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ORIGINAL ARTICLE

Fosaprepitant versus ondansetron for the prevention of postoperative nausea and vomiting in patients who undergo gynecologic abdominal surgery with patient-controlled epidural analgesia: a prospective, randomized, double-blind study

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Abstract
Purpose Postoperative nausea and vomiting (PONV) is the most common postoperative complication. The postoperative use of opioids is known to increase the incidence. We compared fosaprepitant, a neurokinin-1 (NK1) receptor antagonist, and ondansetron for their preventive effects on PONV in patients who underwent gynecologic abdominal surgery with patient-controlled epidural analgesia.
Methods This prospective, double-blind, randomized study comprised 44 patients who underwent gynecologic abdominal surgery. They were randomly allocated to receive 150 mg intravenous fosaprepitant ($n = 24$; NKI group) or 4 mg ondansetron ($n = 20$; ONS group) before anesthesia, which was maintained with volatile anesthetics, remifentanil, fentanyl, and rocuronium. All patients received postoperative fentanyl by patient-controlled epidural anesthesia. The incidence of nausea and vomiting, complete response rate (i.e., no vomiting and no rescue antiemetic use), rescue antiemetic use, nausea score (0–3), and visual analog scale score (VAS 0–10) for pain were recorded at 2, 24, 48, and 72 h after surgery.
Results No (0 %) patient in the NKI group experienced vomiting after surgery; however, 4–6 (20–30 %) of 20 patients in the ONS group experienced vomiting. This difference was significant at 0–24, 0–48, and 0–72 h. During the study period, no significant differences existed between the NK1 and ONS groups in the incidence of PONV, complete response rate, rescue antiemetic use, nausea score, and VAS score for pain.
Conclusion Compared to ondansetron, fosaprepitant more effectively decreased the incidence of vomiting in patients who underwent gynecologic abdominal surgery with patient-controlled epidural analgesia.

Keywords Fosaprepitant · Gynecologic abdominal surgery · Ondansetron · Patient-controlled epidural analgesia · Postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) are serious adverse effects of anesthesia and surgery. PONV and pain are common symptoms that afflict patients, occurring in approximately 30–50 % patients who receive general anesthesia. The incidence can be as high as 70–80 % in a subset of high-risk patients, i.e., female, nonsmoker, history of PONV, and postoperative opioid administration [1–4].

Even in patients receiving prophylactic treatment for PONV such as ondansetron, a selective 5-hydroxytriptamine type 3 (5-HT3) receptor antagonist, the incidence of PONV on the first operative day is 30–40 % [2, 5, 6]. After major abdominal surgery, patient-controlled epidural analgesia (PCEA) with fentanyl effectively lowers wound pain. PCEA using fentanyl and bupivacaine provides better pain relief after thoracic surgery, compared to intravenous patient-controlled analgesia with morphine [7]; however, opioids such as fentanyl may have a greater risk of PONV.

Fosaprepitant is a water-soluble phosphoryl prodrug for aprepitant, which is converted to aprepitant within 30 min

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of intravenous administration via the action of ubiquitous phosphatases [8]. Aprepitant blocks neurokinin-1 (NK-1) receptors and has an antiemetic effect with a long reaction time. Ondansetron (5HT-3 receptor antagonist) can reduce PONV, but it does not provide complete protection [9]. In two large trials, aprepitant had greater antiemetic activity, compared to ondansetron [10–12]. However, there is no report on the PONV protective efficacy of fosaprepitant after major gynecologic surgery.

Our previous study demonstrated that fosaprepitant is more effective than ondansetron in preventing vomiting in the 0–24 and 0–48 h periods after surgery [13]. Thus, the primary objective of this study was to test the hypothesis that the preventive effects of vomiting were more potent with fosaprepitant than with ondansetron in patients undergoing gynecologic abdominal surgery with PCEA. We designed this prospective, randomized, double-blind trial to assess the efficacy of fosaprepitant and ondansetron in preventing vomiting after major gynecologic surgery.

Methods

This study was approved by the Human Research Ethics Committee of the University of Tokushima (Tokushima, Japan) and registered in a clinical trials database (UMIN000007613). Written informed consent was obtained from all patients, and the study was performed in accordance with the principles outlined in the Declaration of Helsinki.

Patients between the ages of 20 and 80 years with an American Society of Anesthesiologists (ASA) physical status of I–II who were undergoing major gynecologic surgery under combined epidural/general anesthesia were enrolled in this double-blind, randomized, controlled study between June 1 2012 and April 28 2014. Exclusion criteria were an ASA status of III–IV, neuronal disease, abnormal liver and/or renal function, and patients receiving other antiemetic drugs. All patients were questioned about a history of PONV, motion sickness, and smoking status.

The patients were randomly allocated in a double-blind manner using computer software (Quickcalcs; GraphPad Inc., La Jolla, CA, USA). To ensure blinding among the investigators, the randomization schedule was generated by a statistician who was not involved in the clinical study. On the day of surgery, patients were randomized to one of two groups—the NK1 group, which received intravenous fosaprepitant (150 mg), and the ONS group, which received intravenous ondansetron (4 mg). The antiemetics were infused for 30 min before the induction of anesthesia, as indicated in the approved prescribing information for drugs.

A thoracic epidural catheter was placed at either Th10–11 or Th11–12. Anesthesia was induced with remifentanil 0.3–0.5 μg/kg/min, propofol 1–2 mg/kg, and rocuronium 0.8 mg/kg to facilitate endotracheal intubation, and then maintained with volatile anesthetics (sevoflurane 1–2 %) in oxygen with air mixture, remifentanil (0.1–0.5 μg/kg/min), and fentanyl (100 μg). Incremental doses of rocuronium were used as necessary for neuromuscular blockade, which was reversed by sugammadex (2 mg/kg) at the end of surgery. For postoperative pain management, PCEA with an infusion balloon catheter was used. Levobupivacaine (0.125 %) and fentanyl (10 μg/ml) were mixed to a total volume of 100 ml, set at 1 ml bolus and a 20-min lockout interval. A rescue antiemetic (10 mg of metoclopramide) and/or analgesic were administered on patient request.

The incidence of nausea and vomiting, complete response rate (i.e., no vomiting and no rescue antiemetic use), rescue antiemetic use, severity of nausea, and severity of pain were evaluated at 2, 24, 48, and 72 h after surgery. The severity of nausea was estimated by the nausea score (0 = absence of nausea, 1 = mild nausea, 2 = moderate nausea, 3 = severe nausea). The severity of pain was recorded by the visual analog scale (VAS; 0 = no pain to 10 = the worst pain imaginable). Any adverse events that occurred during 72 h after surgery were recorded.

Statistics

All results were analyzed with Statistical Package for Social Sciences (SPSS) software, version 22 (SPSS Inc., Chicago, IL, USA), and were expressed as the mean ± the standard deviation. The means of each group were analyzed by the unpaired Student *t* test. The endpoints and exploratory endpoints, i.e., the incidence of PONV, vomiting, complete response, no vomiting, and no rescue, were analyzed with the chi-squared test or Fisher's exact tests. Mann–Whitney *U* tests were used to analyze nausea scores and VAS pain scores. Kaplan–Meier curves were generated for time to first vomiting during the first 72 h, and log rank tests were used to compare treatments. Statistical significance was set at $P < 0.05$ for all tests.

Before this trial, we estimated the precise sample size based on our previous study that compared fosaprepitant and ondansetron for their preventive effects on vomiting in neurosurgery patients [13]. The study demonstrated that the vomiting rate in the NK1 group was 6 % of 32 patients, whereas the vomiting rate in the ONS group was 50 % of 32 patients. Power analysis performed using a test of equality of the two proportions suggested 19 patients per group would have an 80 % power to detect a 44 % absolute decrease in the incidence of vomiting from 50 % in the ONS group to 6 % in NK1 group at $\alpha = 0.05$.

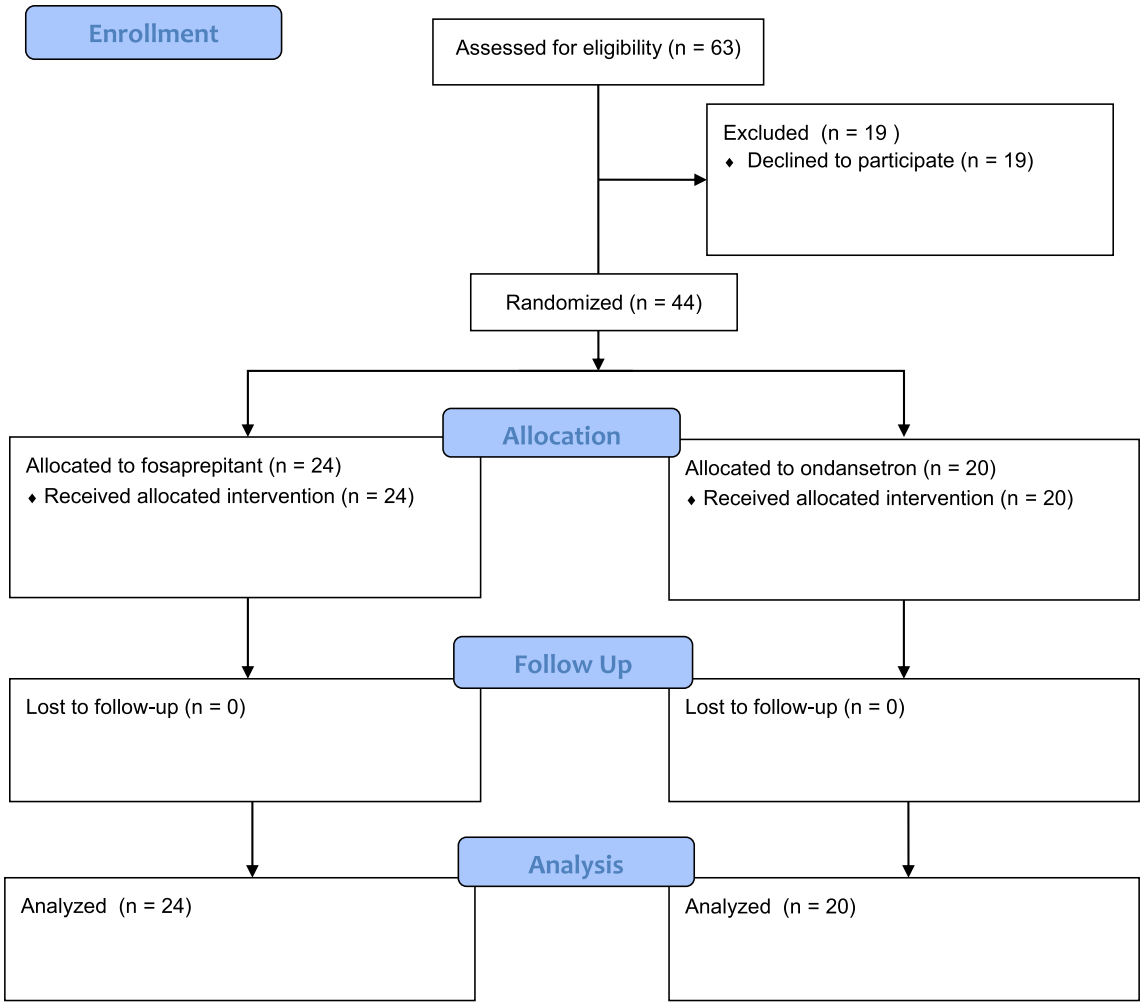

Fig. 1 The CONSORT flow chart of the patient selection process

Results

Of 63 randomized patients, 19 patients refused and 44 patients agreed to participate in this study. All 44 patients received the study medications and completed the trial after being randomized to the NK1 group ($n = 24$) or the ONS group ($n = 20$) (Fig. 1). There were no significant differences in patient demographics or risk factors for PONV (Table 1). The duration of surgery, duration of anesthesia, and intraoperative remifentanil use were not significantly different between the two groups (Table 2).

The PONV incidence, complete response rate, nausea score, and VAS score were not significant between the two groups at all time points, i.e., 0–2, 0–24, 0–48, and 0–72 h, during the 72-h period after surgery. The incidence of vomiting was significantly lower among patients in the NK1 group in comparison to the control group at 0–24 h (0 vs

Table 1 Patient demographics

	NK1 group $n = 24$	ONS group $n = 20$
Patient characteristics		
Age (years)	52 ± 11	52 ± 11
Height (cm)	156 ± 7	156 ± 5
Weight (kg)	54 ± 9	55 ± 10
ASA physical status I/II	11/13	9/11
Risk factor		
Tobacco use	3	2
History of motion sickness/PONV	11	5

The data are presented by the number of patients or by the mean number ± the standard deviation

ASA American Society of Anesthesiologists, *NK1 group* patients who received intravenous fosaprepitant, *ONS group* patients who received intravenous ondansetron, *PONV* postoperative nausea and vomiting

Table 2 Surgery/anesthesia values

	NK1 group	ONS group
Duration of anesthesia (min)	246 ± 94	239 ± 86
Duration of surgery (min)	209 ± 96	198 ± 82
Anesthetics; remifentanil (mg)	2.5 ± 1.0	2.4 ± 1.4
Blood loss (ml)	363 ± 465	291 ± 294
Fluid volume (ml)	2,332 ± 1,150	2,135 ± 968
Type of surgery (*n*)		
ATH	13	10
BSO	5	3
ATH + BSO	6	7

The data are presented by the mean number ± the standard deviation

NK1 group patients who received intravenous fosaprepitant, *ONS group* patients who received intravenous ondansetron, *ATH* abdominal total hysterectomy, *BSO* bilateral salpingo-oophorectomy

20 %, respectively; $P = 0.023$); 0–48 h (0 vs 20 %, respectively; $P = 0.023$); and 0–72 h (0 vs 30 %, respectively; $P = 0.010$) (Table 3).

In the time to event analysis for first vomiting within 72 h, 44 patients were censored at the 72 h time point. Figure 2 shows the Kaplan–Meier plot for time to first vomiting episode. The patients in the NK1 group had a longer time to vomiting compared to the ONS group ($P = 0.004$, based on the log rank test).

Discussion

This study demonstrated that fosaprepitant can effectively decrease vomiting 0–24, 0–48, and 0–72 h after gynecologic abdominal surgery in which postoperative pain is controlled by PCEA using fentanyl. The incidence of PONV, complete response rate, rescue antiemetic use, nausea score, and VAS pain score were not significantly different between the two groups. These results suggest that NK1 blockade using fosaprepitant may be advantageous in suppressing vomiting and may be beneficial if administered before this type of surgery with PCEA.

Because of patient discomfort and the high incidence of PONV, many new drugs for preventing and treating PONV have been developed and studied recently; however, there is no drug that fully prevents and effectively treats PONV. The NK1 antagonist, aprepitant, is used to prevent chemotherapy-induced nausea and vomiting [8, 14]. In 2006, the United States Food and Drug Administration approved aprepitant for the management of PONV; however, the clinical experience with aprepitant remains limited and its role in routine prophylaxis has not been established [15]. Several studies suggest that, compared to ondansetron, orally administered aprepitant has more efficacy in preventing PONV [10–12, 16]. In two large randomized controlled trials, aprepitant was similar to ondansetron in achieving complete response for 24 h after surgery. However, aprepitant was significantly more effective than ondansetron in preventing vomiting at 24 and 48 h after surgery, and in reducing nausea severity during the first 48 h after surgery [10, 11]. Our previous studies also provided evidence that aprepitant effectively reduces the incidence of PONV in patients after laparoscopic gynecologic surgery [17] and that the combination of aprepitant and dexamethasone was more effective than dexamethasone alone in patients with PCEA [18].

The prophylactic administration of fosaprepitant has been approved for acute and delayed chemotherapy-induced nausea and vomiting. Intravenous fosaprepitant (115 mg) was initially considered an alternative to oral aprepitant (125 mg) on day 1 of a 3-day antiemetic regimen [8]. A more recent trial revealed that a single dose of intravenous fosaprepitant (150 mg) on day 1 provided similar protection as that provided by the 3-day oral regimen of aprepitant (125/80/80 mg) in patients scheduled to receive cisplatin chemotherapy [14]. We recently reported that fosaprepitant was more effective in decreasing the incidence of vomiting after neurosurgery [13]. However, to the best of our knowledge, no studies have investigated the preventive effects of fosaprepitant on PONV in high-risk patients who were administered postoperative opioid drugs.

This study has limitations. In the planning stage of this study, the appropriate number of subjects was determined based on the vomiting rate of a previous study. There was no statistical difference in the cumulative incidence of PONV at 72 h (71 % in the NK1 group and 55 % in the ONS group). The study may have been underpowered to detect the incidence of nausea. More subjects should have been enrolled to provide more accurate PONV study results. Additionally, fosaprepitant blockades the central effects of substance P. Substance P is one of the neurotransmitters found in both the central and peripheral nervous systems, and is known to bind to NK1 receptors. NK1 receptor antagonists also work against both peripherally and centrally induced emesis, although 5-HT3 receptor antagonists have questionable efficacy against centrally induced emesis [19, 20]. However, the currently available antiemetics, including fosaprepitant, do not provide complete protection, and the mechanisms of the presentational effects of PONV are not fully understood.

Another possible limitation is the dose and timing of the administered drugs. We administered one dose of fosaprepitant or ondansetron, and we compared outcomes at 2, 24, 48, and 72 h after surgery. Because fosaprepitant has a much longer half-time than ondansetron, it may be asserted that the superiority of fosaprepitant in this study was simply because of its longer half-time. However, the

Table 3 Postoperative values

	NK1 group $n = 24$	ONS group $n = 20$
0–2 h		
PONV	11 (46 %)	4 (20)
Complete response	20 (83 %)	17 (85 %)
Vomiting	0 (0 %)	1 (5 %)
Nausea score (0/1/2/3)[a]	13/5/2/4	16/2/1/1
VAS pain score[b]	1 (0–3)	2 (0–4)
PCEA bolus (episodes/patients)	10/8	10/7
0–24 h		
PONV	17 (71 %)	11 (55 %)
Complete response	17 (71 %)	12 (60 %)
Vomiting	0 (0 %)*	4 (20 %)
Nausea score (0/1/2/3)	15/6/2/1	12/5/1/2
VAS pain score	1 (0–2)	2 (0–3)
PCEA bolus (episodes/patients)	16/10	14/9
0–48 h		
PONV	17 (71 %)	11 (55 %)
Complete response	16 (67 %)	12 (60 %)
Vomiting	0 (0 %)*	5 (25 %)
Nausea score (0/1/2/3)	21/3/0/0	19/1/0/0
VAS pain score	2 (0–4)	3 (0–6)
PCEA bolus (episodes/patients)	16/10	17/9
0–72 h		
PONV	17 (71 %)	11 (55 %)
Complete response	16 (67 %)	11 (55 %)
Vomiting	0 (0 %)*	6 (30 %)
Nausea score (0/1/2/3)	24/0/0/0	17/3/0/0
VAS pain score	2 (0–5)	3 (0–5)
PCEA bolus (episodes/patients)	16/10	17/9

The data are expressed by the number of patients (percentile) or by the median (interquartile range)

NK1 group patients who received intravenous fosaprepitant, *ONS group* patients who received intravenous ondansetron, *PONV* postoperative nausea and vomiting, *PCEA* patient-controlled epidural analgesia bolus

* $P < 0.05$ compared to ONS group

[a] Nausea score (0 absent, 1 mild, 2 moderate, 3 severe)

[b] *VAS pain score* visual analog pain score (0—no pain to 10—the worst pain imaginable)

use of fosaprepitant in patients undergoing major gynecologic surgery with PCEA has not been previously studied. In the current study, we selected the 150-mg dose of fosaprepitant because it is well tolerated and is within the range of previously evaluated fosaprepitant doses [14, 21, 22]. In addition, antiemetics are more efficacious when administered toward the end of surgery rather than at anesthesia induction. Further study is needed to characterize the clinical profile of fosaprepitant in other settings such as the

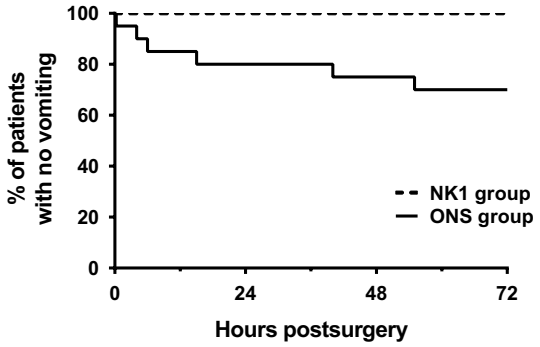

Fig. 2 The Kaplan–Meier curves for the time to the first vomiting episode within 72 h after surgery. *NK1 group* patients who received intravenous fosaprepitant, *ONS group* patients who received intravenous ondansetron

treatment of organized PONV in surgical patients and its potential utility in combination with other antiemetics.

The present study suggested that, compared to ondansetron, fosaprepitant has a superior effect in decreasing the incidence of vomiting during the 0–24 h, 0–48 h, and 0–72 h time periods. However, there were no significant differences between fosaprepitant and ondansetron in PONV.

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