Dexamethasone prevents postoperative nausea and vomiting more effectively in women with motion sickness

[La dexaméthasone prévient plus efficacement les nausées et les vomissements postopératoires chez les femmes atteintes du mal des transports]

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Purpose: To evaluate the antiemetic effect of iv dexamethasone for preventing postoperative nausea and vomiting (PONV) in women with and without a history of motion sickness.

Methods: This randomized, double-blinded, placebo-controlled study was carried out in 168 female patients with ($n = 84$) and without ($n = 84$) a history of motion sickness undergoing gynecological laparoscopy. Patients received 8 mg dexamethasone or saline immediately before induction of anesthesia. Postoperatively patients were assessed for 24 hr for nausea, vomiting, and complete response (no vomiting, no need for rescue antiemetics).

Results: The complete response for patients with a history of motion sickness was 80.5% and 37.5% for recipients of dexamethasone and saline, respectively [$P < 0.001$; number needed-to-treat (NNT) = 2.3]; with corresponding incidences of 83.3% and 53.7% when there was no such history ($P = 0.009$; NNT = 3.4). Calculation of the efficacy of dexamethasone for the different subgroups shows that dexamethasone was 45.3% more effective in patients with motion sickness than in those without it.

Conclusions: Prophylactic administration of dexamethasone is effective in reducing PONV in patients with and without a history of motion sickness. The results of this study were more favourable in patients with a history of motion sickness, demonstrating a higher effectiveness of dexamethasone for preventing PONV in this subgroup of patients.

Objectif : Évaluer l'effet antiémétique de la dexaméthasone iv comme prévention des nausées et vomissements postopératoires (NVPO) chez des femmes ayant, ou non, des antécédents de mal des transports.

Méthode : Une étude randomisée, à double insu et contrôlée contre placebo a été menée auprès de 168 femmes qui présentaient ($n = 84$) ou non ($n = 84$) des antécédents de mal des transports et devaient

subir une laparoscopie gynécologique. Les patientes ont reçu 8 mg de dexaméthasone ou de solution saline immédiatement avant l'induction de l'anesthésie. Après l'intervention, les nausées, les vomissements et la réaction positive aux médicaments (absence de vomissements et d'antiémétiques de secours) ont été évalués pendant 24 h.

Résultats : La réaction positive des patientes, avec antécédents de mal des transports, a été respectivement de 80,5 % et de 37,5 % avec la dexaméthasone et la solution saline [$P < 0,001$; nombre nécessaire à traiter (NNT) = 2,3], et une incidence correspondante de 83,3 % et de 53,7 % chez les femmes sans antécédents ($P = 0,009$; NNT = 3,4). Le calcul de l'efficacité de la dexaméthasone chez les femmes des différents sous-groupes a montré que la dexaméthasone a été plus efficace de 45,3 % chez les patientes atteintes du mal des transports que chez celles qui ne l'étaient pas.

Conclusion : L'administration prophylactique de dexaméthasone est efficace pour réduire les NVPO chez les patientes avec ou sans antécédents de mal des transports. Nos résultats ont été plus favorables chez les patientes atteintes du mal des transports, ce qui indique une efficacité plus élevée de la dexaméthasone à prévenir les NVPO chez ces patientes.

FOR most patients, avoiding postoperative nausea and vomiting (PONV) after general anesthesia is a high priority.¹ The fear of PONV in patients undergoing surgery is more prevalent than that of postoperative pain.² Furthermore, intractable PONV is costly as it is the most common cause of unexpected admission following ambulatory surgery.^{3,4} Previous studies have shown that a history of motion sickness is a known patient-related risk factor for PONV.⁵⁻⁸

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A clinical trial published in 1993 suggested that dexamethasone can prevent PONV.⁹ Subsequent studies indicated that dexamethasone may effectively decrease the incidence of PONV in patients recovering from general anesthesia.^{10–13} Recently, efficacy has also been demonstrated in the prevention of patient-controlled analgesia and epidural-morphine-related nausea and vomiting.^{14–16} However, the efficacy of dexamethasone as a prophylactic antiemetic for PONV in patients with a history of motion sickness remains unclear. The aim of this study was to evaluate the antiemetic effect of 8 mg *iv* dexamethasone administered prior to induction of anesthesia, in a sample population of female surgical patients with or without a history of motion sickness.

Methods

Following Institutional approval and written informed consent from each patient, 168 females (ASA I or II), aged 28–58 yr, with ($n = 84$) or without ($n = 84$) a history of motion sickness were enrolled in this randomized, double-blinded, placebo-controlled study. The study was restricted to patients undergoing gynecological laparoscopic procedures, including salpingo-oophorectomy, oophorectomy, salpingostomy, myomectomy, tubal ligation and diagnostic laparoscopy. A history of motion sickness was collected as a part of the demographic information. Patients who suffered gastrointestinal discomfort, nausea and/or vomiting, pallor and diaphoresis provoked by travel in a car, train, airplane or ship in the past month were considered to have motion sickness. Patients who were pregnant, obese (body mass index $> 30 \text{ kg}\cdot\text{m}^{-2}$), current smokers, needing chronic steroid therapy, diagnosed with gastrointestinal, liver or renal dysfunctions, vestibular disease, and/or

preoperative vomiting, or who were currently receiving antiemetic therapy were excluded from the study.

Routine monitoring included continuous electrocardiogram, noninvasive blood pressure, capnography and pulse oximetry. Patients with or without motion-sickness history (designated MS+ and MS- groups, respectively) were randomly assigned to one of two treatment regimens: dexamethasone 8 mg ($n = 42$ each) or saline ($n = 42$ each). The study medications (2 mL) were prepared by personnel blinded to the study protocols, and were administered intravenously immediately prior to the induction of anesthesia.

The anesthetic regimen was standardized for all patients. Anesthesia was induced with *iv* glycopyrrolate 0.2 mg, fentanyl $1 \mu\text{g}\cdot\text{kg}^{-1}$ and thiopental $5 \text{ mg}\cdot\text{kg}^{-1}$, with endotracheal intubation facilitated by rocuronium $0.8 \text{ mg}\cdot\text{kg}^{-1}$. Anesthesia was maintained using sevoflurane 2–4% and oxygen 50% with air. Ventilation was controlled mechanically and adjusted to maintain the end-tidal CO_2 between 4 and 6 kPa throughout surgery. Muscle relaxants were used as required. During surgery, the abdomen was insufflated with carbon dioxide at an intra-abdominal pressure between 1.5 and 2 kPa. All patients received ketorolac *iv* 30 mg approximately 30 min before the end of surgery, after which the combination of glycopyrrolate and neostigmine (0.6 and 3 mg *iv*, respectively) were administered for reversal of residual muscle relaxation and the endotracheal tube removed. Esophageal temperature was monitored and maintained at $36\text{--}38^\circ\text{C}$ throughout surgery. No additional opioid drugs were administered during the operation.

Postoperatively, the incidence of PONV was collected every six hours for 24 hr. Patients were assessed for the first two hours in the postanesthesia care unit

TABLE I Patient characteristics

	MS+ Dexamethasone ($n = 41$)	Saline ($n = 40$)	MS- Dexamethasone ($n = 42$)	Saline ($n = 41$)
Age (yr)	39.6 ± 7.7	38.7 ± 8.1	40.5 ± 6.8	38.4 ± 9.3
Weight (kg)	56.4 ± 5.8	57.5 ± 6.3	58.2 ± 7.4	55.6 ± 7.6
LMP (days)	7.1 ± 1.5	6.8 ± 1.3	7.6 ± 1.6	6.6 ± 1.7
<i>Laparoscopic procedures</i>				
Salpingo-oophorectomy	9	5	12	7
Oophorectomy	7	10	8	9
Salpingostomy	1	4	2	3
Myomectomy	5	8	4	6
Tubal ligation	15	8	12	13
Diagnostic	4	5	4	3
Duration of insufflation (min)	92.2 ± 6.5	89.7 ± 18.4	86.3 ± 20.2	90.6 ± 21.3
Duration of operation (min)	112.7 ± 18.8	118.8 ± 23.3	109.4 ± 26.5	114.6 ± 21.7
Duration of anesthesia (min)	141.5 ± 21.4	138.3 ± 19.8	136.6 ± 22.9	135.6 ± 23.2

Values are mean $\pm$ SD and number. MS = motion sickness; LMP = last menstrual period.

(PACU). The episodes of PONV were identified by direct enquiry or when complaints were made by the patients. Afterwards, patients were asked to record the time of every emetic episode when they were in the ward. If the patient experienced brief instances of nausea and vomiting within an interval of one minute, this was classified as a single emetic episode. Conversely, when the interval between bouts of emesis exceeded one minute, these were deemed separate events.¹⁷ In this study, vomiting was defined as the synchronous, rhythmic contraction of the respiratory muscles, even without the expulsion of gastric content. Nausea was scored by using an 11-point visual-analogue scale from 0 to 10, with 0 representing no nausea and 10 representing the worst-possible nausea. More than four episodes of vomiting were considered severe. Average postoperative pain intensity was assessed by the patients themselves using an 11-point scale ranging from 0 to 10 and defining a pain continuum qualitatively defined by the descriptors no pain to unbearable pain, respectively. Analgesia was achieved with ketorolac (15 mg *iv*). Metoclopramide (10 mg *iv*) was given as rescue treatment as needed or requested by the patients. The worst score for each symptom during each observation period was recorded. The complete response was defined as no vomiting and no administration of antiemetic rescue medication during the 24-hr observation period.^{16,18,19} All data were collected by a team of trained nurse anesthetists blinded to the type of treatment received.

The sample size of this study was based on the following power calculation: a) the baseline incidence of PONV in the control group would be 60%;^{20,21} b) an expected 40% difference in the occurrence of PONV between groups; and b) the type-I error (α) and type-II error (β) values of 0.05 and 0.2, respectively.²² The estimated sample size was 40 in each group.²² Patient demographic data were analyzed using one-way analysis of variance (ANOVA). The severity of the nausea, vomiting and pain were compared using the Kruskal-Wallis test. The incidence of PONV, antiemetic rescue, and rate of complete response were examined using the χ^2 analyses or Fisher's exact test (two-sided). Data are expressed as mean values with standard deviations, or number and percentage. A *P* value of less than 0.05 was considered significant. The number needed-to-treat (NNT) and the absolute risk reduction (ARR; = control event rate – (minus) experimental event rate) were also calculated. The NNT is calculated as the inverse of the ARR.^{19,23} Commercial software SPSS 10.0 (SPSS Inc., Chicago, IL, USA) was used for data processing.

Results

Except for history of motion sickness, no significant differences were demonstrated between patient groups when comparing demographic data, duration of surgery, CO₂ insufflation and anesthesia (Table I). Of the 168 patients enrolled, four were excluded from the analysis: two required further surgery (laparotomy) during the procedure and two were lost to follow-up.

The data relating to PONV during the different observation periods are presented in Table II. A significantly lower incidence of PONV was demonstrated in MS+ patients receiving dexamethasone than in those receiving saline for the zero to two hours (*P* = 0.028), zero to six hours (*P* = 0.008), 6–12 hr (*P* = 0.035), and 12–18 hr (*P* = 0.037) observation periods. The lower PONV incidence noted in MS- patients who received dexamethasone was not statistically significant for any observation period. Over the entire 24 hr of observation, dexamethasone significantly reduced the total incidence of PONV by 50.7% in the MS+ group (*P* = 0.001) and by 32.3% in the MS- group (*P* = 0.004; Table III). Further, significantly reduced antiemetic requirements (MS+, *P* < 0.001; MS-, *P* = 0.009) and a higher rate of complete response (MS+, *P* < 0.001; MS-, *P* = 0.009) were also demonstrated for both of the dexamethasone-treated MS+ and MS- subgroups. The calculation of the complete response for the different subgroups shows that dexamethasone was 45.3% more effective in patients with motion sickness than in those without it. When assessed in terms of NNT, effectiveness in the MS+ patients was 2.3 while, in MS- patients, the NNT would be 3.4 patients to achieve the same beneficial effect. In addition, the incidence of PONV in the placebo-treated MS+ subgroup was significantly higher than in the MS- subgroup (*P* = 0.032). There was no difference between the MS+ and MS- groups treated with dexamethasone (*P* = 0.804).

No significant pain-score differences were demonstrated comparing the groups during the observation period (dexamethasone group: *P* = 0.306; saline group: *P* = 0.483; Table III). Further, no delays in wound healing or infection accompanying dexamethasone usage were reported.

Discussion

Recently, dexamethasone has been reported to be effective in preventing PONV in patients recovering from general anesthesia,^{10–13} receiving epidural morphine, and using patient-controlled analgesia.^{14–16} The antiemetic effect of dexamethasone after general anesthesia in patients with a history of motion sickness

TABLE II Assessment of postoperative emesis at various time intervals after anesthesia

	MS+ Dexamethasone (n = 41)	Saline (n = 40)	P	MS- Dexamethasone (n = 42)	Saline (n = 41)	P
<i>0–2 hr postoperatively</i>						
Nausea	4 (9.8)	9 (22.5)	0.140	3 (7.1)	7 (17.7)	0.194
Vomiting	3 (7.3)	7 (17.5)	0.194	2 (4.8)	5 (12.2)	0.265
Total PONV	7 (17.1)	16 (40.0)	0.028	5 (11.9)	12 (29.3)	0.161
<i>0–6 hr postoperatively</i>						
Nausea	4 (9.8)	10 (25.0)	0.084	3 (7.1)	8 (19.5)	0.116
Vomiting	3 (7.3)	8 (20.0)	0.116	3 (7.1)	4 (9.8)	0.713
Total PONV	7 (17.1)	18 (45.0)	0.008	6 (14.3)	12 (29.3)	0.116
<i>6–12 hr postoperatively</i>						
Nausea	3 (7.3)	8 (20.0)	0.116	2 (4.8)	5 (12.2)	0.265
Vomiting	2 (4.9)	5 (12.5)	0.264	2 (4.8)	4 (9.8)	0.433
Total PONV	5 (12.2)	13 (32.5)	0.035	4 (9.5)	9 (22.0)	0.141
<i>12–18 hr postoperatively</i>						
Nausea	2 (4.9)	5 (12.5)	0.264	2 (4.8)	4 (9.8)	0.433
Vomiting	1 (2.4)	5 (12.5)	0.109	1 (2.4)	2 (4.9)	0.616
Total PONV	3 (7.3)	10 (25.0)	0.037	3 (7.1)	6 (14.6)	0.313
<i>18–24 hr postoperatively</i>						
Nausea	1 (2.4)	3 (10.0)	0.359	1 (2.4)	3 (7.3)	0.360
Vomiting	1 (2.4)	2 (5.0)	0.616	1 (2.4)	1 (2.4)	1.00
Total PONV	2 (4.9)	5 (12.5)	0.264	2 (4.8)	4 (9.8)	0.433

Values are number of patients (percentage). MS = motion sickness; PONV = postoperative nausea and vomiting.

TABLE III Average nausea score, total incidence of PONV, need for antiemetic rescue, number of complete responses, and average pain score during the first 24 hr postoperatively

	MS+ Dexamethasone (n = 41)	Saline (n = 40)	P	ARR(%) NNT		MS- Dexamethasone (n = 42)	Saline (n = 41)	P	ARR(%) NNT	
Nausea score	2.96 ± 0.99	3.75 ± 1.16	0.002			2.45 ± 0.98	3.29 ± 1.18	0.001		
Nausea	7 (17.1)	18 (45)	0.008	27.9	3.6	6 (14.3)	13 (31.7)	0.071	17.4	5.8
Vomiting	5 (12.2)	14 (35)	0.019	22.8	4.4	4 (9.5)	10 (24.4)	0.141	14.9	6.7
Vomiting > 4 times	3 (7.3)	10 (25)	0.037	17.7	5.6	2 (4.8)	6 (14.6)	0.265	9.8	10.2
Total PONV	12 (29.3)	32 (80)	0.001	50.7	2.0	10 (23.8)	23 (56.1)*	0.004	32.3	3.1
Antiemetic rescue	8 (19.5)	25 (62.5)	< 0.001	43.0	2.3	7 (16.7)	19 (46.3)	0.009	29.6	3.4
Complete response	33 (80.5)	15 (37.5)	< 0.001	43.0	2.3	35 (83.3)	22 (53.7)	0.009	29.6	3.4
Pain score	2.24 ± 0.73	2.43 ± 0.84	0.306			2.14 ± 0.75	2.27 ± 0.87	0.483		

Values are mean ± SD or number of patients (percentage). MS = motion sickness; ARR = absolute risk reduction; NNT = number needed-to-treat; PONV = postoperative nausea and vomiting. * $P = 0.032$ in comparison with patients receiving saline in MS+ group.

remains unclear. In the present study, the incidence of nausea was not different in patients who received dexamethasone and those who received placebo in both MS+ and MS- groups during the different observation periods. This was probably because most patients suffering from nausea also vomited. However, we demonstrated that the prophylactic use of dexamethasone 8 mg significantly reduced the overall incidence of PONV for both MS+ and MS- group patients ($P < 0.001$ and $P = 0.004$, respectively). In addition, a

higher rate of complete response and reduced requirement for antiemetic rescue was demonstrated in subjects receiving dexamethasone in comparison to placebo. Furthermore, we found in MS+ patients, dexamethasone not only lowered the incidence of PONV, but reduced the severity of vomiting (frequency greater than four times; $P = 0.037$). The effectiveness of dexamethasone for preventing PONV was 45.3% greater in patients with a history of motion sickness than in those without.

Most people have suffered from motion sickness at sometime in their lives, however, for many the problem is recurrent and severe.²⁴ Patients with a history of motion sickness have a low threshold for vomiting, and are at increased risk of emetic symptoms.⁵ Several studies have demonstrated that a previous history of motion sickness is one of the most important predictors of postoperative emesis.^{6,7} Further, a recent meta-analysis confirmed that the incidence of postoperative vomiting was significantly greater in patients with a history of motion sickness than in those without (58.5 vs 41.7%).⁸ Fujii *et al.*, also reported a high incidence (70–72%) of PONV for female patients with such a history.^{7,25} In our study, a remarkably high incidence of PONV (80%) was observed during the first 24-hr after anesthesia for women who had a history of motion sickness, significantly higher in comparison to unaffected individuals ($P = 0.032$).

The exact mechanism by which dexamethasone exerts its antiemetic action is not fully understood. Kohl *et al.* have observed that adrenocorticotropin release is more pronounced in response to stressful motion stimuli in individuals who are more resistant to motion. Given the central role of the hypothalamic-pituitary-adrenal axis during the response to stress, this phenomenon has been considered significant in the etiology of motion sickness.^{26,27} Based on this observation, the efficacy of dexamethasone was tested in subjects exposed to cross-coupled accelerative, semicircular-canal stimulation while seated on a rotating chair. It was determined that subjects given 0.5 mg of dexamethasone every six hours for 48 hr could endure motion that was 80% more stressful.²⁸ These workers indicated that the efficacy of dexamethasone for establishing resistance to motion sickness may be explained in terms of neurochemical action across several neurotransmitter systems which are also modulated by the established antimotion-sickness drugs, scopolamine and amphetamine. As dexamethasone induces adaptive changes within the central nervous system, however, it may prove superior to these drugs, which are short acting, rapidly tolerated, and characterized by significant side-effects.^{24,28} Hence, it has been suggested that dexamethasone, administered acutely or chronically, may reduce susceptibility to motion sickness.^{28,29} Furthermore, other studies have shown that glucocorticoid receptors in the nucleus tractus solitarius, the nucleus of raphe, and the area postrema (the chemoreceptor trigger zone) of the brain stem may play important roles in the transmission of impulses to the centre which controls vomiting.^{5,30,31} Therefore, dexamethasone may exert its antiemetic action through these nuclei.

The dosage of dexamethasone in our study was based on previous work indicating that 8–10 mg has been used most frequently in the prevention of postoperative emesis.^{10–15} Despite our positive results, further studies should investigate the optimal dose of dexamethasone for the prevention of PONV in patients who are susceptible to motion sickness.

Previous studies have demonstrated that 5-HT₃ receptor antagonists (granisetron and ondansetron) are effective for the prevention of PONV when there is a history of motion sickness.^{7,8,25,32} The relative risk reduction for PONV achieved by dexamethasone prophylaxis in this study is in the range of the relative risk reductions (50–75%) reported with granisetron or ondansetron.^{7,8} In previous studies, 5-HT₃-receptor antagonists have been criticized because of their high cost.^{33,34} In our hospital, granisetron and ondansetron are approximately 20 and nine times more expensive than dexamethasone at the dosages used, respectively. Therefore, dexamethasone appears to be a cost-effective choice for the prevention of PONV in patients with a history of motion sickness.

In conclusion, the results of our study show that prophylactic antiemetic therapy using *iv* dexamethasone 8 mg before induction of anesthesia effectively prevents PONV in female patients undergoing gynecological laparoscopy, with or without a history of motion sickness. Dexamethasone 8 mg was more effective in patients with a history of motion sickness than in those without such a history.

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