The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (10), Page 5479-5484

Dexamethasone versus Ondansetron in Prevention of Postoperative Nausea and Vomiting After Laparoscopic Surgery

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ABSTRACT

Background: postoperative nausea and vomiting (PONV) are a common distressing symptoms in patients undergoing laparoscopic surgery and can contribute to anxiety, dehydration, metabolic abnormality, wound disruption, delayed recovery and other issues. The incidence of PONV varies from 20 to 80 % of all surgeries, and it is an economic and social burden. **Aim of the Work:** was to assess whether dexamethasone is a cost-effective alternative to ondansetron in the prevention of PONV in patients undergoing laparoscopic surgery. **Patients and Methods:** A study was conducted at Ain Shams University Hospitals between November 2017 and April 2018, after obtaining approval of research ethical committee and patients' informed consents. 80 Patients were included in the study and underwent elective laparoscopic surgery and received general anesthesia. **Results:** The study showed a statistically significant difference between groups regarding PO nausea and other postoperative complications. **Conclusion:** Dexamethasone 8 mg was as effective as ondansetron 4 mg. Dexamethasone provided a simple, safe, cheap, and effective postoperative nausea and emesis prevention method with the advantage of being cheaper decreasing the economic burden.

Keywords: Dexamethasone, Ondansetron, Postoperative Nausea, Vomiting, Laparoscopic Surgery

INTRODUCTION

Postoperative nausea and vomiting (PONV) are a common distressing symptoms in patients undergoing laparoscopic surgery and can contribute to anxiety, dehydration, metabolic abnormality, wound disruption, delayed recovery and other issues. The incidence of PONV varies from 20 to 80 % of all surgeries, and it is an economic and social burden [(1)]. The treatment of nausea and vomiting should be aimed at specific receptors/mediators that appear to be largely contributing to an individual patient's experience. A greater appreciation of which particular mechanisms are playing a major role for an individual patient may lead to targeted therapies in attempts to eliminate nausea and vomiting, minimize treatment induced adverse effects, and optimize patient outcomes [(2)]. **Metoclopramide** is a medication used mostly for stomach and esophageal problems. It is Antiemetic (prokinetic agent) potent dopamine-receptor antagonist. Common side effects include: feeling tired, diarrhea, and feeling restless. More serious side effects include: movement disorder like tardive dyskinesia, a condition called neuroleptic malignant syndrome and depression [(3)]. **Ondansetron** is a selective seretonin (5 hydroxytryptamine, 5-HT_3) receptor antagonist that exhibits an anti-emetic action by antagonizing vomiting signals in the afferent pathway from the stomach, small intestine and solitary tract nucleus, and is effective at preventing PONV, however the high cost of this drug has prevented it from being widely used [(4)]. **Dexamethasone**, a corticosteroid, was first reported as an effective anti-emetic agent in patients undergoing cancer chemotherapy in 1981, Wang et al. [(5)] confirmed that dexamethasone is most effective when it is administered at the induction rather than at the termination of anesthesia. However, the mechanism underlying the anti-emetic effects of dexamethasone is still unknown. It may be involved in central inhibition of prostaglandin synthesis, or it may cause a decrease in serotonin turnover in the central nervous system. Today, cost-benefit analyses have become an important factor when considering what drugs to use as prophylactic antiemetics. However, it has not been established whether dexamethasone is a cost-effective alternative to ondansetron in the prevention of PONV in patients undergoing laparoscopic surgery [(6)].

AIM OF THE WORK

The aim of this study was to assess whether dexamethasone is a cost-effective alternative to ondansetron in the prevention of PONV in patients undergoing laparoscopic surgery.

PATIENTS AND METHODS

This study included a total of 80 patients who underwent elective laparoscopic surgery and received general anesthesia, attending at Ain Shams University Hospitals. **The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from each participant in the study.** This study was conducted between November 2017 and April 2018. Patients were randomly divided into two equal groups, each

Received:21/6/2018
Accepted:30/6/2018

40 patients. Randomization was done by a computer-generated random numbers list and utilizing opaque sealed envelopes. The study drugs were given intravenously 15 minutes before the induction of anesthesia. The groups were: **Group Ondansetron (Ond)**: patients received ondansetron 4 mg and **Group dexamethasone (Dex)**: patients received dexamethasone 8 mg. ***Inclusion Criteria:*** 1. Age 18-60 years, 2. Males and females, 3. Body mass index (BMI) $\leq$ 35 kg/m^2, 4. Elective operation under general anesthesia, 5. Eight fasting hours, 6. Physical Status: ASA I and II. ***Exclusion criteria:*** 1. Patient's refusal of participation in the study, 2. Physical status: ASA III or above, 3. Patients who had past history of nausea or vomiting, 4. History of motion sickness, 5. Facing kidney problems with a high level of BUN or serum creatinine, 6. History of allergy to the study drugs, 7. BMI $\geq$ 35 kg/m^2, 8. Pregnant, lactating or menstruating patients. ***Pre-operative settings:*** 1. All patients were subjected to full history taking and thorough physical examination, 2. Age, sex, body weight and height (and hence BMI was calculated) and ASA physical status were recorded, 3. Preoperative investigations were done to all patients including laboratory investigations as (complete blood picture, bleeding time, prothrombin time and activated partial thromboplastin time) and other investigations as dictated by the patient's medical condition, 4. The patients were fasting for 8 hours preoperatively, 5. Study medications were prepared by one anesthesiologist in identical coded 5-ml syringes and administered in a double-blind fashion, whereas monitoring was done by another anesthesiologist who was blinded to the drug given. ***Intra-operative Settings:*** The same standardized anesthesia technique was used in all patients. Patients were monitored during anesthesia by continued ECG, noninvasive blood pressure, pulse oximetry, capnometry and nasopharyngeal temperature. General anesthesia was induced with thiopental (5-6 mg/kg), and fentanyl (1µg/ kg). Atracurium (0.5 mg/kg) was given to facilitate tracheal intubation. A nasogastric (NG) tube was inserted. Anesthesia was maintained with 1.0%–2.5% (inspired concentration) isoflurane in oxygen as clinically required. Additional fentanyl and atracurium was used if necessary. Ventilation was controlled mechanically and adjusted to keep end-tidal carbon dioxide (CO_2) between 35 and 40 mmHg. The intravenous fluid used during surgery was 0.9% saline and Ringer's lactate. The amounts of fluids administered were calculated. Third-generation cephalosporin was given at the induction of anesthesia. Duration of anesthesia (time from induction of anesthesia to extubation) and surgery (time from skin incision to wound closure) were calculated. Pneumoperitoneum was created with CO_2 laparoscopic surgery was performed, maintaining a 12 mmHg intra-abdominal pressure. ***Post-operative settings:*** At the end of the procedure, the carbon dioxide was carefully evacuated from the abdomen. After completion of surgery, reversal of muscle relaxation was achieved with atropine and neostigmine. The NG tube was removed before the patient was transferred to the ward. The trachea was extubated after thorough oropharyngeal suction. The patients were observed in the Post Anesthesia Care Unit (PACU) untile they fullfilled the criteria of discharge to the ward. In the ward patients were observed for 24 hr post-operatively. Diclofenac sodium 75 mg i.m. was given for the prevention of postoperative pain. If patients complained of pain and requested analgesia, 75 mg of diclofenac sodium i.m was given (maximum total 3 times in 24hr). The occurrence of nausea and vomiting recorded during three assessment periods, 0–6 hr, 6–12 hr, and 12–24 hr, by nursing staff without knowledge of which antiemetic the patients had received. Both nausea and vomiting were assessed at this timing. Nausea was rated using a visual analogue scale score system (no nausea, 0; severe nausea, 10), and the number of vomiting episodes was also recorded. The rescue antiemetic was 10 mg metoclopramide i.v. ***Costs of the study drugs:*** The costs of the study drugs (ondansetron and dexamethasone) and metoclopramide were calculated. **Statistical analysis:** Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. ***The following tests were done:*** Independent-samples t-test of significance was used when comparing between two means, Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters, The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: Probability (P-value): P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant, P-value >0.05 was considered insignificant.

RESULTS

Table (1) shows no statistically significant difference between groups according to demographic data.

Table (1): Comparison between groups according to demographic data.

Demographic Data	Group I: OND (N=40)	Group II: DEXA (N=40)	t/x2#	p-value
Age (years)				
Mean±SD	41.05±10.41	39.73±9.75	0.345	0.559
Range	21-60	22-60		
Sex				
Female	25 (62.5%)	28 (70.0%)	0.503#	0.478
Male	15 (37.5%)	12 (30.0%)		
Weight (kg)				
Mean±SD	79.93±9.58	78.18±11.46	0.549	0.461
Range	60-100	58-100		
Height (m)				
Mean±SD	1.72±0.05	1.71±0.05	0.862	0.356
Range	1.62-1.8	1.59-1.81		
BMI [wt/(ht)^2]				
Mean±SD	27.17±3.38	26.83±3.72	0.183	0.670
Range	21.5-33.8	20.8-34.6		
ASA				
ASA I	33 (82.5%)	32 (80.0%)	0.082#	0.775
ASA II	7 (17.5%)	8 (20.0%)		

Data were expressed as mean±SD

This bar chart shows no statistically significant difference between groups according to type of surgery.

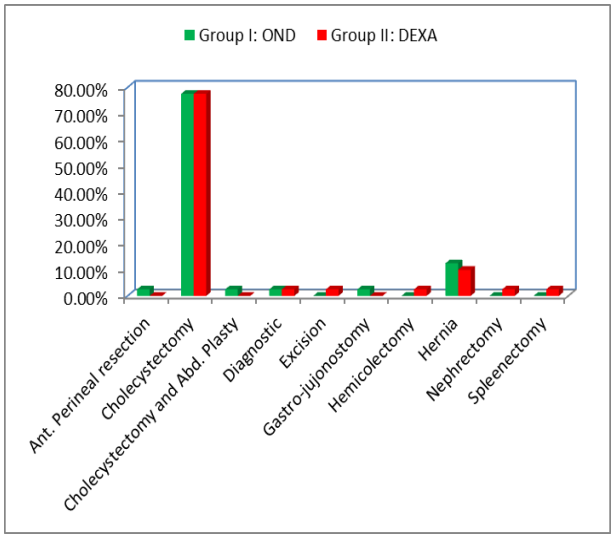

Figure (1): Bar chart between groups according to type of surgery.

This bar chart shows no statistically significant difference between groups according to duration of anesthesia.

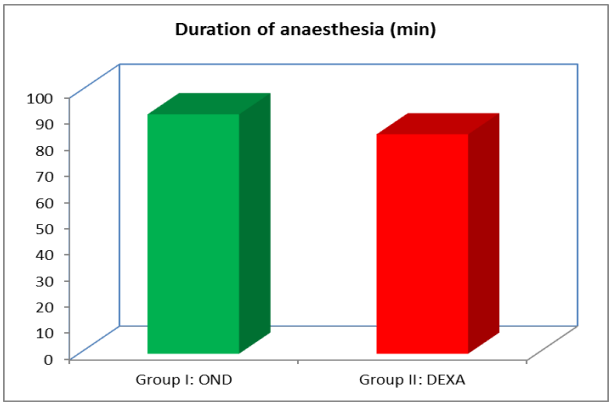

Figure (2): Bar chart between groups according to duration of anaesthesia.

This bar chart shows no statistically significant difference between groups according to duration of operation.

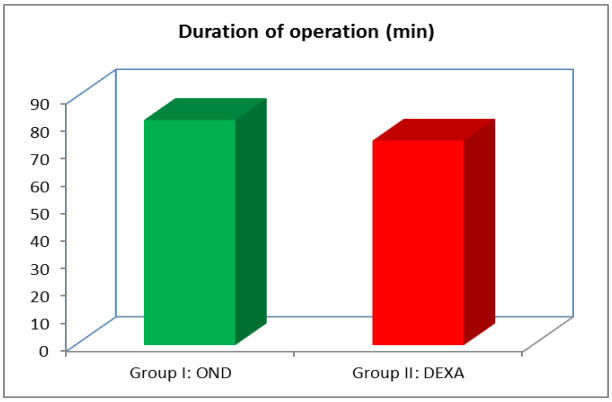

Figure (3): Bar chart between groups according to duration of operation.

Table (2) shows statistically significant difference between groups regarding PO nausea 0-6hrs while 6-24hrs non-significant.

Table (2): Comparison between groups according to PO Nausea.

Nausea	Group I: OND (N=40)	Group II: DEXA (N=40)	x2	p-value
0-6 hr				
No	29 (72.5%)	37 (92.5%)	5.541	0.019*
Yes	11 (27.5%)	3 (7.5%)		
6-12 hr				
No	40 (100.0%)	38 (95.0%)	2.051	0.152
Yes	0 (0.0%)	2 (5.0%)		
12-24hr				
No	40 (100.0%)	40 (100.0%)	0.000	1.000
Yes	0 (0.0%)	0 (0.0%)		

Data are showed as percentage. * Astrexia means significant

Table (3) shows no statistically significant difference between groups regarding PO Vomiting.

Table (3): Comparison between groups according to PO Vomiting.

Vomiting	Group I: OND (N=40)	Group II: DEXA (N=40)	x2	p-value
0-6hr				
No	37 (92.5%)	36 (90.0%)	0.157	0.692
Yes	3 (7.5%)	4 (10.0%)		
6-12hr				
No	38 (95.0%)	36 (90.0%)	0.721	0.396
Yes	2 (5.0%)	4 (10.0%)		
12-24hr				
No	40 (100.0%)	40 (100.0%)	0.000	1.000
Yes	0 (0.0%)	0 (0.0%)		

Data shown as percentage

Table (4) shows no statistically significant difference between regarding the use of antiemetics.

Table (4): Use of antiemetics.

Use of Antiemetics	Group I: OND (N=40)	Group II: DEXA (N=40)	x2	p-value
No	27 (67.5%)	29 (72.5%)	0.238	0.626
Yes	13 (32.5%)	11 (27.5%)		

Data are showed as percentage.

Our study showed that there was a highly statistically significant difference between groups according to cost EGP (Table 5).

Table (5): The cost (EGP).

Cost (EGP)	Group I: OND (N=40)	Group II: DEXA (N=40)	t-test	p-value
Mean±SD	28.16±1.02	5.53±0.90	887.664	<0.001**
Range	27.5-31	5-8.5		

Data expressed as mean±SD. * Astrexia means significant.

DISCUSSION

The origin of postoperative nausea and vomiting after laparoscopic cholecystectomy performed under general anesthesia is not entirely clear, but it is probably multifactorial. The necessity of gas insufflation, which results in the stretching of peritoneum and increased blood pressure in the peritoneal cavity, is a very important factor provoking nausea and vomiting. Prolonged carbon dioxide insufflation, residual pneumoperitoneum after CO_2 insufflation, peritoneum distension, diaphragm irritation, and visceral organ irritation and manipulation have been considered to influence the incidence of PONV [(7)]. Use of nitrous oxide, the utilization of slightly hypoxic mixtures during anesthesia, and postoperative opioid administration have been suggested as other potential risk factors . The effectiveness of various antiemetics has been studied for the prevention and treatment of PONV in patients scheduled for laparoscopic surgeries [(8)]. Glucocorticoids are well known for their analgesic, antiinflammatory, immune-modulating, and antiemetic effects. The mechanism by which glucocorticoids alleviate nausea and vomiting is not fully understood, but the effects are probably centrally mediated via inhibition of prostaglandin synthesis or inhibition of the release of endogenous opioids [(9,10)]. Dexamethasone may act through serotonin inhibition in the gut. It may also reduce tissue inflammation around the surgical sites and thus reduce the ascending parasympathetic impulses (e.g., vagus) to the vomiting center and reduce PONV. Dexamethasone was first reported to be effective in patients receiving cancer chemotherapy in 1981. Since then, several studies have shown that glucocorticoids are equal to or better than other drugs such as metoclopramide, ondansetron, or droperidol in preventing nausea and vomiting associated with chemotherapy [(11)]. Dexamethasone has been shown to be effective in reducing nausea and vomiting after open and laparoscopic surgical procedures. Several randomized controlled trials have shown that dexamethasone alone or in combination with other drugs (granisetron, ondansetron, tropisetron, dolasetron) is effective in reducing postoperative nausea and vomiting and antiemetic requirement after laparoscopic surgeries [(8,12)]. In the present study we have assessed whether dexamethasone is a cost-effective alternative to ondansetron in the prevention of PONV in patients undergoing laparoscopic surgery and we have observed that Dexamethasone 8 mg was as effective as ondansetron 4 mg. Dexamethasone provided a simple, safe, cheap, and effective postoperative nausea and emesis prevention method. These results were consistent with that reached by Wang et al. [(13)] who evaluated the antiemetic effect of dexamethasone 8 mg i.v. in comparison with saline

in the prevention of nausea and vomiting after laparoscopic cholecystectomy. They found that a decreased incidence of nausea and vomiting (23%) in the dexamethasone group and 63% in the saline group and concluded that dexamethasone 8 mg i.v. significantly decreased the incidence of nausea and vomiting after laparoscopic cholecystectomy. In another study, **Feo *et al.*** [11] also, studied the antiemetic effect of dexamethasone 8 mg i.v. compared with saline in the prevention of nausea and vomiting after laparoscopic cholecystectomy. They also observed a decreased incidence of PONV in the dexamethasone group (33%) when compared to saline group (53%). Without side-effects, and recommended its routine use. Moreover, **Nesek *et al.*** [8] found that incidence of PONV was the least on combining dexamethasone and metoclopramide (13%) this incidence increased to 23% when dexamethasone used alone and to 45% when metoclopramide was used, so they concluded that dexamethasone and the combination of dexamethasone plus metoclopramide were more effective in preventing PONV than metoclopramide and placebo. **Bisgaard *et al.*** [10] concluded that preoperative dexamethasone (8 mg) improved surgical outcome after laparoscopic cholecystectomy in terms of significantly less pain, fatigue, nausea, and vomiting, and patients resumed their recreational activity significantly faster than the placebo group. Because the regimen used was safe and without apparent side effects, the authors suggested that dexamethasone should be used as routine in otherwise healthy patients undergoing elective laparoscopic cholecystectomy. We also observed no impaired wound healing, postoperative infection, or other complications associated with the use of dexamethasone in our study. These results are similar to other trials studying dexamethasone as a prophylactic antiemetic for patients undergoing laparoscopic cholecystectomy [10,14]. Ondansetron is the most commonly used prophylactic serotonin subtype 3 antagonists in our daily clinical practice for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. However, cost is a growing concern in today's health care system. Prophylactic antiemetic with dexamethasone is relatively inexpensive [15]. In previous studies dexamethasone was usually combined with the serotonin subtype 3 antagonists, and it was shown that adding dexamethasone to ondansetron improved antiemetic efficacy in PONV [7,12]. In the current study we observed that ondansetrone was as effective as dexamethasone in prevention of postoperative vomiting (POV) in decreasing the incidence of POV , however dexamethasone showed increased incidence of postoperative nausea (PON) in 1st 6 hr. these results were consistant with that reached by ***Feo et al.*** [11], ***Nesek et al*** [8] and **Wang *et al.*** [13] although non of these studies showed that there was no difference regarding POV this may be attributed to the type of the drug we used (different manufacture or different patch number). In our study we compared dexamethasone with ondansetron and found that dexamethasone 8 mg was as effective as ondansetron 4 mg. The dose of dexamethasone used, 8 mg, was based on previous reports shown to decrease PONV when used as an antiemetic regimen. The doses of ondansetron 4 mg was also in accordance with the previous studies in which it was used as antiemetics for PONV [7,8,12]. In this study, we observed that dexamethasone was significantly cheaper than ondansetron and didn't compare with previous studies. One limitation of our study was that sample size was small, including only 80 patients. A retrospective power analysis revealed that a group size of approximately 58 patients (we used 40 if so we should have 58 or 60 patients) in each group would have been required to identify a statistically significant difference of nausea between the ondansetron and dexamethasone groups, with 80% power and p = 0.05 . Therefore further larger studies comparing dexamethasone alone with any of the other more expensive drugs are needed to support our findings. There is a possibility that combined antiemetics with different sites of activity would be more effective than one drug alone for prophylaxis against PONV. Therefore, combination antiemetic therapy can be reserved for patients with the highest PONV risk. These important PONV risk factors include obesity, earlier PONV episodes, motion sickness, and illnesses of the upper alimentary track, especially gastric and duodenal ulcers, esophagitis, or hiatal hernia. Also, women are more susceptible to PONV, especially menstruating women, because of a higher level of sex hormones (e.g., gonadotropin, and mainly progesterone) than in men [7].

CONCLUSION

Prophylactic dexamethasone 8 mg i.v. significantly reduced the incidence of PON but we showed that PON insignificant different in patients undergoing laparoscopic cholecystectomy. Dexamethasone was as effective as ondansetron 4 mg. However, Dexamethasone has the advantage of providing a simple, safe, cheap, and effective postoperative nausea and emesis prevention method which carries an important economic impact. It is difficult to establish which drug can be considered the gold standard in PONV prevention after laparoscopic cholecystectomy. Because many research centers have reported that the effects of different antiemetic drugs are similar, it is wise to administer the cheapest and safest drugs.

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