Regional Anesthesia and Pain

Prophylactic *iv* ondansetron reduces nausea, vomiting and pruritus following epidural morphine for postoperative pain control

[L'administration prophylactique d'ondansétron iv réduit les nausées, les vomissements et le prurit qui suivent l'administration péridurale de morphine analgésique postopératoire]

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Purpose: To evaluate the prophylactic effect of ondansetron on nausea and vomiting following epidural morphine for postoperative pain control.

Methods: Seventy women (n = 35 in each group) undergoing abdominal total hysterectomy under epidural anesthesia were enrolled in this randomized, double-blinded, and placebo-controlled study. At the end of surgery, all patients received epidural morphine 3 mg for postoperative pain relief. Before morphine injection, the ondansetron group received *iv* ondansetron 4 mg, whereas the placebo group received *iv* saline.

Results: Patients in the ondansetron group reported a lower frequency of total postoperative nausea and vomiting (22%) and lower frequency of rescue antiemetic request (12%) than those in the placebo group (52% and 39%, respectively; $P < 0.05$). In addition, ondansetron was associated with a reduced incidence of pruritus following epidural morphine (28% *vs* 58%; $P < 0.05$).

Conclusion: We conclude that *iv* ondansetron 4 mg is effective in the prevention of nausea, vomiting, and pruritus following epidural morphine for postoperative pain control.

Objectif : *Évaluer l'effet prophylactique de l'ondansétron sur les nausées et les vomissements qui suivent l'administration péridurale de morphine analgésique postopératoire.*

Méthode : *Soixante-dix femmes (n = 35 dans chaque groupe) devant subir une hystérectomie abdominale totale sous anesthésie péridurale ont participé à l'étude randomisée, en double aveugle et contrôlée contre placebo. À la fin de l'opération, toutes les patientes ont reçu une analgésie péridurale avec 3 mg de morphine. Avant l'injection de la morphine, 4 mg d'ondansétron iv ont été administrés dans le groupe ondansétron et une solution saline dans le groupe placebo.*

Résultats : *Les patientes ayant reçu l'ondansétron ont présenté une plus faible fréquence de nausées et de vomissements postopératoires totaux (22 %) et ont demandé moins d'antiémétique de secours (12 %), comparées aux femmes du groupe placebo (52 % et 39 %, respectivement ; P < 0,05). Aussi, l'ondansétron a été associé à une incidence réduite de prurit après l'administration péridurale de morphine (28 % vs 58 % ; P < 0,05).*

Conclusion : *L'administration iv de 4 mg d'ondansétron est efficace pour prévenir les nausées, les vomissements et le prurit qui suivent l'administration péridurale de morphine analgésique postopératoire.*

ONDANSETRON is a selective 5-hydroxytryptamine subtype 3 (5-HT_3) receptor antagonist that has been introduced into clinical practice as an antiemetic for nausea and vomiting following chemotherapy and radiotherapy, and for postoperative nausea and vomiting (PONV) after general anesthesia.[1–5] Its use under these circumstances is both prophylactic and therapeutic. It

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has equivalent efficacy and safety compared with other groups of antiemetics: antihistamines, antidopaminergics, and anticholinergics.[1–5] The recommended dose is 8 mg for nausea and vomiting following chemotherapy and radiotherapy, and 4 mg for the prevention of PONV after general anesthesia.[1–5]

In patients receiving epidural morphine for postoperative pain control, the incidence of nausea and vomiting is frequent (30%–56%).[6–9] Because ondansetron provides a significant antiemetic effect in various conditions,[1–5] it may also be effective in the prevention of nausea and vomiting following epidural morphine for postoperative pain control. However, this remains unclear. The aim of the study was to evaluate the prophylactic effect of *iv* ondansetron 4 mg on nausea and vomiting following epidural morphine for postoperative pain control.

Methods

The protocol was approved by the Hospital Committee for Human Investigation, and informed consent was obtained from each patient. Seventy patients, ASA physical status I or II, 35 to 55 yr old, who were to receive epidural anesthesia for abdominal hysterectomy (with or without oophorectomy) were enrolled in a randomized, double-blinded, and placebo-controlled study. Patients with a history of PONV, motion sickness or gastrointestinal disorders, a major systemic disease (e.g., hypertension, diabetes mellitus, and morbid obesity), contraindications to epidural anesthesia and analgesia, chronic opioid use, or who had received an antiemetic within 48 hr before surgery were excluded. Patients who needed rescue analgesics for pain during surgery were also excluded from the study, and this was considered a failure of epidural catheterization.

Before the study, patients provided detailed medical histories and demographic information, including age, weight, height, time of last menstrual cycle, and drug consumption. All operations took place between 8:00 AM and 2:00 PM. Surgical anesthesia to the T6 dermatome level was provided by 0.3 $mL \cdot kg^{-1}$ lidocaine 2% (with 1:100,000 epinephrine) followed by intermittent injections of 3 mL of lidocaine 2% (with epinephrine) as necessary through an epidural catheter in the L3–4 or L4–5 interspace. During surgery, *iv* midazolam 2.5 to 5 mg were given for sedation; no supplemental analgesic was given.

Before surgery, a randomization table was used to assign patients to one of two groups of 35 patients to receive *iv* ondansetron 4 mg or saline at the end of surgery. The medications were given by *iv* drip (> one minute). One minute later, all patients received 3 mg of preservative-free morphine in 10 mL of isotonic sodium chloride solution through the epidural catheter for postoperative analgesia. Randomization and the identity of the study drugs were blinded from the patients, the anesthesiologists during surgery, and the investigators who collected the postoperative data.

Postoperatively, patients were observed for 24 hr. A team of nurse-anesthetists collected the postoperative data. During the observation period, arterial blood pressure, heart rate, and respiratory rate were monitored every four hours (from 8:00 AM to 10:00 PM).

The occurrence of PONV was recorded. Nausea was defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit. It was assessed while patients were lying still. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. For the purpose of data collection, retching (the same as vomiting but without expulsion of gastric contents) was considered vomiting. Rescue antiemetics (*iv* metoclopramide 10 mg) were given when vomiting occurred, or at the patient's request for intolerable nausea. The treatment was repeated if necessary with an interval of one hour.

Wound pain at rest was assessed with a 10-cm visual analogue scale (VAS; 0 = no pain to 10 = most severe pain) score. To ensure adequate pain relief in all patients, *iv* ketorolac 30 mg (a potent nonsteroidal anti-inflammatory drug) was given every eight hours. The postoperative data (e.g., nausea, vomiting, and pain) were collected every four hours (between 8:00 AM and 10:00 PM) by direct questioning by a team of nurse-anesthetists.

Pruritus was assessed by using a three-point ordinal scale (0 = none, 1 = pruritus but only in a small area of the body, 2 = generalized pruritus).[8,9] Pruritus was treated with im diphenhydramine (20 mg every four hours as needed).[8,9]

Sample size was predetermined by using a power analysis based on the assumptions that (a) the total frequency of nausea and vomiting in the saline group would be 50%,[8,9] (b) a 30% reduction in the total frequency of PONV (from 50% to 20%) in the ondansetron groups would be of clinical relevance, and (c) $\alpha = 0.05$ and $ß = 0.2$.[10] The analysis showed that 35 patients per group would be sufficient. Parametric data were analyzed by using an unpaired t test; the frequencies of nausea, vomiting, and pruritus were analyzed by using a χ^2 test. The VAS data were analyzed by using the Mann-Whitney U test. A P value < 0.05 was considered significant.

Results

Of the 70 patients enrolled in the study, five were withdrawn for the following reasons: failure of the epidural catheterization during surgery ($n = 3$) or incomplete

TABLE I Patient demographics and operative characteristics

	Ondansetron 4 mg (n = 32)	*Saline (n = 33)*
Age (yr)	42 ± 6	43 ± 7
Weight (kg)	60 ± 8	61 ± 9
Height (cm)	156 ± 3	158 ± 3
Last menstrual cycle (days)(*n*)*	14 ± 4(26)	15 ± 3(24)
Abdominal total hysterectomy (with/without oophorectomy)	11/21	12/21
Duration of operation (min)	120±22	124±20
Duration of anesthesia (min)	141±23	145±25
Total lidocaine administered (mg) (with 1:100,000 epinephrine)	540(420–580)	540(440–600)
Total midazolam administered (mg)	4.2 ± 0.8	4.0 ± 0.7

Values are number of patients, mean ± SD, or median (range).
*Patients who experienced menopause were excluded.

TABLE II Postoperative wound pain at rest (VAS scores)

	Ondansetron 4 mg	*Saline*
Time (hr)		
4	2.5 ± 2.1	2.4 ± 2.2
8	2.5 ± 1.8	2.8 ± 1.8
20	2.6 ± 0.8	2.5 ± 0.8
24	2.9 ± 1.6	3.2 ± 1.5

Values are mean ± SD; VAS = visual analogue scale.

TABLE III The Evaluation of postoperative nausea and vomiting following epidural morphine

Variables	*Ondansetron 4 mg (n = 32*	*Saline (n = 33)*
Nausea/vomiting		
Nausea alone	4	11
Nausea with vomiting	3	6
Total	7 (22%)*	17 (52%)
Rescue antiemetics	4 (12%)*	13 (39%)

Values are number of patients. Rescue antiemetics (*iv* metoclopramide 10 mg) were given if vomiting occurred or at the patient's request for intolerable nausea. *$P < 0.05$, when compared with the saline group using a χ^2 test.

TABLE IV Frequencies of pruritus following epidural morphine

	Ondansetron 4 mg (n = 32)	*Saline (n = 33)*
Pruritus		
Pruritus in a small area of the body	6	14
Generalized pruritus	3	5
Total	9 (28%)*	19 (58%)

Values are number of patients. *$P < 0.05$ when compared with the saline group using a χ^2 test.

data collection ($n = 2$). Therefore, 65 patients completed the trial. There were no differences between groups with respect to age, weight, height, last menstrual cycle, type of surgery, duration of surgery and anesthesia, total lidocaine administered, and total midazolam administered (Table I). In addition, there were no differences between groups with respect to blood pressure, heart rate, and respiratory rate.

Postoperative wound pain (VAS) scores are reported in Table II. All patients in our study received both epidural morphine and *iv* ketorolac for the prevention of postoperative pain. Pain scores were less than 5 in all patients. No significant differences were found in pain scores between groups. Patients who received prophylactic ondansetron 4 mg reported a lower frequency of total PONV (22%) and a lower frequency of rescue antiemetic request (12%) than those who received placebo (52% and 39%, respectively, $P < 0.05$; Table III). Ondansetron was also associated with a reduced incidence of pruritus following epidural morphine (Table IV). The total frequency of pruritus in the ondansetron group (28%) was lower than that in the placebo group (58%; $P < 0.05$).

Discussion

Epidural morphine is an effective means to control postoperative pain. However, side effects such as nausea and vomiting occur frequently.[6–9] In the current study, 52% of patients in the control group reported PONV. After prophylactic *iv* ondansetron 4 mg, the frequency of PONV was significantly decreased to 22%. Prophylactic *iv* ondansetron effectively decreases PONV following epidural morphine for postoperative pain control. In our study, we questioned whether ondansetron has a central antiemetic effect, therefore a model of epidural morphine was used. Our results suggest that ondansetron should have a central antiemetic effect.

Ondansetron is a 5-HT_3-receptor antagonist. 5-HT_3 receptors are widely distributed peripherally in the gastrointestinal tract and centrally in the area postrema (chemoreceptor trigger zone), nucleus tractus solitarius, nucleus dorsalis nervi vagi, etc.[1–5] 5-HT_3 receptor antagonists may exert their antiemetic action through these receptors. It has been suggested that epidural morphine exerts its emetic action via the activation of opioid receptors in the chemoreceptor trigger zone, following its cephalad migration.[6–9] Ondansetron may exert its antiemetic action through binding to the central 5-HT_3 receptors system. In addition to 5-HT_3 receptor binding, ondansetron also binds at μ-opioid receptors as an antagonist.[1–3,11,12] Since the μ-opioid receptor system is also involved in

the regulation of epidural morphine-related nausea and vomiting,[6,7] ondansetron may also exert its antiemetic action at this level.

Ondansetron provides a significant preventive antiemetic effect in various conditions.[1–5] Commonly-used doses range between 4 and 8 mg *iv*.[1–5] In our study, a single 4-mg dose of ondansetron was used. Although this might not be the optimal dose, 4 mg of ondansetron significantly prevented nausea and vomiting associated with epidural morphine. The optimal dose of ondansetron in the prevention of nausea and vomiting associated with epidural morphine requires further evaluation.

The study was designed to study PONV, however, we also found that prophylactic ondansetron was associated with a reduction in the incidence of pruritus after epidural morphine. This was a secondary objective of the trial and is reported with due caution. Pruritus is a well-known side effect after epidural morphine.[6,7] This symptom typically spreads rostrally from the trunk to the face. The precise cause of pruritus is not clear but the most convincing hypothesis remains that pruritus is caused by a direct, excitatory effect of morphine on the dorsal horn of the spinal cord and the trigeminal nuclei by the cephalad migration of morphine following its epidural administration.[6,7,13] Since both the 5-HT_3 and μ-opioid receptor systems in the central nervous system are involved in the regulation of pruritus,[1–3,6,7,14–16] ondansetron may exert its anti-pruritic action through one or both of these receptor systems.

In conclusion, *iv* ondansetron 4 mg is effective in the prevention of nausea and vomiting following epidural morphine for postoperative pain control. In addition, we noted that ondansetron reduces the incidence of epidural morphine-related pruritus.

References

1 *Wolf H.* Preclinical and clinical pharmacology of the 5-HT_3 receptor antagonists. Scand J Rheumatol 2000; 29(Suppl): 37–45.

2 *Tyers MB.* Pharmacology and preclinical antiemetic properties of ondansetron. Semin Oncol 1992; 19(Suppl 10): 1–8.

3 *Cunningham RS.* 5-HT_3-receptor antagonists: a review of pharmacology and clinical efficacy. Oncol Nurs Forum 1997; 24: 33–40.

4 *Gregory RE, Ettinger DS.* 5-HT_3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998; 55: 173–89.

5 *Maranzano E.* Radiation-induced emesis: a problem with many open questions. Tumori 2001; 87: 213–8.

6 *Chaney MA.* Side effects of intrathecal and epidural opioids. Can J Anaesth 1995; 42: 891–903.

7 *Choi JH, Lee J, Choi JH, Bishop MJ.* Epidural naloxone reduces pruritus and nausea without affecting analgesia by epidural morphine in bupivacaine. Can J Anesth 2000; 47: 33–7.

8 *Ho ST, Wang JJ, Tzeng JI, Liu HS, Ger LP, Liaw WJ.* Dexamethasone for preventing nausea and vomiting associated with epidural morphine: a dose-ranging study. Anesth Analg 2001; 92: 745–8.

9 *Tzeng JI, Wang JJ, Ho ST, Tang CS, Liu YC, Lee SC.* Dexamethasone for prophylaxis of nausea and vomiting after epidural morphine for post-caesarean section analgesia: comparison of droperidol and saline. Br J Anaesth 2000; 85: 865–8.

10 *Lerman J.* Study design in clinical research: sample size estimation and power analysis. Can J Anaesth 1996; 43: 184–91.

11 *Higgins GA, Kilpatrick GJ, Bunce KT, Jones BJ, Tyers MB.* 5-HT_3 receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. Br J Pharmacol 1989; 97: 247–55.

12 *Ye JH, Ponnudurai R, Schaefer R.* Ondansetron: a selective 5-HT_3 receptor antagonist and its applications in CNS-related disorders. CNS Drug Reviews 2001; 7: 199–213.

13 *Ballantyne JC, Loach AB, Carr DB.* Itching after epidural and spinal opiates. Pain 1988; 33: 149–60.

14 *Charuluxananan S, Somboonviboon W, Kyokong O, Nimcharoendee K.* Ondansetron for treatment of intrathecal morphine-induced pruritus after cesarean delivery. Reg Anesth Pain Med 2000; 25: 535–9.

15 *Yeh HM, Chen LK, Lin CJ, et al.* Prophylactic intravenous ondansetron reduces the incidence of intrathecal morphine-induced pruritus in patients undergoing cesarean delivery. Anesth Analg 2000; 91: 172–5.

16 *Borgeat A, Stirnemann HR.* Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. Anesthesiology 1999; 90: 432–6.