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## ***Menstruation Increases the Risk of Nausea and Vomiting after Laparoscopy***

### ***A Prospective Randomized Study***

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**Background:** Several factors may influence the incidences of postoperative nausea and vomiting. In women, one of these factors may be the timing of their surgery in relation to their menstrual cycle. The purpose of this study was to assess the effect of menstruation and efficacy of the antiemetic droperidol on postoperative nausea and vomiting.

**Methods:** In a prospective randomized double-blind clinical trial, 100 female patients who were scheduled for laparoscopic tubal sterilization were stratified on the basis of the date of their last menses into menstrual (days 1-8) and nonmenstrual (days 9-28) groups. Patients in both groups were then randomized to receive placebo or 10, 20, or 30 µg/kg droperidol before induction of anesthesia, and data were obtained for 24 h after completion of their surgery.

**Results:** Nausea and vomiting were reported in 55 patients, and the risk was 2.92 times greater in the menstrual group (71.4%) than in the nonmenstrual group (46.2%;  $P = .013$ ). Droperidol (30 µg/kg) reduced the incidence of vomiting from 47.1% (placebo) to 13.3% in the nonmenstrual group ( $P = .045$ ) but had no effect in the menstrual group. Five prognostic variables (menstrual stratum, droperidol, age 30 yr or younger, weight 65 kg or less, and history of nausea and vomiting) for postoperative nausea and vomiting were tested by stepwise logistic regression. Menstrual stratum was the only variable identified as a significant ( $P = .017$ ) predictor, having a percent probability equal to 2.21.

**Conclusions:** The risk of postoperative nausea and vomiting is increased in women undergoing laparoscopic tubal sterilization during the first 8 days of their menstrual cycle, and droperidol up to 30 µg/kg is not as effective in these patients. (Key words: Antiemetic: droperidol. Complications, postop-

erative: menstruation; nausea; vomiting. Surgery: laparoscopy.)

THE incidence of postoperative nausea and vomiting may be influenced by the presence of certain risk factors, including the choice of anesthetic agent and technique.<sup>1</sup> The use of multiple stepwise logistic regressions in one large prospective clinical trial of general anesthesia<sup>2</sup> identified several independent predictors of postoperative nausea and vomiting. These predictors included female gender, age 30 yr or younger, intraabdominal surgical procedures (especially laparoscopic procedures), and the use of opioids.

We recently reported the results of a retrospective study of female patients following abdominal laparoscopy<sup>3</sup> in which the incidence of postoperative nausea and vomiting was increased fourfold in patients who were menstruating at the time of their surgery. This study also questioned the efficacy of the antiemetic droperidol in such patients.

In this article, we report the results of a prospective randomized double-blind clinical trial of postoperative nausea and vomiting in menstruating and nonmenstruating women and assess the efficacy of three different doses of droperidol.

### **Methods**

This study was performed after institutional ethical review and written informed consent was obtained from the participants. We studied 100 female ASA physical status 1 or 2 patients who were scheduled for elective laparoscopic tubal ligation. We excluded patients who were taking contraceptive or antiemetic medication, who were not sure of the date of their last menses, or who had given birth recently but had not yet had a normal menses.

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## MENSTRUATION AND POSTOPERATIVE VOMITING

Patients were interviewed during the routine preoperative medical and physical assessment, and details of previous anesthesia, postoperative nausea or vomiting, history of motion sickness, migraine headache, or recent flu-like illness were noted. Age, weight, and the date of onset of their last menses were recorded for all patients.

Patients were stratified on the basis of the recorded date of their last menses (day 1) into menstrual (days 1–8) and nonmenstrual (days 9–28) groups. Patients in both groups were then randomized in a double-blind manner to receive placebo or 10, 20, or 30  $\mu\text{g}/\text{kg}$  droperidol just before induction of anesthesia.

### Anesthesia

Patients were taken into the operating suite after insertion of an intravenous catheter. No pre-anesthetic medications were given. The randomized study drug injection was given before induction of anesthesia with thiopental (3–5 mg/kg) plus fentanyl (1–2  $\mu\text{g}/\text{kg}$ ). Muscle relaxation was achieved with atracurium (0.4 mg/kg) or vecuronium (0.1 mg/kg), and the trachea was intubated. The choice of muscle relaxant drug was at the discretion of the attending anesthesiologists' preference for intubation. Anesthesia was maintained with nitrous oxide (70%), oxygen (30%), and isoflurane (0.5–1.5%), with respiration controlled by a volume cycled ventilator at a tidal volume of 10 ml/kg and frequency of 10 cycles per minute, adjusted to maintain end-tidal carbon dioxide at pre-anesthesia levels. Muscle relaxation was monitored continuously by a peripheral nerve stimulator and, at the end of surgery, was reversed with neostigmine (50  $\mu\text{g}/\text{kg}$ ) and glycopyrrolate (10  $\mu\text{g}/\text{kg}$ ).

After extubation, patients were transferred to the postanesthesia care unit for observation for up to 2 h then moved to the short stay unit for further observation until discharge, then followed up *via* telephone after 24 h. The onset of nausea or vomiting was recorded in a blinded manner and rated for severity using a rating scale (0 = no nausea or vomiting, 1 = nausea, 2 = retching, 3 = vomited once, 4 = vomited more than once) at 2, 6, and 24 h after completion of surgery.

### Statistics

The incidences of nausea and vomiting were tabulated as crude rates and by severity rating for each stratum (menstrual and nonmenstrual) and for each treatment group (placebo and 10, 20, and 30  $\mu\text{g}/\text{kg}$  droperidol). Continuous variables such as age and weight were

compared by Students' *t* test, while dichotomous variables were analyzed by chi-square (Mantel-Haenszel). Odds ratio was computed as a measure of risk. A result was considered significant if  $P \leq .05$ . Differences between nausea and vomiting scores were assessed by Wilcoxon rank sum test. For the comparison of menstrual *versus* nonmenstrual groups, pooled and within-strata treatment data were used.

A stepwise logistic regression used data from all patients in the study to test five prognostic variables, that had a significant univariate chi-square, for postoperative nausea and vomiting. These prognostic variables were menstrual stratum, droperidol, age 30 yr or younger, weight 65 kg or less, and a history of nausea and vomiting. The logistic constant (*k*) at the final step was used if a logistic coefficient (*b*) for a prognostic variable was significant ( $P \leq .05$ ). The probability (*Pr*) was calculated from

$$\text{Pr} = e^{-\chi} / 1 + e^{-\chi},$$

where  $\chi = k + b_1 \dots b_n$  and  $n$  is the number of variables in the model. For the purpose of this regression, the droperidol data were pooled and the placebo group was used as the reference group.

## Results

One hundred patients were entered into this trial, of which 35 were stratified to a menstrual group and 65 to a nonmenstrual group. All patients were studied for 24 h. The age, weight, history of nausea and vomiting, migraine headaches, and duration of surgery and anesthesia did not differ among the treatment groups or between strata. The average age (1SD) in the menstrual group and nonmenstrual group was 33.4 yr (5.5; range 20–45) and 32.4 yr (5.1; range 21–47), respectively; the average weight (1SD) 67.5 kg (11.5; range 52–104) and 66.5 kg (10.0; range 50–94), respectively. The average duration of anesthesia was 22.2 min (1SD = 5.8) in the menstrual group and 20.2 min (1SD = 6.8) in the nonmenstrual group. A history of nausea and vomiting was reported in 14 patients, of which 4 were in the menstrual group (11.4%) and 10 were in the nonmenstrual group (15.4%). Two patients in the menstrual group and five in the nonmenstrual group had a history of migraine headaches.

During the first 24 h postoperatively, nausea and vomiting was noted in 55 patients; 25 patients were in the menstrual group (71.4%) and 30 (46.2%) were in the nonmenstrual group ( $P = .013$ ). Sixteen patients

in the menstrual group (45.7%) and 20 in the nonmenstrual group (30.8%) vomited at least once after surgery. It is notable that of the patients who vomited, 15 of 16 in the menstrual group and 16 of 20 in the nonmenstrual group did so after discharge from hospital.

The number of patients within each nausea and vomiting score category is shown in table A1 for each stratum, treatment group, and period of observation. Table 1 shows the number of patients in each stratum and

**Table A1. Number of Patients by Nausea and Vomiting Score for Each Stratum (menstrual and nonmenstrual groups), each Treatment Group (placebo, 10, 20, and 30  $\mu\text{g}/\text{kg}$  droperidol), and Period of Observation (<6 h, at 24 h, anytime up to 24 h)**

	N	Nausea and Vomiting Score				
		0	1	2	3	4
<b>Menstrual group</b>						
Placebo						
Max	9	2	0	2	1	4
<6 h	9	2	0	2	3	2
24 h	9	5	0	0	1	3
Droperidol 10 $\mu\text{g}/\text{kg}$						
Max	9	2	0	1	4	2
<6 h	9	2	1	4	2	0
24 h	9	2	0	1	4	2
Droperidol 20 $\mu\text{g}/\text{kg}$						
Max	8	4	0	1	1	2
<6 h	8	4	0	1	2	1
24 h	8	4	0	1	1	2
Droperidol 30 $\mu\text{g}/\text{kg}$						
Max	9	2	1	4	1	1
<6 h	9	2	1	4	1	1
24 h	9	5	2	0	1	1
<b>Nonmenstrual group</b>						
Placebo						
Max	17	8	0	1	1	7
<6 h	17	8	0	3	2	4
24 h	17	8	0	1	1	7
Droperidol 10 $\mu\text{g}/\text{kg}$						
Max	17	6	0	3	4	4
<6 h	17	7	0	4	5	1
24 h	17	10	1	1	2	3
Droperidol 20 $\mu\text{g}/\text{kg}$						
Max	16	10	2	2	1	1
<6 h	16	12	1	2	1	0
24 h	16	12	2	0	1	1
Droperidol 30 $\mu\text{g}/\text{kg}$						
Max	15	11	2	0	2	0
<6 h	15	12	2	0	1	0
24 h	15	14	0	0	1	0

Max = maximum reported nausea and vomiting score at anytime up to 24 h after surgery.

treatment group who had nausea (nausea and vomiting score 1 or 2) and who vomited (nausea and vomiting score 3 or 4). Patients in the menstrual group had no change in the incidence of nausea and vomiting with any dose of droperidol. Patients in the nonmenstrual group had a reduced incidence of vomiting with 20  $\mu\text{g}/\text{kg}$  droperidol (12.5%) or 30  $\mu\text{g}/\text{kg}$  droperidol (13.3%) compared to placebo (30.8%). Of the 14 patients who had a history of nausea and vomiting, 12 had nausea in the present study, equal to 21.8% of patients with nausea and vomiting.

Table 2 shows the odds ratios and *P* values for significant results for nausea and vomiting. The risk of postoperative nausea and vomiting was 2.92 times greater in the menstrual group than in the nonmenstrual group (*P* = .013). Overall, 20 and 30  $\mu\text{g}/\text{kg}$  droperidol reduced the risk of postoperative vomiting by a factor of four and five times, respectively, compared to placebo. In the nonmenstrual group, 20  $\mu\text{g}/\text{kg}$  droperidol reduced the risk of vomiting by more than six times (*P* = .036). A power analysis using Bayes' theorem confirmed the lack of effect by 20 or 30  $\mu\text{g}/\text{kg}$  droperidol in the menstrual group (probability of a Type II error equals 0.836 and 0.920, respectively).

The stepwise logistic regression identified only one significant predictor of postoperative nausea and vomiting. Menstrual stratum (using the nonmenstrual stratum as the reference group) had a logistic coefficient of  $-1.83$  (*P* = .017) and a calculated probability (Pr) of 2.21% (Pr for the reference group was 0.4%).

The incidence of nausea and vomiting was increased between days 24 and 4 for droperidol and placebo groups, compared to other phases of the menstrual cycle. This raises the possibility that the peak risk for postoperative nausea and vomiting could be earlier than our stratification. We therefore examined this possibility by redefining our stratification to days 25–4, instead of days 1–8, as a perimenstrual group, and days 5–24 as a periovulatory group. There were 35 patients in the former and 65 patients in the latter group. The result in the placebo groups was to increase the incidence of postoperative nausea and vomiting in the perimenstrual group to 92.3%, while the periovulatory group was 41.7%. As before, droperidol had no effect on nausea and vomiting in the perimenstrual group but reduced its incidence to 15.3% with 20  $\mu\text{g}/\text{kg}$  and 15.4% with 30  $\mu\text{g}/\text{kg}$  in the periovulatory group. We caution that this redefinition of our stratification may not be valid since our design was specific for days 1–8.

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Table 1. Incidence of Postoperative Nausea and Vomiting

	N	Nausea (NVS = 1 or 2)	Vomiting (NVS = 3 or 4)	Total
Menstrual group (%)	35	9 (25.7)	16 (45.7)	25 (71.4)
Placebo	9	2	5	7
10 µg/kg droperidol	9	1	6	7
20 µg/kg droperidol	8	1	3	4
30 µg/kg droperidol	9	5	2	7
Nonmenstrual group (%)	65	10 (15.4)	20 (30.8)	30 (46.2)
Placebo	17	1	8	9
10 µg/kg Droperidol	17	3	8	11
20 µg/kg droperidol	16	4	2	6
30 µg/kg Droperidol	15	2	2	4
All patients	100	19	36	55

NVS = nausea and vomiting score.

## Discussion

The results of this study show that the risk of postoperative nausea and vomiting following laparoscopy is increased in menstruating women compared to nonmenstruating women. Droperidol in a dose of 20 µg/kg was effective in reducing the incidence of vomiting in nonmenstruating women but not in menstruating women.

Postoperative nausea and vomiting is a clinically important and frequent cause of postoperative morbidity,<sup>1</sup> especially in female patients.<sup>2</sup> In a retrospective study of female patients undergoing abdominal laparoscopic surgery,<sup>3</sup> we reported an increased incidence of postoperative nausea and vomiting when their surgery was

performed during the first 8 days of their menstrual cycle. The results of the present prospective randomized clinical trial are essentially similar. There was an apparent increase in the incidence and severity of postoperative nausea and vomiting between days 25 and 4.

Following our original suggestion that menstruation could influence the incidence of postoperative nausea and vomiting<sup>3,4</sup> after gynecologic surgery, Honkavaara *et al.*<sup>5</sup> did a retrospective analysis of their data from a previous study of the effect of nitrous oxide and volatile anesthetics on the incidence of nausea and vomiting after laparoscopy.<sup>6</sup> These investigators claim similar findings to the results in our own retrospective study,<sup>3</sup> with the noted exception that none of the 11 menstruating women in their study reported postoperative vomiting.

We designed this prospective randomized clinical trial on the basis of our previous studies.<sup>3,4</sup> Clearly, some assumptions made were incorrect. Firstly, we assumed there would be a peak incidence of postoperative nausea and vomiting during the first 8 days of the menstrual cycle. In fact, it appears that the peak incidence may occur between days 24 and 4. Secondly, we assumed that a fourfold difference for postoperative nausea and vomiting would exist between the menstrual and nonmenstrual patients, and we calculated the sample size (power of 0.95, error of 0.05) on this basis. Our results show differences in rates approximately half of those expected. The third assumption we made was that droperidol would have little effect on nausea and vomiting after hospital discharge. We found that droperidol was effective in reducing the incidence of vomiting throughout the 24-h observation in the nonmenstrual group. The pooling of droperidol

Table 2. Significant Risks for Postoperative Nausea and Vomiting

Univariate Risk Factor	Odds Ratio	P
Nausea and vomiting		
Menses	2.92	.013
History of nausea and vomiting	6.00	.011
Vomiting (NVS = 3 or 4)		
20 µg/kg droperidol*	0.26	.031
30 µg/kg droperidol*	0.20	.013
Vomiting (NVS = 3 or 4) (nonmenses)†		
20 µg/kg droperidol*	0.16	.036
30 µg/kg droperidol*	0.17	.045
Stepwise logistic regression	k      b      OR‡	P
Nausea and vomiting menses	5.62    -1.83    6.23	.017

k = logistic constant; b = logistic coefficient; NVS = nausea and vomiting score.

\*  $P \leq .05$  versus placebo.

†  $P \leq .05$  within nonmenstrual stratum.

‡ Adjusted odds ratio calculated from  $e^{-b}$ .

data for the purposes of the stepwise logistic regression may not be justified because of the dose effect, and our results should be interpreted with caution. Also, the probabilities we found for a Type II error for 20 and 30  $\mu\text{g}/\text{kg}$  droperidol in the menstrual group were higher than expected. We interpret this to mean that a larger sample size was required.

A consistent finding from our study was the increased risk of postoperative nausea and vomiting in women whose surgery was performed during their menses. The possibility that this increased risk may precede the menses should be investigated further in a larger trial.

Droperidol is a dopamine receptor antagonist. The interval between days 8 and 24 of the menstrual cycle is associated with increased estrogen levels.<sup>7,8</sup> Estrogen is known to increase the number and sensitivity of dopamine receptors<sup>9,10</sup> and to increase the incidence of nausea and vomiting.<sup>4</sup> It is possible that estrogen could sensitize dopamine receptors to an as yet unidentified "trigger" whose effects are blocked by dopamine antagonists such as droperidol. Since we found that droperidol was ineffective in reducing the incidence of nausea and vomiting in menstruating women, a second possible mechanism of antagonism of the receptor effects of droperidol seems likely.

Serotonin is another neurotransmitter that has been found to increase the incidence of nausea and vomiting.<sup>11</sup> Ondansetron is a serotonin antagonist that is effective in the treatment of nausea and vomiting with chemotherapy.<sup>12,13</sup> Ondansetron has limited efficacy for postoperative nausea and vomiting,<sup>14</sup> suggesting that only part of this mechanism may involve serotonin.

Several premenstrual syndromes have been reported to be mediated by serotonin, including premenstrual headache.<sup>15</sup> The number of patients in our study who reported a history of migraine headache was too low for any conclusions to be made about this as a risk factor. Estrogen has a reciprocal effect on serotonin receptors<sup>16</sup>; thus, during the premenstrual phase, serotonin receptors may be upregulated by the low estrogen levels found at this time. Any stress-released serotonin could precipitate the onset of nausea and vomiting. It seems possible that serotonin antagonists may be effective antiemetics during the perimenstrual phase.

We conclude from our study that menstruation increases the risk of postoperative nausea and vomiting and that droperidol is not effective for such patients. The possibility that other receptor mechanisms may be involved should be investigated further.

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