Ephedrine-Dexamethasone Combination Reduces Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Cholecystectomy

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Citation

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Abstract

Objective: Postoperative nausea and vomiting (PONV) are important causes of morbidity after anesthesia and surgery. The present study was designed to evaluate the effect of prophylactic combination of dexamethasone and ephedrine for prevention of PONV in patients undergoing laparoscopic cholecystectomy.
Methods: ninety adult patients of ASA physical status I undergoing elective laparoscopic cholecystectomy were enrolled in this study. Patients were randomly allocated into one of three groups (30 patients each), to receive either saline or dexamethasone or both dexamethasone and ephedrine.
Results: The incidence of PONV in combination group was only 23% in comparison to placebo 77% and dexamethasone groups 40%.
Conclusion: combination group had significantly less nausea and vomiting and significantly greater number of patients with a complete response.

INTRODUCTION

The etiology of postoperative nausea and vomiting (PONV) is multifactorial. Patient, anesthesia, and surgery related risk factors have been identified. Patient-related factors include pediatric age group, female gender, obesity, non smoking, preoperative anxiety, and a history of severe motion sickness. The type of surgery is an important variable; PONV occurs frequently in laparoscopic surgery (50 to 90%), and in strabismus surgery (60 to 90%). Prolonged duration of surgery and anesthesia also leads to more frequent PONV. Postoperative factors that may increase the incidence of PONV include: pain, dizziness, ambulation, early oral intake, and aggressive use of postoperative opiate analgesics ([1]). The overall incidence of PONV is currently estimated to be around 20 to 30%. In certain high-risk patients, this incidence is still as high as 70%. PONV can cause prolonged postanesthesia care unit (PACU) stay and unanticipated admissions following ambulatory surgery, therefore increasing medical costs ([2]). Effective antiemetic agents include: transdermal scopolamine, prochlorperazine, promethazine, droperidol, ondansetron, dolasetron, granisetron, dexamethasone and ephedrine ([3]). Identification of patients at high-risk of PONV allows targeting prophylaxis to those who will benefit most from it. For patients at moderate risk for PONV, prophylaxis using a single antiemetic or a combination of two agents should be considered. Double and triple antiemetic combinations should be considered for patients at high risk for PONV ([3,4]). Although reported in the aerospace literature and anecdotally by anesthesiologists, the putative antiemetic effect of ephedrine remains unquantitated. Ephedrine is effective in treating emesis secondary to hypotension induced by spinal anesthesia. It was shown to have similar antiemetic efficacy as droperidol and propofol in 2 separate studies when given to prevent PONV ([5]). Ephedrine is cheap, and for this indication poorly documented.

This randomized, double-blind placebo-controlled study was designed to evaluate the effect of prophylactic combination of dexamethasone and ephedrine for prevention of PONV in patients undergoing laparoscopic cholecystectomy.

PATIENTS AND METHODS

Following institutional ethics board approval and informed written consent, 90 non smoker adult patients ASA physical status I undergoing elective laparoscopic cholecystectomy with general anesthesia in Riyadh armed forces hospital

were enrolled in the study. Patients with a history of gastro-esophageal reflux or taking medications with known antiemetic activity were excluded.

All patients fasted for at least 6 h before surgery and were premedicated with midazolam 150 μg kg^{-1} orally one hour preoperative. Anesthesia was induced with thiopentone sodium 4 mg kg^{-1} and fentanyl 1 μg kg^{-1} and muscle relaxation with cisatracurium 0.15 mg kg^{-1} to facilitate tracheal intubation and the patient's lungs were ventilated mechanically to an end-tidal CO_2 of 30-35 mmHg. Anesthesia was maintained with 35% oxygen in nitrous oxide with added 0.6-1% isoflurane. All patients were monitored by continuous electrocardiogram (ECG), non invasive blood pressure (NIBP), pulse oximetry (SPO_2), capnography ($ETCO_2$). Carbo-peritoneum was established according to standard laparoscopic techniques.

Patients were randomized into three groups, each of 30 patients to receive either saline IV (group S), dexamethazone 5 mg IV(group D) or combination of dexamethasone 5 mg IV and ephedrine 0.5 mg kg^{-1} IM (group DE) . These drugs were prepared and given ten minutes before the end of the procedure by a single anesthetist who took no part in data collection. At the end of surgery, muscle relaxation was reversed with neostigmine 40 μg kg^{-1} and atropine 15 μg kg^{-1} , and patients received diclofenac 100 mg IM for postoperative analgesia.

In the recovery room, basic monitoring included (ECG), (NIPB), and (SPO_2). The incidence of PONV was evaluated at 3 time periods: 0–2 (in the recovery area), 2–6, and 6–24 h. Vomiting which occurred more than four times within 24 hr was considered as severe vomiting. Rescue antiemetic (4 mg ondansetron IV) was given as necessary for severe nausea or vomiting by trained nurse without knowledge of which drugs the patients had received. Emesis score < 2 and no antiemetic medication during the 24-hr postoperative period was defined as successful prevention. Postoperative pain at the surgical wound was assessed with a 10-cm visual analog scale (VAS; 0= no pain to 10= most severe pain) score and ketorolac 30 mg IM was given as required. . Suspected side effects associated with the use of dexamethasone and ephedrine were also studied. Blood glucose levels were recorded preoperatively and 4 hours postoperatively.

Patients were discharged from the day-case unit when they were able to take oral fluids and walk independently.

Patients were asked to report any complications that may occur after discharge from recovery room for the 24 hours.

All obtained data were organized, tabulated and statistically analyzed using SPSS software statistical computer package version 10. The difference between 2 means measured at different timing was statistically analyzed using the student's paired (t) test. Fisher's test was employed to compare the categorical data.

RESULTS

Patient characteristics such as age, weight, duration of anesthesia and surgery, recovery time, and intraoperative fluid requirement were comparable in the 3 groups (Table 1).

Figure 1

Table 1: Study group characteristics

Group	S	D	DE	P*
Age (years)	30 ± 5.3	29 ± 7.4	29 ± 6.1	n.s
Weight (Kg)	73 ± 14	76 ± 10	75 ± 12	n.s
Duration of anesthesia (min)	105 ± 20	115 ± 15	100 ± 20	n.s
Stay in PACU (min)	120	120	120	n.s

Values are mean ± SD or numbers.
(*) Statistically significant at p<0.05

Compared with the placebo group (group S), group D had a significantly lower incidence of vomiting (P=0.02). Compared with group D, the combination group (group DE) had significantly less vomiting (P=0.01) and need for rescue antiemetic (P=0.03) before discharge, tended to vomit less after discharge (P=0.08) and had a significantly greater number of patients with a complete response (P=0.03). The incidence of vomiting in the combination group was less than 7% overall compared to 14% in group D and 23% in group S (Table 2).

Compared with the group D, the combination group tended to have a lower incidence of moderate or severe nausea before discharge (P=0.06), and a significantly lower incidence and severity of nausea after discharge. No patients in the combination group required overnight admission for the management of PONV.

All patients reported low VAS pain scores and the differences among groups were not significant. In addition, the proportions of patients requiring rescue analgesic among groups were not significantly different. (Table 2).

Figure 2

Table 2: Perioperative data of patients in the three groups.

Group	S	D	DE	P^
Nausea/Vomiting:				
- Nausea	9	5	3	n.s
- Vomiting	7	4	2	<0.05*
- Retching	7	3	2	<0.05*
Total	23 (77%)	12 (40%)	7 (23%)	<0.05*
Rescue antiemetic:	14 (47%)	7 (23%)	3 (10%)	<0.05*
Successful prevention:	16 (43%)	23 (77%)	27 (90%)	<0.05*
Visual Analog Score:				
- On arrival to PACU	2.5 ± 1.2	2.3 ± 1.1	2.4 ± 0.9	
- 6 hours later	2.1 ± 1.1	1.9 ± 1.3	2.1 ± 1.1	n.s
- 12 hours later	2.2 ± 1.2	2.1 ± 1.5	2.2 ± 1.5	
- 24 hours later	1.9 ± 1.4	1.9 ± 1.1	2.1 ± 1.2	
Patients requiring rescue analgesics:	7/30	6/30	7/30	n.s

Values are mean ± SD or numbers.
(*) Statistically significant at p<0.05

There were no statistically significant differences as regard the postoperative vital signs (Figure 1,2). No patients experienced wound infection or delayed wound healing at follow-up after 1 week. Preoperative blood glucose was comparable in all groups (Figure 3). There was no significant increase in blood glucose levels recorded at the end of 4 h after baseline levels in any of the groups and there were no significant differences among the 3 groups. No side effects accompanying dexamethasone usage were observed.

Figure 3

Figure 1: Postoperative Change in Blood Pressure

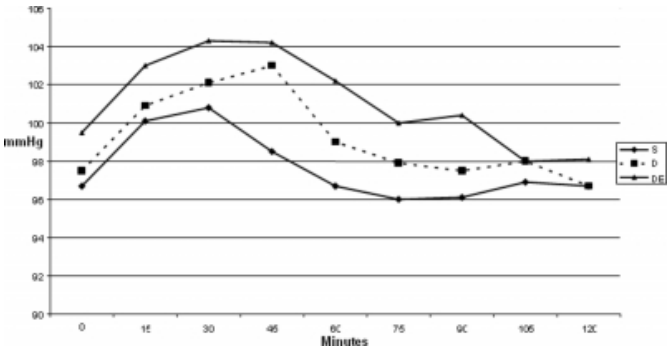


Figure 4

Figure 2: : Postoperative Change in Heart Rate

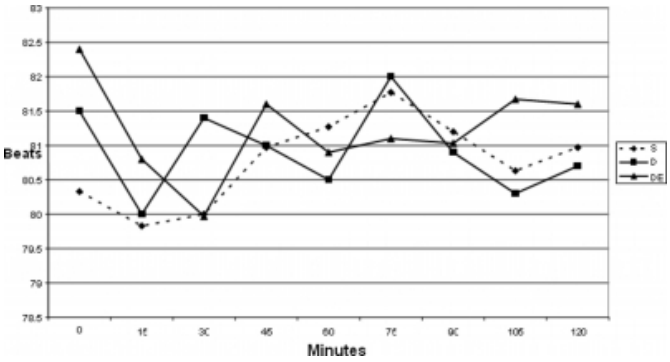
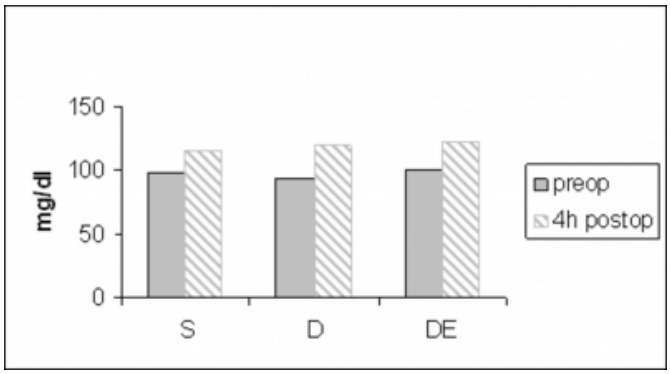


Figure 5

Figure 3: Blood glucose level



DISCUSSION

Nausea and vomiting are among the most unpleasant experiences associated with surgery and one of the most common reasons for poor patient satisfaction rating in the postoperative period ($_6$). The incidence of PONV in the present study in ephedrine-dexamethasone combination group was only 23% with significantly better antiemetic effect than placebo and dexamethasone alone, which might be due to the combination of antiemetic effect of both drugs. Combination prophylaxis may also have important economic implications. These include reduced costs of antiemetic medications and costs associated with nursing time spent managing PONV as well as the costs of delayed discharge or unplanned admission.

Hagemann et al explained that ephedrine is a sympathomimetic amine, it has ? and ß- effects and acts both directly and indirectly with a considerable stimulation of the cerebral cortex and medulla. As a reduction in medullary blood flow to the chemoreceptor trigger zone may provoke and initiate nausea and vomiting, therefore ephedrine through an increase in mean arterial blood pressure and

presumably improve medullary blood flow minimizes the risk of PONV ([7]).

Ephedrine was found to have a significant antiemetic effect when compared with placebo and an antiemetic effect similar to that of droperidol and variations in mean arterial blood pressure among the groups were not statistically significant in patients undergoing outpatient laparoscopy ([8,9]) . Ephedrine 0.5 mg/kg I.M. administered at the end of abdominal hysterectomy has a significant antiemetic effect during the first 3 hours after administration with no evident side-effects ([7]).

Henzi et al stated that glucocorticoids have been shown to have various effects on the central nervous system; they regulate transmitter levels, receptor densities, signal transduction, and neuronal configuration. In the nucleus of the solitary tract, the nucleus of raphe, and the area postrema, numerous glucocoriticoid receptors are found. These nuclei are well known to have considerable neuronal activities on the regulation of nausea and vomiting responses. Other theories include: prostaglandin antagonism, release of endorphins resulting in mood elevation, a sense of well-being, reduced levels of serotonin in neural tissue, and prevention of release of serotonin in the gut. Following the successful use of dexamethasone in the prevention and treatment of chemotherapy induced emesis, this agent has been evaluated and found to be effective for the management of PONV ([10,11]).

Coloma et al and Rüsch et al reported that ondansetron plus dexamethasone prevents PONV more effectively than ondansetron alone in patients at high risk for PONV ([12,13]). Also in agreement with these results Eberhart et al who proved that antiemetic effects of dexamethasone for preventing PONV are comparable to those of traditional antiemetics (specifically, 5-HT_3- and D_2-receptor antagonists) ([14]). Bisgaard et al noted that dexamethasone may offer additional benefits over traditional antiemetics in improving surgical outcomes, compared with placebo, dexamethasone phosphate 8 mg I.V. given 90 minutes before laparoscopic cholecystectomy has been demonstrated to significantly reduce postoperative fatigue, pain, total opioid requirements, and levels of C-reactive protein, in addition to reducing the frequency of PONV ([15]). While Heffernan and Rowbotham said that dexamethasone has now emerged as potentially useful prophylaxis for PONV; its efficacy is comparable with other antiemetics but it may be more effective in the prevention of late PONV ([16]).

Multiple-dose corticosteroid therapy (>1 week) may cause side effects, such as increased risk of infection, glucose intolerance, delayed wound healing, superficial ulceration of gastric mucosa, avascular necrosis of femoral head, and adrenal suppression. However, these side effects are not found after a single dose of dexamethasone therapy ([17]). In the current study, a single dose of 2.5 to 10 mg dexamethasone did not cause wound infection or delay wound healing. In addition, no other side effects were found after the usage of a single dose of dexamethasone ([18]).

In conclusion, ephedrine-dexamethasone combination proved to be effective for the prevention of postoperative nausea and vomiting in female patients undergoing gynecological laparoscopy. It is recommended that further evaluation of this combination with alternative antiemetic combinations need to be performed for different patient groups.

References

1. Morgan D. Management of Postoperative Nausea and Vomiting: The Role of Droperidol, Metoclopramide, and Ondansetron. P&T News: 1994; 14 (7): 245-51.
2. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk scores for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999; 91: 693-700.
3. Habib AS, and Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. Can J Anesth 2004; 51:326-341.
4. Scuderi PE, James RL, Harris L, Mims GR III. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. Anesth Analg 2000;91:1408-14.
5. KY Ho, JW Chiu. Multimodal antiemetic therapy and emetic risk profiling. Ann Acad Med Singapore 2005; 34: 196- 205.
6. Klockgesthes R., Piorck V., Crozier TC., Kettler D. Nausea and vomiting after laparoscopic surgery: a comparison of propofol and thiopentone/halothane anesthesia. Eur J anaesthiol 1996; 13:3-9.
7. Hagemann E, Halvorsen A, Holgersen O, Tveit T, Raeder JC. Intramuscular ephedrine reduces emesis during the first three hours after abdominal hysterectomy. Acta Anaesthesiol Scand. 2000;44(1):107-11.
8. DM Rothenberg, SM Parnass, K Litwack, RJ McCarthy and LM Newman. Efficacy of ephedrine in the prevention of postoperative nausea and vomiting. Anesth Analg 1991; 72, 58-61.
9. Naguib K, Osman HA, Al-Khayat HC, Zikri AM. Prevention of post-operative nausea and vomiting following laparoscopic surgery ephedrine vs propofol. Middle East J Anesthesiol 1998;14(4):219-30.
10. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000; 90: 186-94.
11. Bolton CM, Myles PS, Nolan T, Sterne JA. Prophylaxis of postoperative vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis. Br J

Anaesth 2006; 97(5): 593-604.
12. Coloma M, White PF, Ogunnaike BO, Markowitz SD, Brown PM, Lee AQ, Berrisford SB, Wakefield CA, Issioui T, Jones SB, and Jones D: Comparison of Acustimulation and Ondansetron for the treatment of established PONV. Anesthesiology 2002; 97:1387-92.
13. Rüsch D, Eberhart L, Biedler A, Dethling J, and Apfel CC. Prospective application of a simplified risk score to prevent postoperative nausea and vomiting. Can J Anesth 2005; 52:478-84.
14. Eberhart LH, Morin AM, Georgieff M. Dexamethasone for prophylaxis of postoperative nausea and vomiting. A meta-analysis of randomized controlled studies. Anaesthesia 2000; 49:713-20.
15. Bisgaard T, Klarskov B, Kehlet H. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy. Ann Surg. 2003; 238:651-60
16. Heffernan AM , Rowbotham DJ. Postoperative nausea and vomiting-time for balanced antiemesis? Br J Anaesth, 2000, 85,(5): 675-77.
17. Madan R, Bhatia A, Chakithandy S, Subramaniam R, Rammohan G, Deshpande S, Singh M, and Kaul HL . Prophylactic Dexamethasone for Postoperative Nausea and Vomiting in Pediatric Strabismus Surgery: A Dose Ranging and Safety Evaluation Study. Anesth Analg 2005;100:1622-26.
18. Wang JJ, Ho ST , Wong CH , Tzeng JI, Liu HS, and Ger LP. Dexamethasone prophylaxis of nausea and vomiting after epidural morphine for post-Cesarean analgesia. Can J Anesth 2001; 48:185-90.

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