 patients undergoing general anesthesia for elective laparoscopic cholecystectomy was run.One hundred sixty one patients (124 females and 37 males) requiring general anesthesia for laparoscopic cholecystectomy were studied. The dexamethasone group (n = 53) received dexamethasone 8mg IV, the metoclopramide group (n = 55) received metoclopramide 10mg IV and the placebo group (n = 53) received 2ml saline IV at the induction of anesthesia.

Results: In the current study, 26.4 %, 32.7 % and 52.8 % of patients reported vomiting in the dexamethasone, metoclopramide and placebo group ($P \leq 0.001$), respectively. The total incidence of nausea and vomiting also reduced to 30.2 % with dexamethasone in comparison with 49.1 % in metoclopramide group and 58.5 % in placebo group. ($P \leq 0.001$)

Conclusions: Dexamethasone 8mg is a better anti-emetic agent than metoclopramide for the prevention of post-operative nausea and vomiting after laparoscopic cholecystectomy.

Keywords: Vomiting; Dexamethasone; Cholecystectomy, Laparoscopic

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Implication for health policy makers/practice/research/medical education:
This research demonstrated the significant efficacy of dexametazon on post-operative nausa and vomiting comparison of metoclopramide.

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1. Background

Postoperative nausea and vomiting (PONV) are unpleasant, distressing adverse effects after general anesthesia and surgery (1-3). The incidence of PONV is high in patients (53 % - 72 %) undergoing laparoscopic cholecystectomy (2, 3). It has been reported that dexamethasone is effective against emesis in patients undergoing chemotherapy, and also it has been recently reported to be effective in prevention of nausea and vomiting after surgery (4-6) and (7, 8).So this study was conducted as a randomized, double-blind and placebo-controlled trial to determine the effect of dexamethasone in the prevention of PONV in patients undergoing laparoscopic cholecystectomy.

2. Objectives

The current study aimed to evaluate the prophylactic anti-emetic effect of dexamethasone in comparison with that of metoclopramide and placebo for the prevention of post-operative nausea and vomiting in patients undergoing elective laparoscopic cholecystectomy.

3. Patients and Methods

Medical Ethic committee of Shahed University approved the study, and 161 patients (124 females and 37 males) undergoing general anesthesia for elective laparoscopic cholecystectomy in Mostafa Khomeini hospital during 2003-2005 were enrolled in a randomized, double-blind and placebo-controlled study. Patients with a history of motion sickness, intestinal diseases or the patients who had received antiemetic within 24 h before surgery, women who were pregnant or breast-feeding, and those who had evidence of hepatic dysfunction were excluded from the study. Patients were randomly allocated to receive dexamethasone 8 mg, metoclopramide 10m, or placebo (0.9 % saline) intravenously immediately prior to the induction of anesthesia. The anesthetic condition was standardized. Laparoscopic cholecystectomy was performed as a standard procedure with pre-operative cholangiography. The duration of the surgery, anesthesia, CO2 insufflation and rate of cholangiography were recorded. Post-operative analgesia was provided by pethidine 25mg IM. During the first 24h after anesthesia, all episodes of post-operative PONV were recorded by direct questioning from nursing staff 7 times in the time of 0, 1 h, 2 h, 4 h, 8 h, 12 h and 24 h without the knowledge that which anti-emetic agents the patient had received, if he had received any. Nausea was defined as the subjectively un-pleasant sensation associated with awareness of the urge to vomit whereas vomiting was defined as the forceful expulsion of gastric contents from the mouth (9). Retching was not associated a separate entity and patients who experienced retching were classified as vomiting. Complete response was defined as the absence of nausea and vomiting throughout the study period. Patient data were analyzed through a one-way analysis of variances (ANOVA), students T test and chi-square test, where appropriate. A P-value of < 0.05 was considered significant. All values were expressed as Mean SD and number (%).

4. Result

After randomization, 53 patients were allocated to group 1 to receive dexamethasone, 55 patients to group 2 to receive metoclopramide and 53 patients to group 3 to receive normal saline. Patients' characteristics (age, weight and sex), information about operation (duration of anesthesia, surgery and rate of cholangiography as well as CO2 insufflation) had no significant difference among the three groups (Table 1). No significant side-effects were found after the use of either dexamethasone or metoclopramide compared with that of normal saline.

Table 1. Patient Characteristics and Operative Information

	Dexamethasone (n = 53)	Metoclopramide (n = 55)	Placebo (n = 53)
Age, y, Mean ± SD	52.9 ± 15.04	52.38 ± 15.25	53.92 ± 16.23
Weight, Kg, Mean ± SD	70.47 ± 11.61	71.94 ± 10.33	70.88 ± 10.78
Sex, No.			
Female	41	43	4013
Male	12	12	
Duration of Anesthesia, min, Mean ± SD	121.69 ± 21.34	124.72 ± 21.04	118.58 ± 21.28
Duration of Surgery, min, Mean ± SD	89.52 ± 19.29	94.90 ± 20.01	87.83 ± 21.51
Duration of CO2insufflation, min, Mean ± SD	79.81 ± 18.88	85.63 ± 19.76	78.39 ± 21.36
Rate of Cholangiography, %	75.5	81.8	73.6

After the first 24 h following the anesthesia, PONV still occurred in 16% of patients in group 1, in 23.9 % of group 2 and in 32.3 % of group 3 respectively (Table 2). The total incidence of nausea and vomiting during 24 h of observation was 30.2 %, 49.1 % and 58.5 % in the 1st, 2nd and the 3rd group ($P < 0.001$), respectively.

Table 2. Occurrence of PNOV among Different Groups of Study

	Dexamethasone (n = 53)	Metoclopramide (n = 55)	Placebo (n = 53)	P value
1st Hour After Surgery				
Nausea (+), No. (%)	14 (26.4)	18 (32.7)	23 (43.49)	0.176
Vomiting				0.066
No	44 (83.0)	47 (85.5)	37 (69.8)	
Once	8 (15.1)	7 (12.7	10 (18.9)	
Twice or More	1 (1.9)	1 (1.8)	6 (11.3)	
2nd Hours After Surgery				
Nausea (+), No. (%)	14 (26.4)	18 (32.7)	23 (43.49)	0.176
Vomiting				
No	45 (89.9)	40 (72.7)	29 (54.7)	
Once	8 (15.1)	10 (18.2)	14 (26.4)	
Twice or More	0 (0.0)	5 (9.1)	10 (18.9)	
4th Hours After Surgery				
Nausea (+), No. (%)	16 (30.2)	27 (49.1)	31 (58.5)	0.012[a]
Vomiting				0.013[a]
No	39 (73.6)	38 (69.1)	25 (47.2)	
Once	9 (17)	8 (14.5)	15 (28.3)	
Twice or More	5 (9.4)	9 (16.4)	13 (24.5)	
8th Hours After Surgery				
Nausea (+), No. (%)	10 (18.9)	23 (41.8)	27 (50.9)	0.002[a]
Vomiting				0.002[a]
No	47 (88.7)	37 (67.3)	31 (58.5)	
Once	4 (7.5)	9 (16.4)	10 (18.9)	
Twice or More	2 (3.8)	9 (16.4)	12 (22.6)	
12th Hours After Surgery				
Nausea (+), No. (%)	9 (17)	15 (27.3)	16 (30.2)	0.254
Vomiting				0.019[a]
No	50 (94.3)	50 (90.9)	41 (77.4)	
Once	2 (3.8)	4 (7.3)	7 (13.2)	
Twice or More	1 (1.9)	1 (1.8)	5 (9.4)	
24th Hours After Surgery				
Nausea (+), No. (%)	0 (0)	3 (5.5)	3 (5.7)	0.216
Vomiting				0.610
No	53 (100)	54 (98.2)	52 (98.1)	
Once	0 (0)	1 (1.8)	1 (1.9)	
Twice or More	53 (100)	54 (98.2)	52 (98.1)	

[a] Statistically significant

5. Discussion

PONV is a distressing and frequent adverse effect after general anesthesia and surgery with high rate of occurrence after laparoscopic cholecystectomy to treat cholelithiasis (2, 3). However, Laparoscopic cholecystectomy is associated with shorter post-operative hospital stay and less post-operative pain and has become a widely used surgical technique (10). The physiological mecha-

nism of PONV has not been fully understood, although it seems that nitrous oxide, abdominal operations, female gender, laparoscopy and operation on the gastrointestinal tract have been involved. Some previous reports claimed that the anti-emetic effect of dexamethasone aooeared to be equal or better than the antagonists of 5-HT3 receptors such as ondansetron and granisetron (5, 11); However, due to the multifactorial origin of PONV, none of currently available antiemetic drugs are fully effective in all patients (6). Recently dexamethasone has also been reported to be effective in the prevention of nausea and vomiting after pediatric and gynecological surgery (7, 8). The current study shows that dexamethasone reduces PONV in patients undergoing elective laparoscopic cholecystectomy. It was also found that dexamethasone is significantly more effective than MPO in such patients. In the current experiment the incidence of PONV during the first 12h after anesthesia and the total incidence of PONV had significant reduction of 18.3% and 28.3 % with dexamethasone in comparison with placebo respectively. Both incidences were higher in MPO group. These findings supported the previous studies which implied the notion that dexamethasone had better effect than the other after surgery anti-emetics (12-15). The exact mechanism by which dexamethasone, a corticosteroid, exerts an anti-emetic action has not been fully understood. However, there have been some suggestions such as central or peripheral inhibition of the production or secretion of serotonin (6,9,13,16-23) by releasing endorphins (24) and central inhibition of synthesis of prostaglandins (16) or changes in the permeability of the blood brain barrier to serum proteins. Its anti-emetic action, at least in part, may be elicited via the blockage of corticosteroid receptors in the nucleus tractussolitarius of the CNS (8). Dexamethasone may also exert its anti-emetic action through some peripheral mechanisms (25, 26). Dexamethasone have strong anti-inflammatory effects and may significantly reduce inflammation around the surgical sites and does reduce the ascending parasympathetic impulses (Vagus) to the vomiting center and PONV(3,6,9,12,13,16-24,27). The etiology of PONV has not been precisely realized, but it is probably multifactorial (18). Dexamethasone was more effective when administered before induction (28). Risk factors such as a long period of carbon-dioxide insufflation (19), gall-bladder surgery, female sex (3, 20) and post-operative pain may contribute to these episodes (20, 21); since these risk factors may interfere with the interpretation of the study data they were controlled within the study design. The duration of anesthesia, surgery, CO2 insufflation and the anesthetic drugs were similar among the three groups. In addition, after random patient selection, sex distributions among groups were similar. Therefore the difference in the occurrence of PONV among groups can be attributed to the tested drugs. A wide dose range of dexamethasone (8-32 mg) has been used in the prophylaxis of emesis related to chemotherapy and after pediatric and gynecological surgeries (7, 26, 29). The effectiveness of small doses of dexamethasone (2.5 – 5 mg) in the prevention of PONV has already been validated (13). However, in a study performed by Víctor Contreras-Domínguez et al., the dose of 4 mg was used and they had not found dexamethasone to be superior to placebo (28). Since 8mg dose of dexamethasone has been the most frequently used dosage of dexamethasone in the previous similar studies, in the current study, a single bolus dose of 8 mg dexamethasone was administered and this could be the reason of this conflict. The inherent risks of dexamethasone include infection and adrenal suppression. However no report of complications associated with a single bolus of dexamethasone is reported so far (28). The frequent incidence of PONV has been reported to be 53-72% (12, 30,31). In the current study, the total incidence of PONV in the control group, without any prophylactic administration of antiemetic, was 58% which is compatible with the other studies. Since the postoperative pain and residual CO2 in peritoneum are risk factors of PONV (1) it is better to measure them to make sure that they are the same between groups. In the current study, although postoperative pain was not measured, adequate analgesia was provided for all patients. As it can be seen in table 2 there was no significant difference between the study groups regarding other potential confounding factors. Also as it is mentioned above, laparoscopy is another risk factor and to avoid this potential source of bias all surgeries were done by one surgeon. Results of the current study indicated that prophylactic IV dexamethasone 8mg significantly reduces the incidence of PONV in patients undergoing laparoscopic cholecystectomy and that dexamethasone is more effective than metoclopramide and placebo without any important side effects. It can be concluded that the best way to reduce post-operative nausea and vomiting in patients who undergo laparoscopic cholecystectomy is the prophylactic administration of 8 mg of dexamethasone.

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Authors' Contribution

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