Dexamethasone Effectively Reduces Postoperative Nausea and Vomiting in A General Surgical Adult Patient Population

Ming-Shan Chen, MD; Chian-Lang Hong, MD; Ham-See Chung, MD; Peter PC Tan[1], MD; Chih-Chung Tsai, MD; Han-Hsiang Su, MD; Chung-Hang Wong[2], MD

Background: Postoperative nausea and vomiting (PONV) is still a common and major complication for surgical patients, which may delay post-anesthetic care unit discharge, prolong hospital stay and thus increase the cost of hospitalization. It is understood that PONV is a multi-factorial outcome and occurs more often with general anesthesia than with other anesthetic methods. Prophylactic administration of antihistamines, antidopaminergics, anticholinergics, phenothiazines, serotonin antagonist, steroids and even acupuncture has been shown to be effective. However, expenses and side effects of these agents have also been a concern for clinical doctors. The aim for this prospective study was to find an agent that is cost effective and side effect free (or at least with a low incidence of side effects) for the prevention of PONV.

Methods: A total of 700 adult surgical patients who planned to have surgery under general anesthesia were enrolled in this double-blinded, randomized and placebo-controlled study. Group P received the placebo (0.9% normal saline 2 ml) and Group D received 10 mg dexamethasone intravenously right before the induction of anesthesia.

Results: We found that during the postoperative period of 1-8 h, patients in Group D reported a lower incidence of PONV (24%) than those in Group P (39%, $p < 0.001$). Patients in Group D also requested less rescue anti-emetic (17%) than those in Group P (30%, $p < 0.05$). The same phenomenon was also noted in the 8-to-24-hour interval (PONV 4% vs. 12%, $p < 0.05$ and rescue anti-emetic 3% vs. 9%, $p < 0.05$ in Group D vs. Group P, respectively.)

Conclusions: We conclude that the prophylactic intravenous administration of 10 mg dexamethasone immediately before the induction of anesthesia is effective in preventing PONV in the general surgical adult patient population.

(Chang Gung Med J 2006;29:175-81)

Key words: Dexamethasone, general anesthesia, postoperative nausea and vomiting.

Although better anesthetic technique, short-acting anesthetic agents and better anti-emetic drugs have been used to reduce the incidence of postoperative nausea and vomiting (PONV), PONV is still a

From the Departments of Anesthesiology, Chang Gung Memorial Hospital, Chia-Yi; Departments of Anesthesiology, [1]Chung Shan Hospital, Taipei; [2]Department of Anesthesiology, Chang Gung Memorial Hospital, Chia-Yi and Chia-Yi School, Chang Gung Institute of Technology.

Received: Sep. 2, 2005; Accepted: Jan. 5, 2006

Correspondence to: Dr. Chung-Hang Wong, Department of Anesthesiology, Chang Gung Memorial Hospital. 6, Section West, Chia-Pu Rd., Puzih City, Chiayi, Taiwan 613, R.O.C. Tel.: 886-5-3621000 ext. 2525; Fax: 886-5-3707858; E-mail: wong@adm.cgmh.org.tw

common and major complication for surgical patients. Although PONV is not fatal, it is an unpleasant, distressing and common problem that may decrease patient satisfaction, delay post-anesthetic care unit discharge, prolong hospital stay and thus increase the total cost of patient care and hospitalization. It is understood that PONV is a multi-factorial outcome comprised of patient, surgical, and anesthetic factors. Published evidence suggests that patients who are non-smoking, female, young, or obese, and those with history of motion sickness or PONV; surgical procedures that are prolonged, use intra-operative and/or postoperative narcotics, involve the oro-pharynx, auditory system, eyes, or intra-abdominal surgery; as well as the type of pre-anesthetic medication and gastric distention during the course of anesthesia all contribute to PONV. General anesthesia, in comparison to other anesthetic methods, carries a higher incidence of PONV.[1-5]

Prophylactic administration of antidopaminergics (e.g., droperidol, metoclopramide), antihistamines (e.g., promethazine, dimenhydrinate), anticholinergics (e.g., scopolamine), phenothiazines (e.g., promethazine, prochlorperazine), serotonin antagonist (especially 5-HT_3 antagonist, e.g., ondansetron, dolasetron, granisetron) and steroids (e.g., dexamethasone, betamethasone) has been shown to be effective for the prevention of PONV. Simple acupuncture procedures also have the same effects.[6] Because 5-HT_3 antagonists are expensive, universal use for the prevention of PONV is not cost effective. On the other hand, the side effects of the less expensive medication, including sedation, dysphoria, and extra-pyramidal tract syndrome, lead to only conservative applications of the medication. The aim of the study was to find an agent that is cost-effective, free of side effects, or at least with a low incidence of side effects for this troublesome postoperative complication.

Dexamethasone has been shown to have anti-emetic effects by many means, not limited to PONV but also for nausea and vomiting induced by chemotherapy for the treatment of cancer. Most of the trials for PONV were limited to selected cases and/or specific patient populations.[7-11] We designed this study to evaluate the anti-emetic effect of 10 mg dexamethasone in the prevention of PONV in the general surgical adult patient population.

METHODS

The study was conducted with the appropriate institutional approval, and written informed consent was obtained from each patient. A total of 700 ASA physical status I-II surgical patients, about to undergo surgery under general anesthesia, were enrolled in this randomized, double-blinded, placebo-controlled study. The randomization was achieved using the envelope method (700 envelopes, 350 stated as control group and 350 stated as study group were polled together. The researcher picked one of these envelopes after the patient agreed to enroll into the study). Patients who had suffered from significant medical diseases; had received anti-emetics within 24 hours before surgery; had history of immuno-suppression, significant esophageal-gastric reflux, Cushing's syndrome, or liver/renal diseases; and those who presented difficult intubation during induction of anesthesia were excluded from our study. Patients were assigned randomly into two groups: Group P received 2 ml 0.9% normal saline intravenously as a placebo 1 minute before the induction of anesthesia, and Group D received 10 mg dexamethasone (Veterans Pharmaceutical Plant, Taiwan. 5 mg/ml/amp) intravenously 1 minute before the induction of anesthesia.

We used 3 μg/kg Fentanyl, 30 mg 2% xylocaine and 2 mg/kg propofol for the induction of anesthesia. Tracheal intubation was facilitated with 0.8 mg/kg rocuronium. Anesthesia was maintained with 2% to 5% sevoflurane (inspired concentration) in oxygen to keep stable vital signs. Supplemental analgesia was provided with 50 to 100 μg boluses of fentanyl if signs of inadequate anesthesia were noted. Additional muscle relaxants were administered as required. At the cessation of the surgery, antagonists to residual neuromuscular blocks were given only to those in need. All of the patients were extubated before they were sent to the post-anesthetic care unit (PACU).

All patients were closely observed for at least 1 hour in the PACU. During their stay in the PACU, vital signs, such as blood pressure, heart rate, and respiratory rate, were monitored every 5 minutes and oxygen saturation was monitored continuously. Patients were transferred to the postoperative ward for further observation if their conditions were stable. We prescribed 50 mg intramuscular meperidine

for post-operative pain control, which was given every 4 hours as requested.

The incidence of PONV and the intensity of postoperative pain were recorded on arrival in the PACU and, subsequently, during the 1-to-8-hour, 8-to-24-hour, and longer than 24-hour intervals (only in those who had PONV in the 8-to-24-hour interval) in the ward. Nausea was defined as a subjectively unpleasant sensation associated with the awareness of the urge to vomit. Vomiting was the forceful expulsion of gastric contents from the mouth. Nausea and vomiting were evaluated on a three-point ordinal scale (0 = none, 1 = nausea, 2 = vomiting). If patients experienced nausea for 30 minutes or more than one emetic episode within 15 minutes, rescue anti-emetic treatment consisting of 10 mg metoclopramide intramuscularly was given as the patient requested every 8 hours. Pain scores were measured at rest (supine) using a 10 cm visual analog scale (VAS; 0 = no pain, 10 = most severe pain). Duration of the hospital stay and the incidence of side effects (itching, urinary retention, headache, sedation and others if mentioned) were recorded.

Data were reported as mean ± SD. The demographic characteristics of the two groups were statistically compared using chi square analysis, or analysis of variance followed by Student's *t*-test, corrected for multiple comparisons. Because repeated assessments were performed during follow-up period, we used logistic regression models with the Generalized estimating equations (PROC GENMOD in SAS statistical software) to analyze the repeated assessments made at the various follow-up periods. Differences were considered to be statistically significant if $p < 0.05$.

RESULTS

Data obtained from the 700 patients (350 in each group) were analyzed. The incidence of background factors and factors related to operation and anesthesia, which may modify PONV, did not differ between the two groups (Table 1).

During the 24-hour study, arterial pressure, heart rate and respiratory frequency were stable and there were no significant differences between the groups. No patient demonstrated a $SpO_2 < 90\%$.

PONV during the different observation time intervals are presented in Table 2. We used the total

Table 1. Demographic Data

	Group P	Group D
n	350	350
Age (year)	51 ± 15	52 ± 15
Height (cm)	161 ± 8	160 ± 7
Weight (kg)	65.2 ± 7.1	61.7 ± 6.7
Female	227 (65)	211 (60)
Male	123 (35)	139 (40)
History of MS or PONV	115 (33)	128 (37)
Smoker	87 (25)	91 (26)
Duration of anesthesia (min)	170 ± 28	163 ± 31
Perioperative fentanyl (ug)	167 ± 47	177 ± 48
Surgical type		
Otolaryngologic	46 (13)	48 (14)
Orthopedic	92 (26)	98 (28)
Ophthalmologic	11 (3)	13 (4)
Laparoscopy	74 (21)	75 (22)
Laparotomy	71 (20)	64 (19)
Other	56 (16)	52 (15)

Abbreviations: Group P: placebo group; Group D: dexamethasone group. MS: motion sickness; PONV: postoperative nausea or vomiting.
Values are given as mean ± SD or n (%), as appropriate.
There were no significant differences between the groups in any variable.

Table 2. Incidence of Nausea and Vomiting after Surgery

	Group P	Group D	*p* value
In the PACU (0-1 h postoperatively)			
Nausea	14 (4)	19 (5)	
Vomiting	39 (11)	18 (5)	
Total	53 (14)	37 (11)	NS
Rescue antiemetics	41 (12)	24 (7)	NS
In the ward (1-8 h postoperatively)			
Nausea	41 (12)	31 (9)	
Vomiting	96 (27)	54 (15)	
Total	137 (39)	85 (24)	< 0.05
Rescue antiemetics	106 (30)	61 (17)	< 0.05
In the ward (8-24 h postoperatively)			
Nausea	18 (5)	3 (1)	
Vomiting	25 (7)	11 (3)	
Total	43 (12)	14 (4)	< 0.05
Rescue antiemetics	30 (9)	11 (3)	< 0.05
In the ward (> 24 h postoperatively)			
Nausea	1 (1)	2 (1)	
Vomiting	7 (2)	1 (1)	
Total	8 (2)	3 (1)	NS
Rescue antiemetics	3 (1)	0 (0)	NS

Abbreviations: Group P: placebo group; Group D: dexamethasone group.
Values are given as n (%).

incidence of nausea and vomiting to present PONV. The incidence of PONV between the two groups was not significantly different during their stay in the PACU (within 1 hour post-operatively). A lower incidence of PONV (24%) was noted in Group D patients than those in Group P (39%, $p < 0.001$) during the 1-8 hour post-operatively time interval. Patients in Group D also requested less rescue anti-emetic (17%) than those in Group P (30%, $p < 0.05$). The same phenomenon was also noted in the 8-to-24- hour interval (PONV 4% vs. 12%, $p < 0.05$ and rescue anti-emetic 3% vs. 9%, $p < 0.05$ in Group D vs. Group P, respectively). Late incidence of PONV (defined as PONV noted after 24 hours post-operatively) was low in our study group and shown no significant differences between the two groups.

The mean pain scores as well as the requirements for rescue analgesics were similar in the two groups. None of the patients experienced any side effects related to dexamethasone or metoclopramide.

Table 3. Postoperative VAS Pain Scores and Meperidine Consumption

	Group P	Group D
In the ward (at 12 h postoperatively)		
VAS	3.5 ± 0.9	3.7 ± 1.2
Meperidine consumption	21.2 ± 2.9	22.3 ± 2.5
In the ward (24 h after surgery)		
VAS	2.9 ± 1.2	3.1 ± 1.2
Meperidine consumption	12.4 ± 1.7	11.7 ± 1.5

Abbreviations: Group P: placebo group; group D: dexamethasone group. VAS: visual analog score

Values are given as mean ± SD.

There were no significant differences between the groups in any variable.

DISCUSSION

Many articles have been published suggesting the use of dexamethasone as a prophylactic anti-emetic for PONV.[8-13] However, most of those studies only included patients considered to be at "high risk" for developing PONV. Study designs that analyze specific surgical procedures or restricted patient populations have recently been criticized.[14-16] In fact, large prospective investigations have shown that the different incidences of PONV were mainly caused by the associated risk factors and not by the operation itself.[15] Therefore, we used Apfel's simplified risk score instead of selecting patients undergoing just one type of surgery to identify patients with an increased risk.[17]

The results of our study suggest that prophylactic administration of 10 mg intravenous dexamethasone given before induction of anesthesia is effective in decreasing the incidence of PONV, with no delay in PACU discharge. When compared with the placebo, the incidence of PONV during the observation period of 1-8 hour decreased from 39% to 24% and during the observation period of 8-24 hour decreased from 12% to 4% in patients who received dexamethasone before induction. In our study, the types of surgery and the number of risk factors were similar among the groups (Table 3). Since we standardized the anesthesia protocol, we believe that the differences in these two groups with respect to PONV were directly related to the prophylactic administration of dexamethasone. The reasons the differences in PONV were not significant during the PACU may due to the short PACU stay (1 hour) and insignificant data were obtained during this short period.

The minimum effective dose of dexamethasone for the prevention of PONV was suggested to be 2.5 mg for major gynecological surgery,[18] however, an 8 to 10 mg dose of dexamethasone was most frequently used.[19-24] Because of the wide variety of surgical procedures in our study and we wanted to observed the side effect profiles, we chose a 10 mg dose in our study.

The exact mechanism by which dexamethasone exerts an anti-emetic action is still unknown, but it may involve central inhibition of prostaglandin synthesis or a decrease in serotonin turnover in the central nervous system.[25,26] Nevertheless, 10 mg dexamethasone, when given intravenously, is prophylactically effective for PONV when administered before induction of anesthesia. However, whether smaller doses of dexamethasone have the similar effects still need to be evaluated.

The long-term administration of corticosteroids causes side effects such as additional wound infection, glucose intolerance, adrenal suppression, superficial ulceration of gastric mucosa, and delayed healing.[27] However, a single dose of dexamethasone is considered safe.[7,8,10] In this current study, except for a burning and/or itching sensation which was noted in the urinary tract (which may disappear sponta-

neously within minutes) in some of our patients (55%, female:male = 4:1) when receiving dexamethasone, no other obvious side effects accompanying a single dose of 10 mg dexamethasone was found (e.g., dysphoria, urinary retention, headache, sedation, extra-pyramidal tract syndrome, wound infection or delayed wound healing). The cause of this dexamethasone-induced urinary tract burning/itching sensation is still unknown.

According to our data, a 10 mg intravenous dexamethasone, given immediately before the induction of anesthesia, is cost-effective and produces few side effects in the prevention of PONV in the general surgical adult patient population. This may have benefits in patient care and decrease the total medical expenses.

REFERENCES

1. Camu F, Lauwers MH, Verbessem D. Incidence and aetiology of postoperative nausea and vomiting. Eur J Anesthesiol 1992;9 (suppl 6):25-31.
2. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: Assessing risk factors for nausea and vomiting. Anesth Analg 1994;78:7-16.
3. Koivuranta M, Laara E, Snare L, Alahuhta S. A survey of postoperative nausea and vomiting. Anesthesia 1997;52:443-9.
4. Plazzo MG, Strunin L. Anesthesia and emesis: I. Etiology. Can Anaesth Soc J 1984;31:178-87.
5. Watcha MF, White PF. Postoperative nausea and vomiting: Its etiology, treatment and prevention. Anesthesiology 1992;77:162-84.
6. Shyr MH, Hsu JC, Wu YW, Hui YL, Tan PP. P6 acupoint injection reduced postoperative nausea and vomiting. Ma Zui Xue Za Zhi 1990;28:357-60.
7. Lee Y. Lin PC. Lai HY. Huang SJ. Lin YS. Cheng CR. Prevention of PONV with dexamethasone in female patients undergoing desflurane anesthesia for thyroidectomy. Acta Anaesthesiologica Sinica 2001;39:151-6.
8. Fujii Y, Tanaka H, Toyooka H. The effects of dexamethasone on anti-emetics in female patients undergoing gynecologic surgery. Anesth Analg 1997;85:913-7.
9. Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, Ho CM. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth 1999;83:772-5.
10. Wang JJ, Ho ST, Lee SC, Liu YC, Liu YH, Liao YC. The prophylactic effect of dexamethasone on postoperative nausea and vomiting in women undergoing thyroidectomy: a comparison of droperidol with saline. Anesth Analg 1999;89:200-3.
11. Wang JJ, Ho ST, Liu HS, Ho CM. Prophylactic anti-emetic effect of dexamethasone in women undergoing ambulatory laparoscopic surgery. Br J Anaesth 2000;84:459-62.
12. Liu K, Hsu CC, Chia YY. Effect of dexamethasone on postoperative emesis and pain. Br J Anaesth 1998;80:85-6.
13. Henzi I, Walder B, Tramer M. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systemic review. Anesth Analg 2000;90:186-94.
14. Kreisler NS, Spiekermann BF, Ascari CM, Rhyne HA, Kloth RL, Sullivan LM, Durieux ME. Small-dose droperidol effectively reduces nausea in a general surgical adult patient population. Anesth Analg 2000;91:1256-61.
15. Apfel CC, Roewer N, Korttila K. How to study postoperative nausea and vomiting. Acta Anaesthesiol Scand 2002;46:921-8.
16. Lee Y, Lai HY, Lin PC, Lin YS, Huang SJ, Shyr MH. A dose ranging study of dexamethasone for preventing patient-controlled analgesia-related nausea and vomiting: a comparison of droperidol with saline. Anesth Analg 2004;98:1066-71.
17. Apfel CC, Lira E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centres. Anesthesiology 1999;91:693-700.
18. Liu K, Hsu CC, Chia YY. The effective dose of dexamethasone for antiemesis after major gynecological surgery. Anesth Analg 1999;89:1316-8.
19. Pappas ALS, Sukhani R, Hotaling AJ, Mikat-Stevens M, Javorski JJ, Donzelli J, Shenoy K. The effect of preoperative dexamethasone on the immediate and delayed postoperative morbidity in children undergoing adenotonsillectomy. Anesth Analg 1998;87:57-61.
20. Splinter WM, Robert DJ. Dexamethasone decreases vomiting by children after tonsillectomy. Anesth Analg 1996;83:913-6.
21. Splinter WM, Roberts DJ. Prophylaxis for vomiting by children after tonsillectomy: dexamethasone versus perphenazine. Anesth Analg 1997;85:534-7.
22. Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth 1996;76:835-40.
23. Mckenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H. Comparison of ondansetron with ondasetron plus dexamethasone in the prevention of postoperative nausea and vomiting. Anesth Analg 1994;79:961-4.
24. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systemic review. Anesth Analg 2000;90:186-94.
25. Fredrickson M, Hursti T, Furst CJ, Steineck G, Borjeson S, Wikblom M, Peterson C. Nausea in cancer chemotherapy is inversely related to urinary cortisol excretion. Br J Cancer 1992;65:779-80.

26. Aapro MS, Plezia PM, Alberts DS, Graham V, Jones SE, Surwit EA, Moon TE. Double-blind cross-over study of the anti-emetic efficacy of high dose dexamethasone versus high dose metoclopramide. J Clin Oncol 1984;2:466-71.
27. Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gillman AG, eds. Goodman and Gillman's the Pharmacological Basis of Therapeutics, 9th ed. New York: McGraw-Hill, 1996:1459-86.

Dexamethasone 應用於預防術後噁心與嘔吐

陳明山 洪健朗 鍾涵濡 譚培炯[1] 蔡志忠 蘇翰香 黃仲衡[2]

背 景： 對於接受手術的病人來說，術後噁心嘔吐依然是主要而且常見的併發症。這不僅會延長病人停留於恢復室時間與增加住院天數，也會使得醫療費用高漲。目前認爲術後噁心嘔吐的原因是多重因子引發，而且較容易發生於接受全身麻醉的病人。目前有研究指出預防性的給予抗組織胺、抗多巴胺、抗膽鹼、phenothiazines、血清素拮抗劑、類固醇及針灸，均能有效降低術後噁心嘔吐發生的機率。本實驗的目的在於找出經濟而又有效的預防方法。

方 法： 選定 700 位需要手術而接受全身麻醉的病人。分爲對照組與實驗組。對照組於麻醉誘導前靜脈注射生理食鹽水2ml，實驗組則給予 Dexamethasone 10 mg。

結 果： 術後 1-8 小時，實驗組病人噁心嘔吐的機會爲 24% 而對照組爲 39%，使用止吐劑的頻率實驗組爲 17% 而對照組爲 30%，兩組均有顯著差異。相同的情況也發現於術後 8-24 小時。術後 8-24 小時實驗組病人噁心嘔吐的機會爲 4% 而對照組爲 12%，使用止吐劑的頻率實驗組爲3% 而對照組爲 9%，兩組均有顯著差異。

結 論： 在不限定特別手術的病人群中，麻醉誘導前先靜脈給予 Dexamethasone 10 mg，可有效減少病人術後噁心嘔吐之發生率。

(長庚醫誌 2006;29:175-81)

關鍵字：Dexamethasone，全身麻醉，術後噁心嘔吐。

長庚紀念醫院 嘉義院區 麻醉科；[1]中山醫院 麻醉科；[2]長庚紀念醫院 嘉義院區 麻醉科及長庚技術學院 嘉義分部
受文日期：民國94年9月2日；接受刊載：民國95年1月5日
通訊作者：黃仲衡醫師，長庚紀念醫院 麻醉科。嘉義縣613朴子市嘉朴路西段 6 號。Tel.： (05)3621000轉2525; Fax：(05)3707858; E-mail: wong@adm.cgmh.org.tw