The Prophylactic Effect of Tropisetron on Epidural Morphine-Related Nausea and Vomiting: A Comparison of Dexamethasone with Saline

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Tropisetron is a 5-hydroxytryptamine subtype 3 receptor antagonist that is primarily used in the prevention of chemotherapy-induced nausea and vomiting. We evaluated the prophylactic effect of tropisetron on postoperative nausea and vomiting associated with epidural morphine. Dexamethasone and saline served as controls. One-hundred twenty women ($n = 40$ in each of three groups) undergoing abdominal total hysterectomy under epidural anesthesia were enrolled in this randomized, double-blinded, and placebo-controlled study. At the end of surgery, Group 1 received IV tropisetron 5 mg, whereas Groups 2 and 3 received dexamethasone 5 mg and saline, respectively. We found that tropisetron did not significantly reduce the occurrence of nausea and vomiting associated with epidural morphine. Dexamethasone, however, reduced the total incidence of nausea and vomiting from 59% to 21% ($P < 0.01$) and the percentage of patients requiring rescue antiemetic from 38% to 13% ($P < 0.05$). We conclude that IV tropisetron 5 mg did not prevent the occurrence of postoperative nausea and vomiting associated with epidural morphine. IV dexamethasone 5 mg was effective for this purpose.

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Tropisetron is a 5-hydroxytryptamine (5-HT_3) receptor antagonist that is primarily used in the prevention of chemotherapy-induced nausea and vomiting (1–3). Its elimination half-life (8–12 h) is longer than that of other 5-HT_3 antagonists (e.g., ondansetron, 3.2–3.7 h; granisetron, 3–4 h) (4–6). It is also used in the prevention of radiotherapy-induced emesis and postoperative nausea and vomiting (PONV) after general anesthesia. The recommended dose is 5 mg for chemotherapy- and radiotherapy-related nausea and vomiting and 2 mg for PONV after general anesthesia (1–4).

In patients receiving epidural morphine for postoperative pain control, the incidence of nausea and vomiting is frequent (30%–62%) (7,8). Because tropisetron provides a significant antiemetic effect in various conditions, it may also be effective in the prevention of epidural morphine-related nausea and vomiting. However, this has never been tested. The aim of the study was to evaluate the prophylactic effect on PONV of tropisetron 5 mg, dexamethasone, and saline in women who after abdominal surgery received epidural morphine for postoperative pain relief.

Methods

The protocol was approved by the Hospital Committee for Human Investigation, and previous informed consent was obtained from each patient. One-hundred twenty patients, ASA physical status I or II, 35–55 yr old, who were approved 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, or major systemic diseases (e.g., hypertension, diabetes mellitus, and morbid obesity) or who had received an antiemetic within 48 h before surgery were excluded. Patients who needed rescue analgesic for pain during surgery were also excluded from the study, and this was considered a failure of epidural catheterization.

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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/kg 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 2.5–5 mg was given for sedation; no supplemental analgesic was given.

Before surgery, a randomization table was used to assign patients to one of three groups of 40 patients to receive IV tropisetron 5 mg, dexamethasone 5 mg, or saline at the end of surgery. The medications (5 mL) were given by slow IV push (>30 s). One minute after injection, all patients received 3 mg of preservative-free morphine in 10 mL of isotonic sodium chloride solution through the epidural catheter for postoperative analgesia. The randomized process 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 h. A team of nurse-anesthetists collected the postoperative data. During the observation period, arterial blood pressure, heart rate, and respiratory rate were monitored every 4 h (from 8:00 AM to 10:00 PM).

PONV was evaluated by using the following variables: the incidences, the number of episodes of vomiting, and rescue antiemetics. 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. A vomiting episode was defined as the events of vomiting that occurred in a rapid sequence (<1 min between events). If events of vomiting were separated by more than 1 min, they were considered to be separate episodes (9,10). Rescue antiemetics (IV droperidol 1.25 mg) were given at patient request. The treatment was repeated if necessary.

Postoperative wound pain at rest was assessed with a 10-cm visual analog scale (VAS; 0 = no pain to 10 = most severe pain) score. When patients complained of excessive pain and requested analgesia, IM diclofenac 75 mg (every 12 h) was given (11). The postoperative data (e.g., nausea, vomiting, and pain) were collected every 4 h (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) (10,12). Pruritus was treated with IM diphenhydramine (20 mg every 4 h as needed) (10,12). The occurrence of side effects related to the use of tropisetron, such as headache, was also evaluated. Headache was assessed as mild, moderate, or severe.

Sample size was predetermined by using a power analysis based on the assumptions that (a) the total incidence of PONV in the Saline group would be 56% (9,10), (b) a 40% reduction in the total incidence of PONV (from 56% to 34%) in the treatment groups would be of clinical relevance, and (c) $\alpha = 0.05$ and $\beta = 0.2$ (13). The analysis showed that 40 patients per group would be sufficient. A series of one-way analyses of variance was conducted to examine differences among the three groups with respect to parametric variables. If a significant difference was found, the Bonferroni *t*-test was used to detect the intergroup differences. The Kruskal-Wallis test was used to determine differences among the three groups with respect to nonparametric variables, followed by the Mann-Whitney ranked sum test for intergroup differences. Categorical variables were analyzed by using a series of 3×2 χ^2 tests to determine differences among the three groups, followed by a 2×2 χ^2 test or Fisher's exact test, as appropriate, for intergroup differences. All follow-up analyses were corrected for the number of simultaneous contracts by using Bonferroni adjustments. A P value <0.05 was considered significant.

Results

Of the 120 patients enrolled in the study, 6 were withdrawn for one of the following reasons: failure of the epidural catheterization during surgery ($n = 4$) or incomplete data collection ($n = 2$). Therefore, 114 patients completed the trial. There were no differences among 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 1). All patients reported low VAS pain scores and a modest request for rescue analgesic. These variables were not different in the three groups (Table 2).

Patients who received dexamethasone 5 mg were different from those who received tropisetron 5 mg and saline in the following variables: the total incidence of PONV ($P < 0.01$) and the percentage of patients requiring rescue antiemetics ($P < 0.05$) (Table 3). The differences between the Tropisetron and Saline groups were not significant.

The incidences of pruritus among groups were not significantly different: 47% in the Tropisetron group, 44% in the Dexamethasone group, and 49% in the Saline group (Table 4). Twenty-six percent (10 of 38) of patients in the Tropisetron group reported headache ($P < 0.05$ versus Saline group) (Table 4).

Table 1. Patient Demographics and Operative Characteristics

Variable	Tropisetron 5 mg (n = 38)	Dexamethasone 5 mg (n = 39)	Saline (n = 37)
Age (yr)	45 ± 7	43 ± 7	43 ± 6
Weight (kg)	57 ± 6	56 ± 6	56 ± 7
Height (cm)	158 ± 3	156 ± 3	157 ± 3
Last menstrual cycle, days, mean ± SD (n)[a]	14 ± 4 (26)	16 ± 4 (25)	15 ± 3 (24)
Abdominal total hysterectomy (with/without oophorectomy)	12/26	14/25	14/23
Duration of operation (min)	120 ± 23	125 ± 26	124 ± 25
Duration of anesthesia (min)	143 ± 25	152 ± 28	148 ± 27
Total lidocaine administered (mg) (with 1:100,000 epinephrine)	540 (420–580)	560 (440–620)	540 (440–600)
Total midazolam administered (mg)	4.2 ± 0.9	4.2 ± 0.8	4.3 ± 0.8

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

Table 2. Postoperative Wound Pain at Rest (VAS Scores) and Percentage of Patients Requiring Rescue Analgesic

Variable	Tropisetron 5 mg	Dexamethasone 5 mg	Saline
Time (h)			
4	2.9 ± 1.9	2.7 ± 1.2	2.8 ± 0.9
8	2.3 ± 1.2	2.2 ± 1.2	2.6 ± 1.4
20	2.4 ± 0.9	2.2 ± 0.9	2.4 ± 0.8
24	2.1 ± 0.8	2.1 ± 0.7	2.2 ± 0.8
Patients requiring rescue analgesic	12/38	10/39	14/37

Values are mean ± SD or number of patients.
VAS = visual analog scale.

Table 3. The Evaluation of Nausea and Vomiting Associated with Epidural Morphine

Variable	Tropisetron 5 mg (n = 38)	Dexamethasone 5 mg (n = 39)	Saline (n = 37)
Nausea/vomiting			
Nausea alone	11 (29)	5 (13)	12 (32)
Nausea with vomiting	9 (24)	3 (8)	10 (27)
Total	20 (53)	8 (21)*	22 (59)
Vomiting episodes			
0–4 times	4 (11)	2 (5)	4 (11)
>4 times	5 (13)	1 (3)	6 (16)
Rescue antiemetics	14 (37)	5 (13)†	14 (38)

Values are number of patients (%).
Rescue antiemetics (IV droperidol 1.25 mg) were given if vomiting occurred or at the patient's request for intolerable nausea.
* $P < 0.01$; † when compared with the Saline and Tropisetron groups by using a 3 × 2 χ^2 test followed by a 2 × 2 χ^2 test or Fisher's exact test, as appropriate. The differences between the Tropisetron and Saline groups were not significant.

Table 4. Incidence of Pruritus and Headache

	Tropisetron 5 mg (n = 38)	Dexamethasone 5 mg (n = 39)	Saline (n = 37)
Pruritus			
Pruritus in a small area of the body	12 (32)	11 (28)	11 (30)
Generalized pruritus	6 (16)	6 (15)	7 (19)
Total	18 (47)	17 (44)	18 (49)
Diphenhydramine for pruritus	8 (21)	8 (21)	9 (24)
Headache			
Mild	7 (18)	2 (5)	2 (5)
Moderate	3 (8)	0 (0)	0 (0)
Severe	0 (0)	0 (0)	0 (0)
Total	10 (26)*	2 (5)	2 (5)

Values are number of patients (%).
* $P < 0.05$ when compared with the Saline and Dexamethasone groups by using a 3 × 2 χ^2 test followed by the Fisher's exact test.

Discussion

It is surprising that tropisetron 5 mg did not prevent the occurrence of PONV associated with epidural morphine. Tropisetron is a selective 5-HT_3 receptor antagonist and is effective in the prevention of chemotherapy- and radiotherapy-related emesis and PONV after general anesthesia (1–4); however, it did not prevent the occurrence of PONV associated with epidural morphine. The discrepancies among these results are discussed below.

5-HT_3, or serotonin, is a neurotransmitter that is associated with a variety of clinical disorders, including nausea and vomiting (2–4). 5-HT_3 receptors are widely distributed peripherally in the gastrointestinal tract and centrally in the nucleus tractus solitarius and area postrema (chemoreceptor trigger zone) (1–6,14–16). Approximately 80% of the body's total 5-HT_3 is stored in the enterochromaffin cells of the gastrointestinal tract (2). 5-HT_3 receptor antagonists exert their pharmacologic effects by competitive and selective binding to the 5-HT_3 receptors and thus prevent agonism of the 5-HT_3 receptors by 5-HT_3 (1–6).

Several human studies suggest that emesis caused by chemotherapy and radiotherapy may be due to the release of 5-HT_3 from the enterochromaffin cells of the gastrointestinal tract (2–4). 5-HT_3, once liberated, binds to the 5-HT_3 receptors at the gastrointestinal site; these receptors send impulses via vagal afferents to the nucleus tractus solitarius and then to the vomiting center, which causes emesis (1–4). 5-HT_3 receptor

antagonists are effective for this purpose and are considered most likely to exert their actions through the blockage of the 5-HT_3 receptors from the peripheral site at the gastrointestinal tract, thus preventing the occurrence of nausea and vomiting (1–6).

For the prevention of PONV after general anesthesia, all 5-HT_3 antagonists are also effective. Although 5-HT_3 antagonists may bind to the 5-HT_3 receptors located centrally or peripherally (1–6,14–16), the exact mechanism by which 5-HT_3 antagonists exert their actions in the prevention of PONV after general anesthesia has not been elucidated.

In this study, we questioned whether tropisetron, a 5-HT_3 antagonist, has a significant central antiemetic action. Epidural morphine-related PONV was studied. It has been suggested that epidural morphine exerts an emetic action via the activation of opioid receptors in the chemoreceptor trigger zone, caused by cephalad migration of morphine. Therefore, if tropisetron has a significant central antiemetic action, it may effectively prevent the occurrence of PONV after epidural morphine. However, we did not find this, suggesting that tropisetron does not have a significant central antiemetic effect.

After a review of the literature, we found only two clinical studies that evaluated the central antiemetic effect of 5-HT_3 antagonists (17,18). In these studies, either ondansetron 8 mg twice daily or tropisetron 5 mg once daily were used to prevent the occurrence of PONV after intrathecal morphine (0.3 mg). However, neither ondansetron nor tropisetron was effective for this purpose (17,18).

The dose of tropisetron used in our study was 5 mg. This dose was chosen because it is the dose recommended for prophylaxis of nausea and vomiting in patients receiving potent emetogenic drugs (e.g., cisplatin in chemotherapy) (1–4). For the prevention of PONV after general anesthesia, the recommended dose of tropisetron is smaller (2 mg for adult patients) (1–4).

Tropisetron caused a more frequent incidence of headache (26%) than the other two treatments. In direct comparisons of tropisetron with other 5-HT_3 antagonists, the adverse event profiles of all 5-HT_3 antagonists were very similar (2,3). Headache was the most frequently reported event, with reporting rates of 5%–35% (2,3). However, the exact mechanism of this adverse event was not known.

Dexamethasone, a corticosteroid, is a potent antiemetic drug that exerts its antiemetic action though the blockage of the corticoreceptors in the nucleus tractus solitarius of the central nervous system (19). It is effective in reducing the incidence of emesis in patients undergoing chemotherapy (20,21). It is also effective in reducing the incidence of PONV after general anesthesia and after epidural morphine (9,10,21,22). The minimal effective dose is 5 mg for the prevention of PONV after general anesthesia and after epidural morphine (10,22). Our study is in agreement with this finding.

Tropisetron and dexamethasone did not influence the intensity of surgical pain. Both the severity of pain (VAS) scores and the number of patients requiring rescue analgesia were similar among groups. Tropisetron and dexamethasone did not influence the occurrence of pruritus related to epidural morphine.

In conclusion, IV tropisetron 5 mg did not prevent the occurrence of PONV associated with epidural morphine. IV dexamethasone 5 mg was effective for this purpose.

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