

# Dexamethasone 8 mg in combination with ondansetron 4 mg appears to be the optimal dose for the prevention of nausea and vomiting after laparoscopic cholecystectomy

*[Une dose de 8 mg de dexaméthasone combinée à 4 mg d'ondansétron apparaît comme la dose optimale pour prévenir les nausées et les vomissements post cholécystectomie laparoscopique]*

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**Purpose:** The combination of antiemetic drugs could be a solution to prevent severe postoperative nausea and vomiting (PONV). The aim of this randomized double blind, dose-ranging study was to determine the minimum single effective dose of dexamethasone combined with ondansetron for the prevention of PONV in patients undergoing laparoscopic cholecystectomy.

**Methods:** One hundred eighty patients were allocated randomly to one of six groups to receive saline (P group), ondansetron 4 mg (O group), or ondansetron 4 mg and dexamethasone at doses of 2 mg (OD2 group), 4 mg (OD4 group), 8 mg (OD8 group), and 16 mg (OD16 group). A standardized general anesthetic was used. All episodes of PONV during the intervals of zero to six hours, 6–12 hr and 12–24 hr after surgery were evaluated using a numeric scoring system. Mean visual analogue scale pain scores at rest and on movement, the time to first demand of analgesia, total analgesic consumption in 12 hr epochs, duration of hospital stay, and side effects were recorded.

**Results:** The incidence of PONV in the OD8 (16%) and OD16 (16%) groups was lower than in the P 83% ( $P < 0.001$ ) and O groups (50%) at the 12–24 hr epoch ( $P < 0.05$ ). There were no differences in antiemetic effect between the O, OD2 and OD4 groups and between the OD8 and OD16 groups. Pain scores, total analgesic consumption, duration of hospital stay and side effects were similar among groups.

**Conclusion:** Our results suggest that 8 mg is the minimum dose of dexamethasone that, combined with ondansetron 4 mg will effectively prevent PONV in patients undergoing laparoscopic cholecystectomy.

**Objectif :** La combinaison de médicaments antiémétiques pourrait être la solution de la prévention des nausées et vomissements postopératoires sévères (NVPO). Le but de notre étude de dosage randomisée et à double insu était de déterminer la dose minimale efficace unique de dexaméthasone qui, combinée à l'ondansétron, puisse prévenir les NVPO chez des patients qui subissent une cholécystectomie laparoscopique.

**Méthode :** Cent quatre-vingt patients ont été répartis au hasard en six groupes et ont reçu une solution saline (groupe P), 4 mg d'ondansétron (groupe O) ou 4 mg d'ondansétron et de la dexaméthasone en doses de 2 mg (groupe OD2), 4 mg (groupe OD4), 8 mg (groupe OD8) ou 16 mg (groupe OD16). Une anesthésie générale normalisée a été utilisée. Tous les épisodes de NVPO survenus entre zéro et six heures, 6–12 h et 12–24 h après l'opération ont été évalués au moyen d'un système de cotation numérique. Les scores de douleur ont été enregistrés avec l'échelle visuelle analogique au repos et lors de mouvement, de même que le moment de la première demande d'analgesie, la consommation totale d'analgesique pour la période de 12 h, la durée du séjour hospitalier et les effets secondaires.

**Résultats :** L'incidence de NVPO dans les groupes OD8 (16 %) et OD16 (16 %) a été plus faible que dans les groupes P (83 %,  $P < 0,001$ ) et O (50 %) pendant la période de 12–24 h ( $P < 0,05$ ). L'effet antiémétique n'a pas présenté de différence entre les groupes O, OD2 et OD4 et entre les groupes OD8 et OD16. Les scores de douleur, la consommation totale d'analgesique, la durée du séjour hospitalier et les effets secondaires ont été similaires d'un groupe à l'autre.

**Conclusion :** Nos résultats permettent de dire que 8 mg constituent la dose minimale de dexaméthasone qui, combinée à 4 mg d'ondansétron, pourra efficacement prévenir les NVPO chez des patients qui subissent une cholécystectomie laparoscopique.

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Accepted for publication April 15, 2002.

Revision accepted July 22, 2002.

**D**EXAMETHASONE has been used as an antiemetic for more than 20 years in patients undergoing chemotherapy, with limited side effects.<sup>1</sup> Ondansetron a 5-HT<sub>3</sub> receptor antagonist has provided effective antiemesis in surgical patients.<sup>2</sup> Combination of antiemetic drugs could be an effective method to control severe postoperative nausea and vomiting (PONV), perhaps because there is no single stimulus or cause for PONV.<sup>3</sup>

In patients undergoing laparoscopic cholecystectomy, high incidences of PONV have been reported (50-70%).<sup>4</sup> Dexamethasone in a dose of 8-10 mg has been used frequently in the prevention of PONV.<sup>5-8</sup> In this study, in order to avoid possible adverse events after cortisone administration, we determined the minimal single dose of dexamethasone that, combined with ondansetron, provides effective prophylaxis of PONV after laparoscopic cholecystectomy.

### Material and methods

The local Ethics Committee approved the study and a written informed consent was obtained from each patient. We studied 180 patients undergoing general anesthesia for elective laparoscopic cholecystectomy. Patients who received opioid, non-steroidal anti-inflammatory drugs, steroids or antiemetic agents during the week before surgery were excluded. The severity of biliary symptoms was graded according to McSherry and colleagues<sup>9</sup> on a scale ranging from 0 to 3: 0 = gastrointestinal symptoms not caused by gall stones; 1 = infrequent episodes of biliary colic without cholecystitis; 2 = frequent episodes of biliary colic, at intervals of about one month; 3 = acute cholecystitis or obstructive jaundice without acute cholecystitis.

All patients had their last oral intake eight hours before the start of anesthesia and were premedicated with diazepam 10 mg orally the night before surgery.

Patients were allocated randomly to one of six groups ( $n = 30$  each) using a computer-generated random number table. Study medications were prepared by a single nurse anesthetist in two identical syringes with 2 mL of solution to ensure blinding. Before induction of anesthesia, patients received saline P (placebo), ondansetron 4 mg (O), or ondansetron 4 mg and dexamethasone at doses of 2 mg (OD2), 4 mg (OD4), 8 mg (OD8), and 16 mg (OD16).

Anesthesia was standardized. Anesthesia was induced with propofol 2-2.5 mg·kg<sup>-1</sup> and fentanyl 2 µg·kg<sup>-1</sup>. Tracheal intubation was facilitated with suxamethonium 1 mg·kg<sup>-1</sup>. A nasogastric tube was placed to promote baseline emptying of gastric contents. Anesthesia was maintained with isoflurane (1-2.5%),

nitrous oxide in 40% oxygen and muscle relaxation with atracurium 0.5 mg·kg<sup>-1</sup>. Intermittent doses of atracurium were given during anesthesia to maintain adequate muscle relaxation throughout the procedure. The respiratory tidal volume was adjusted to keep end-tidal CO<sub>2</sub> at 4.8-5.2%. Electrocardiography, heart rate, blood pressure, SpO<sub>2</sub>, peripheral temperature, and urine output were monitored.

Patients were positioned in the reverse Trendelenburg position with the right side of the table elevated. The four-laparoscopy entry sites were infiltrated with 10 mL of 2.5 mg·mL<sup>-1</sup> bupivacaine. The abdomen was insufflated with carbon dioxide with an intra-abdominal pressure of 13 mmHg. Ease of operation was scored by the surgeon for each patient on a 0-10 scale. The score was based on intra-abdominal adhesions necessitating dissection, difficult gall bladder anatomy, duration of operation (> 90 min), cholangiography, gall bladder perforation during surgery, bleeding, bowel or visceral puncture, enlargement of the laparoscopic entry for extraction of the gall bladder, need for drainage, and associated procedures, e.g., umbilical hernia repair.<sup>10</sup>

All surgical procedures were completed by the same surgeon. At the end of the laparoscopic procedure, 200 mg lidocaine diluted in 0.9% normal saline, were instilled in the peritoneum under the right diaphragm and on the gall bladder bed. Thereafter, patients were kept in a head-down tilt to bathe the tissues with the solution for 20 min. At the end of surgery, glycopyrrolate 0.6 mg and neostigmine 3 mg were given *iv* for antagonism of neuromuscular blockade, and the trachea was extubated. The nasogastric tube was removed before the patients were transferred to the recovery room.

Postoperatively, nalbuphine 20 mg *im* was prescribed every four hours or as requested by patients. The ward nurses were instructed to omit the four hourly doses if they considered that the patient was over sedated or pain free (pain levels below 4 on the visual analogue scale; VAS). All nurses were blinded to the study groups. The intensity of postoperative pain was measured on arrival in the recovery room and, subsequently, at time intervals of two, four, six, 12, and 24 hr using a 10-cm VAS (0 = no pain, 10 = most severe pain). Pain scores were measured at rest (supine) and with activity (sitting up from supine). The time interval from extubation to the first administration of nalbuphine was recorded, as was the consumption of postoperative analgesics.

All episodes of nausea and vomiting while in the hospital, during the zero to six-hour, six to 12-hr and 12 to 24-hr intervals after surgery were recorded. Nausea was

TABLE I Patient characteristics, surgical and anesthetic data for patients undergoing laparoscopic cholecystectomy

Characteristics	Groups					
	P	O	OD2	OD4	OD8	OD16
<i>n</i>	30	30	30	30	30	30
Age (yr)	41 (32-58)	43 (30-56)	42 (30-55)	41 (32-61)	42 (28-59)	43 (25-60)
Sex (F/M)	21/4	21/4	22/3	22/3	21/4	22/3
Weight (kg)	70 (8)	71 (9)	72 (8)	70 (10)	71 (9)	72 (10)
Height (cm)	160 (5)	160 (6)	160 (5)	162 (6)	164 (5)	160 (4)
ASA I/II	20/5	20/5	21/4	20/5	22/3	20/5
<i>History of:</i>						
Motion sickness ( <i>n</i> )	6	4	6	8	7	6
PONV ( <i>n</i> )	3	4	5	4	5	5
Nonsmoker	16	17	14	15	18	16
<i>Operative factor</i>						
Surgical score	2(0-4)	2(0-3)	2(0-4)	2(0-4)	2(1-3)	2(1-3)
McSherry score	1(0-2)	1(1-3)	1(0-2)	1(0-2)	1(0-2)	1(0-3)
Total CO <sub>2</sub> (L)	47(20)	51(30)	46(21)	50(22)	52(22)	48(20)
Fentanyl µg·kg <sup>-1</sup>	5.8(0.8)	6.0(0.9)	5.7(0.8)	5.9(0.6)	5.6(1.1)	5.7(0.8)
Duration of surgery (min)	104(28)	103(37)	106(23)	108(32)	106(33)	100(23)

Values given as mean ( $\pm$  SD or range) or number of patients. Surgical and McSherry scores given as median (range). PONV = postoperative nausea and vomiting.

TABLE II Number of patients (%) with nausea and vomiting, at intervals 0-6, 6-12, 12-24 hr after the end of surgery

	Groups					
	P	O	OD2	OD4	OD8	OD16
<i>n</i>	30	30	30	30	30	30
<i>0-6 hr</i>						
Nausea	10 (33)	3 (10)*	3 (10)*	3 (10)*	1 (3)*	1 (3)*
Vomiting	9 (30)	3 (10)*	1 (3)*	0 (0)*	0 (0)*	1 (3)*
Total	19 (63)	6 (20)*	4 (13)*	3 (10)*	1 (3)*	2 (6)*
Rescue antiemetic	8 (27)	2 (7)*	1 (3)*	2 (7)*	0 (0)*	0 (0)*
<i>6-12 hr</i>						
Nausea	16 (53)	9 (30)*	9 (30)*	6 (20)*	4 (13)*†‡	4 (13)*†‡
Vomiting	9 (30)	4 (13)*	3 (10)*	5 (17)	2 (7)*	2 (7)*
Total	25 (83)	13 (43)*	12 (40)*	11 (37)*	6 (20)*	6 (20)*†
Rescue antiemetic	9 (30)	3 (10)*	1 (3)*	1 (3)*	1 (3)*	0 (0)*
<i>12-24 hr</i>						
Nausea	16 (53)	9 (30)*	9 (30)*	6 (20)*	4 (13)*†‡	4 (13)*†‡
Vomiting	9 (30)	6 (20)	6 (20)	5 (17)	1 (3)*†‡	1 (3)*†‡
Total	25 (83)	15 (50)*	15 (50)*	11 (37)*	5 (16)*†‡	5 (16)*†‡
Rescue antiemetic	9 (30)	5 (17)	5 (17)	2 (7)*	0 (0)*	1 (3)*

Significant difference compared with \*group P; † group O, and ‡ group OD 2 mg.

TABLE III Pain scores, first opioid request, nalbuphine consumption, incidence of side effects and time to discharge

	Groups					
	P	O	OD2	OD4	OD8	OD16
<i>Pain score (24 hr)</i>						
At rest	3.6 (1)	3.6 (1.4)	3.2 (1.5)	3.0 (1.2)	2.9 (1.1)	2.9 (1.1)
With activity	3.9 (1.1)	3.8 (1.3)	3.4 (1.5)	3.1 (1.1)	3.0 (1.2)	3.0 (1.1)
First opioid demand (min)	60.2 (20.5)	60.2 (20.5)	87.8 (17.7)	91.2 (19.6)	98.5 (23.4)	100.1 (32.9)
<i>Nalbuphine consumption (mg)</i>						
At 12 hr	39.3 (4.9)	35.9 (4.7)	35.5 (7.2)	34.9 (7.7)	35.7 (6.9)	34.6 (6.7)
24 hr after surgery	39.4 (4.1)	30.1 (2.3)	23.6 (5.2)	22.1 (3.3)	20.6 (4.3)	20.1 (4.1)
<i>Side effects</i>						
Headache	2	3	1	3	2	2
Itching	—	1	1	1	2	1
Sweating, dizziness	1	—	—	1	1	—
Urinary retention	—	2	1	1	—	1
<i>Hospital discharge (hr)</i>	28.3 (2.6)	27.7 (3.1)	26.6 (4.2)	27.5 (2.2)	23.6 (2.1)	22.2 (1.2)

Values are given as mean ( $\pm$  SD), or number of patients.

defined as a subjectively unpleasant sensation associated with 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 min or more than one emetic episode in 15 min, rescue antiemetic treatment consisted of metoclopramide 10 mg *iv* every eight hours. Duration of hospital stay and incidence of side effects (itching, urinary retention, headache) were recorded. Data were analyzed using one-way analysis of variance with a linear contrast, Chi-square test ( $\chi^2$  test) with Yates correction and the Kruskal-Wallis test as appropriate. Power analysis before the study showed that 30 patients would be required in each group to have a 90% chance with an error of 5% to detect a decrease in the incidence of vomiting from 60% to 40% after treatment.<sup>11</sup>  $P < 0.05$  was considered statistically significant.

## Results

Patients' characteristics, factors related to operation and anesthesia, and simplified Apfel score,<sup>12</sup> did not differ between groups (Table I).

Complete response (no PONV) in the 12–24 hr interval after surgery occurred in 84% of patients in groups OD 8 and OD 16, and in 17% of patients in the P group ( $P < 0.001$ ). No difference was found between groups OD8 and OD16. In the O group, complete response occurred in 50% of patients, in 50% of patients in the OD2 group, and in 63% of patients in the OD4 group. The differences between groups OD8 and P were significant at all times, as were differences between group OD8 and group O at 12–24 hr after surgery ( $P < 0.05$ ).

Only one patient (3%) in groups OD8 and OD16 required antiemetic rescue compared to 12 (40%) patients in group P ( $P < 0.01$ ). Eight (27%) patients in group O required antiemetic rescue and five (17%) patients in each of OD2 and OD4 groups (Table II).

There were no significant differences in time to first nalbuphine request or pain intensity at rest or during activity between groups at any time. Mean total consumption of nalbuphine for each time interval was similar among groups. Duration of hospital stay and incidence of side effects were similar among groups (Table III).

## Discussion

Our results suggest that dexamethasone 8 mg represents the most effective dose of dexamethasone combined with ondansetron for the prevention of PONV during the first 24 hr after laparoscopy. The combina-

tion of ondansetron and dexamethasone 8 mg was more effective than placebo, and ondansetron alone for control of nausea and vomiting. Moreover, there were no significant differences between ondansetron and the combination of ondansetron and dexamethasone at doses of 2 or 4 mg which reduced the incidence of PONV compared to placebo.

Ondansetron is a selective 5-HT receptor antagonist effective in preventing PONV.<sup>13,14</sup> McKenzie and colleagues<sup>15</sup> found that a single 4-mg *iv* dose appeared to be the lowest effective dose for this purpose.

Dexamethasone is a glucocorticoid that produces a strong antiemetic effect<sup>16,17</sup> by an undetermined mechanism. It may act through prostaglandin antagonism,<sup>18</sup> serotonin inhibition in the gut,<sup>19</sup> and by releasing endorphins.<sup>20</sup> Liu and colleagues<sup>21,22</sup> demonstrated that dexamethasone alone at doses of 5 mg and 2.5 mg are as effective as 10 mg, in reducing the incidence of PONV. The total incidence of PONV, after pretreatment with dexamethasone was reduced by about 43–37% compared to placebo. These results suggest that dexamethasone 2.5 mg represents the minimum effective dose for the prevention of PONV after major gynecological surgery. In a study by Huang *et al.*,<sup>23</sup> the incidence of PONV was reduced by about 35% after pretreatment with a low dose of dexamethasone (5 mg) in patients undergoing laparoscopy for tubal ligation.

In the present study we found that the total incidence of PONV after laparoscopy was 83% when no antiemetic was given prophylactically. After pretreatment with dexamethasone at doses of 2 or 4 mg in combination with ondansetron 4 mg, the total incidence of PONV was reduced by 37 to 50%. The maximal response from combination therapy (a reduction of PONV by 67%) was reported only after pretreatment with dexamethasone 8 mg or 16 mg with ondansetron. Further, dexamethasone 8 mg and 16 mg were equally effective, suggesting that dexamethasone 8 mg represents the minimal effective dose in combination with ondansetron to prevent PONV after laparoscopic cholecystectomy.

With its strong anti-inflammatory action, dexamethasone has been shown to decrease postoperative pain. Baxendale *et al.*,<sup>24</sup> reported that pain after tooth extraction was decreased after a single prophylactic dose of oral dexamethasone 8 mg. In our study, time to first nalbuphine administration, pain score, and analgesic consumption were similar among groups. An insignificant decrease in analgesic consumption was observed in the dexamethasone groups in the late postoperative period. Pain from multiple sources as after laparoscopic cholecystectomy may not be less-

ened with dexamethasone administration especially in the early postoperative period.

The long-term administration of corticosteroids is associated with side effects, such as increased risk of infection, delayed wound healing, glucose intolerance, and adrenal suppression. The lack of difference in hospital stay or side effects among groups suggests that wound infection or delayed healing was not a problem. Although a single dose of dexamethasone is considered safe, further studies with more patients and a longer follow-up are indicated.

In conclusion, our results suggest that dexamethasone 8 mg is, in combination with ondansetron 4 mg, the optimal dose to prevent PONV after laparoscopic surgery.

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