General Anesthesia

Nausea and vomiting after laparoscopic surgery are not associated with an increased peripheral release of serotonin

[Les nausées et vomissements suite à une chirurgie laparoscopique ne sont pas associés à une sécrétion périphérique accrue de sérotonine]

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Purpose: To determine whether patients suffering postoperative nausea and vomiting (PONV) present a different serotonin release pattern from those who do not present this complication.

Methods: Forty-eight consecutive women undergoing outpatient laparoscopic tubal ligation were enrolled in this prospective, cumulative case-control study. The study compared serotonin activity in 15 patients totally free of emetic symptoms (asymptomatic group) and, among patients with PONV ($n = 33$), those 15 who presented the most severe symptoms (PONV group). Patients were anesthetized with a regimen including sufentanil (0.1–0.3 $\mu g \cdot kg^{-1}$) plus thiopental (3–5 $mg \cdot kg^{-1}$) for induction and isoflurane (0.6–1%) in nitrous oxide (60%) for maintenance. Peripheral serotonin activity was assessed by measurement with high-performance liquid chromatography of serotonin's principal urinary metabolite: 5-hydroxyindoacetic acid (5-HIAA) corrected for urinary creatinine.

Results: The preoperative and postoperative urinary 5-HIAA:creatinine ratios were 6.9 $ng \cdot \mu g^{-1}$ (confidence interval; CI 95%, 2.7–11.0) and 5.9 $ng \cdot \mu g^{-1}$ (CI 95%, 2.4–9.4) respectively in the asymptomatic group ($P = 0.69$), and were 5.1 $ng \cdot \mu g^{-1}$ (CI 95%, 2.5–7.7) and 5.6 $ng \cdot \mu g^{-1}$ (CI 95%, 3.4–7.7) respectively in the PONV group ($P = 0.75$). There was also no difference between groups in the variation of 5-HIAA:creatinine ratios from the preoperative to the postoperative period ($P = 0.21$).

Conclusion: PONV after laparoscopic tubal ligation are not associated with an increased urinary excretion of serotonin metabolites. Patients with severe PONV present a peripheral serotonin release comparable to asymptomatic patients.

Objectif : *Déterminer si les patientes souffrant de nausées et vomissements postopératoires (NVPO) ont un profil de sécrétion de la sérotonine différent de celles qui ne présentent pas cette complication.*

Méthode : *Quarante-huit femmes qui se sont présentées successivement en chirurgie ambulatoire pour une ligature tubaire par laparoscopie ont participé à cette étude prospective cas-témoins. Le profil de sécrétion de la sérotonine chez 15 patientes qui ne présentaient aucun symptôme émétique (groupe asymptomatique) a été, comparé à celui des 15 patientes ayant présenté les symptômes les plus sévères (groupe NVPO). L'anesthésie a été induite avec du sufentanil (0,1 – 0,3 $\mu g \cdot kg^{-1}$) et du thiopental (3 – 5 $mg \cdot kg^{-1}$) et maintenue avec de l'isoflurane (à 0,6 – 1 %) dans du protoxyde d'azote (à 60 %). L'activité périphérique de la sérotonine a été évaluée par la mesure du principal métabolite urinaire de la sérotonine au moyen de la chromatographie liquide haute performance : l'acide 5-hydroxy-indole acétique (5-HIAA) corrigé pour la créatinine urinaire.*

Résultats : *Les ratios 5-HIAA urinaire préopératoire et postopératoire:créatinine ont été de 6,9 $ng \cdot \mu g^{-1}$ (intervalle de confiance IC de 95 %, 2,7–11,0) et de 5,9 $ng \cdot \mu g^{-1}$ (IC 95 %, 2,4–9,4) respectivement chez les patientes asymptomatiques ($P = 0, 69$), et de 5,1 $ng \cdot \mu g^{-1}$ (IC 95 %, 2,5–7,7) et 5,6 $ng \cdot \mu g^{-1}$ (IC 95 %, 3,4–7,7) respectivement pour les patientes du groupe NVPO ($P = 0,75$). Il n'y a pas eu de différence intergroupe pour la variation des ratios 5-HIAA:créatinine entre les périodes préopératoire et postopératoire ($P = 0,21$).*

Conclusion : *Les NVPO suivant la ligature des trompes laparoscopique ne sont pas associés à une sécrétion urinaire accrue des métabolites de la sérotonine. La sécrétion périphérique de sérotonine est comparable pour les patientes qui souffrent de NVPO sévères et les patientes asymptomatiques.*

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Accepted for publication December 7, 2001.

Revision accepted February 12, 2002.

THE pathophysiology of postoperative nausea and vomiting (PONV) is not completely understood and is believed to be multifactorial.[1] Many neuromediators such as dopamine, acetylcholine, histamine and serotonin (5-hydroxytryptamine) are thought to be involved and receptor antagonists to these neuromediators are the mainstay of the prevention and treatment of PONV.[1] Serotonin can induce nausea and vomiting by a central or a peripheral mechanism of action through activation of 5-hydroxytryptamine-3 (5-HT_3) receptors.[2] Centrally, these receptors are located at the area postrema (chemoreceptor trigger zone) and in the nucleus tractus solitarius, near the vomiting centre.[2,3] Animal studies have shown that activation of these central receptors produces nausea and vomiting.[4] However the most important reserves of body serotonin (> 90%) are located in the enterochromaffin cells of the gastrointestinal mucosa.[5] Their release can activate 5-HT_3 receptors located on the vagal afferent fibres in the gastrointestinal mucosa, triggering an emetic signal mediated by the vagus nerve to the chemoreceptor trigger zone and the vomiting centre.[5] This latter mechanism has been well documented by Cubbedu *et al.* for chemotherapy-associated nausea and vomiting.[6] Administration of cisplatin, a potent emetogenic drug, is associated with a marked release of serotonin from the gut mucosa accompanied by nausea and vomiting.[6] It has also been shown that 5-HT_3 receptor antagonists are highly effective for the prevention and treatment of nausea and vomiting associated with cisplatin chemotherapy.[7]

Selective 5-HT_3 receptor antagonists, such as ondansetron, granisetron, tropisetron and dolasetron are also effective for the prevention and treatment of PONV.[8–11] It has been speculated that some surgical procedures, such as those requiring the establishment of a pneumoperitoneum, might trigger a serotonin release from the gut.[11] However it has not been investigated whether PONV is associated with such a peripheral release of serotonin.

The working hypothesis of this study was that patients suffering PONV have a pattern of peripheral serotonin release different (increased) from those who do not present this complication. This hypothesis was tested by the measurement of perioperative urinary levels of 5-hydroxyindoacetic acid (5-HIAA), the principal metabolite of serotonin, in outpatients scheduled for laparoscopic tubal ligation.

Methods

Hospital Ethics Committee approval was obtained and each patient gave written informed consent to the study. All women with an ASA physical status I or II undergoing outpatient laparoscopic tubal ligation were invited to participate in this prospective, cumulative, case-control study. Exclusion criteria were pregnancy, breast-feeding, and use of an antiemetic drug within 24 hr before surgery. The study intended to compare the perioperative urinary concentrations of 5-HIAA obtained in 15 women with severe PONV (PONV group) to those of women who were totally free of PONV during a 24-hr observation period (asymptomatic group).

The following anesthetic protocol was used. Patients received no premedication. Anesthesia was induced with sufentanil 0.1–0.3 $\mu g \cdot kg^{-1}$ and thiopental 3–5 $mg \cdot kg^{-1}$. The trachea was intubated with the help of rocuronium bromide 0.45–1 $mg \cdot kg^{-1}$. An orogastric tube was inserted in all patients. Isoflurane (expired fraction 0.6–1%) in a mixture of N_2O/O_2 (60/40%) was used for maintenance. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine 40–70 $\mu g \cdot kg^{-1}$ and glycopyrrolate 7–15 $\mu g \cdot kg^{-1}$ if needed. The endotracheal tube was removed when the patient was fully awake. Postoperative pain was controlled with ketorolac 30–60 mg *iv*. If patients remained in pain, meperidine 0.5–1 $mg \cdot kg^{-1}$ *im* was given. Episodes of nausea and vomiting were treated first by metoclopramide 10 mg *iv*. If symptoms persisted, droperidol 0.625–1.25 mg *iv* was then given, followed by ondansetron 4 mg *iv* if required.

Two urinary samples were obtained from each patient. A preoperative sample was obtained by spontaneous micturition just before surgery and completed by bladder catheterization at the time of anesthesia induction. The postoperative sample was obtained by spontaneous micturition before discharge from the ambulatory surgery unit (ASU). Urine samples were diluted with 0.1 M perchloric acid (1:50 vol/vol), mixed and centrifugated. An aliquot (2 mL) of this solution was immediately frozen at -30°C for ulterior assay. Urinary 5-HIAA concentration was measured by high performance liquid chromatography with electrochemical detection.[6] For each sample, urinary creatinine concentration was also measured using a Synchron LX System® which determines creatinine concentration in urine by the Jaffe rate method (Beckman Coulter, Fullerton, CA, USA). To compensate for differences in urine concentration during the perioperative period, the urinary 5-HIAA concentration was corrected for urinary creatinine concentration.

The following data were collected in the postanesthesia care unit (PACU) and the ASU: episodes of nausea and their severity (light, moderate, severe), episodes of retching or vomiting and episodes of arte-

TABLE I Patient characteristics

	PONV	*Asymptomatic*
Number of patients	15	15
Age (yr)	33.4 ± 6.4	32.7 ± 5.7
ASA physical status (I/II)	14/1	15/0
Weight (kg)	60.8 ± 8.8	62.1 ± 12.9
Height (cm)	161.6 ± 8.9	162.8 ± 6.7
History of motion sickness (%)	13.3	6.7
History of PONV (%)	40	20

Data are reported as number, mean ± SD or percentage where applicable. P = ns between groups for all variables; PONV = postoperative nausea and vomiting.

TABLE II

	PONV	*Asymptomatic*
Duration of anesthesia (min)	41.8 ± 7.7	41.6 ± 6.4
Intraoperative sufentanil (μg)	16.0 ± 3.9	15.5 ± 3.0
Neuromuscular block reversal (%)	66.7	86.7
Meperidine use in the PACU (%)	60.0	66.7

Data are reported as mean ± SD or percentage. P = ns between groups for all variables; PONV = postoperative nausea and vomiting; PACU = postanesthesia care unit.

rial hypotension (systolic blood pressure lower than 90 mmHg). Data on the use of analgesic and antiemetic drugs were also collected. The following day, during a telephone interview, patients were questioned about the occurrence of nausea and vomiting after discharge.

All data were collected either by a research nurse or one of the investigators (P.C.N.). The laboratory personnel who performed the 5-HIAA and creatinine assays were unaware of the purpose of the study. Using type I (α) and type II (ß) errors of 0.05 and 0.2 respectively, and considering a twofold increase of postoperative urinary 5HIAA:creatinine ratio in the PONV group compared to the asymptomatic group as the minimal relevant difference,[7] we calculated that a sample of 15 patients per group would be necessary. The student t test and the alternate Welch t test for paired and unpaired data were used for parametric data. Fisher's exact test was used for proportions. All tests were two-tailed and $P < 0.05$ was considered significant. Results are reported as mean with 95% confidence interval (CI 95%).

Results

Forty-eight consecutive patients were enrolled in the study. Fifteen were totally free of emetic symptoms (asymptomatic group). Among all patients with PONV (n = 33), the 15 patients who presented the most severe symptoms were retained for the PONV group. These included 12 patients with both nausea and vomiting and three patients with the highest nausea score but without vomiting. The remaining 18 patients suffered only mild or moderate nausea. The PONV group and the asymptomatic group were comparable for age, ASA physical status, weight, height, and previous history of motion sickness or PONV (Table I). The duration of anesthesia, the dose of intraoperative sufentanil received, and the number of patients who received neuromuscular blockade reversal agents at the end of anesthesia or meperidine in the PACU were also comparable for the two groups (Table II). No episode of arterial hypotension was observed during the postoperative period.

Postoperative urinary samples were obtained 235 min (CI 95%, 184.6–285.4) after induction of anesthesia in the asymptomatic group and 266 min (CI 95%, 226.7–305.3) in the PONV group (P = 0.31). There was no difference within each group between the preoperative and the postoperative 5-HIAA:creatinine ratios (Figure). The preoperative and postoperative 5-HIAA:creatinine ratios were 6.9 ng·μg^{-1} (CI 95%, 2.7–11.0) and 5.9 ng·μg^{-1} (CI 95%, 2.4–9.4) respectively in the asymptomatic group (P = 0.69), and were 5.1 ng·μg^{-1} (CI 95%, 2.5–7.7) and 5.6 ng·μg^{-1} (CI 95%, 3.4–7.7) respectively in the PONV group (P = 0.75). There was also no difference between groups in the variation of 5-HIAA:creatinine ratios from the preoperative sampling to the postoperative sampling (P = 0.21).

Discussion

In this study, the occurrence of PONV following laparoscopic tubal ligation could not be related to an increased urinary excretion of 5-HIAA, the main metabolite of serotonin. The 5-HIAA:creatinine urinary concentration remained low throughout the perioperative period, both in patients who presented severe PONV and in patients who remained totally free of emetic symptoms. These results do not support the hypothesis that patients suffering PONV have a pattern of peripheral serotonin release different from those who do not present this complication.

Our results suggest that the pathophysiology of PONV is different from cisplatin-induced nausea and vomiting. Cubeddu *et al.* have shown that an increase of 5-HIAA: creatinine ratio from 7.0 to 17.5 ng·μg^{-1} four to six hours after administration of cisplatin correlated with a significant increase in the incidence of nausea and vomiting.[7] In the same study, prophylactic administration of ondansetron, a selective antagonist of 5-HT$_3$ receptor, markedly decreased the incidence of nausea and vomiting. These data are consistent with a

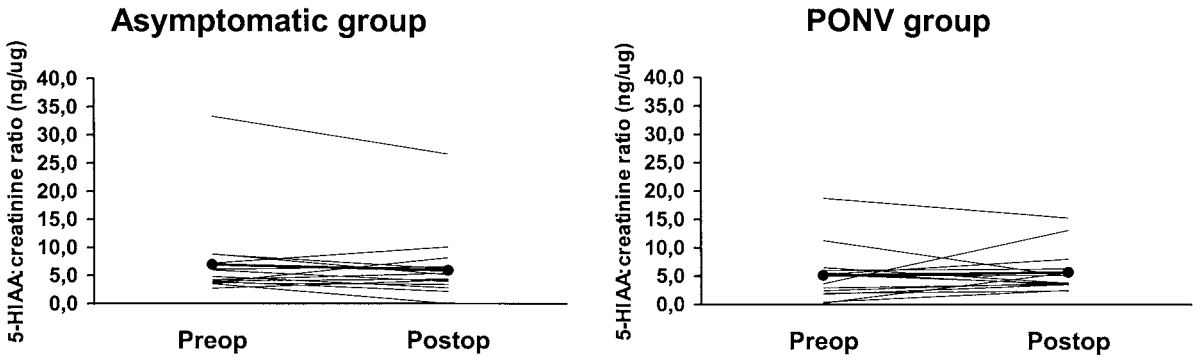

FIGURE Individual preoperative and postoperative 5-HIAA:creatinine ratios in asymptomatic and PONV groups. Dark lines indicate mean preoperative and postoperative values for each group (P = ns, paired t test).

peripheral mechanism involving serotonin in the gastrointestinal mucosa as a mediator of emesis. Our results, along with the limited efficacy of 5-HT_3 receptor antagonists in PONV compared to the almost complete response in cisplatin-induced nausea and vomiting, suggest that this pathway is not an important mechanism in the production of PONV.[7,11,12] However, it cannot be excluded that a perioperative serotonin increase might occur in the central nervous system and have a role in the pathophysiology of PONV.

Some have suggested that compression of the gastrointestinal mucosa by the surgical pneumoperitoneum could induce intestinal ischemia and trigger a serotonin release that could lead to PONV.[12] On the other hand, Borgeat *et al.* reported recently that laparoscopy and laparotomy were associated with similar perioperative 5-HIAA urinary levels, and found no difference between patients presenting PONV and those without symptom.[13] However the anesthesia regimen was based on propofol, which has been shown to decrease plasma serotonin activity.[14] The present study yielded similar results with an anesthetic protocol, both for induction and maintenance, usually associated with a higher incidence of PONV.

A selection bias was introduced voluntarily when patients with the more severe symptoms were chosen to form the PONV group. With respect to the study hypothesis, this selection bias was considered desirable. This selection bias allowed the comparison of two well differentiated groups according to their PONV status, strengthening interpretation of the data. The fact that both the asymptomatic patients and those with the more severe symptoms had a similar serotonin release pattern reinforces the conclusion that, in the population studied, PONV is not related to a peripheral release of serotonin. It must be stated that our results may not necessarily apply to other populations. Indeed it cannot be ruled out that different surgical procedures might result in different serotonin release patterns.

In this study, as well as in others, serotonin could not be measured directly. Serotonin released from the gastrointestinal mucosa has a high hepatic extraction ratio and is almost entirely transformed to 5-HIAA during its hepatic first pass. Therefore, plasma serotonin half-life is extremely short and the measurement of its urinary metabolite 5-HIAA is the standard method to assess plasma serotonin activity. In order to compensate for any difference in hydration and urine concentration during the perioperative period, a correction factor using urinary creatinine concentrations must be applied. Cubbedu *et al.* used a similar protocol to study chemotherapy-induced emesis.[3,7] In the present study, the sampling protocol used covered the intraoperative and the postoperative periods in the PACU and the ASU. These are periods when serotonin release might be expected. However only two urinary samples were obtained during the observation period. Ideally, sequential urinary samples should have been collected. Although a 5-HIAA urinary peak may have been missed due to the limited number of samples, it is unlikely that a large increase, of the same magnitude as that observed with cisplatin, was missed.

In conclusion, PONV after laparoscopic tubal ligation was not associated with an increased urinary excretion of 5-HIAA. Patients with PONV present a peripheral serotonin release pattern similar to asymptomatic patients. Our study suggests that PONV is not related to a peripheral release of serotonin.

Acknowledgements

The authors wish to thank Diane Martineau RN, Gilles Turcotte MD, and Line Godin for their assistance. This study was partially funded by the Direction de la Recherche du Centre hospitalier affilié universitaire de Québec.

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