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Original Research Article

A Retrospective Database Analysis Comparing Fosaprepitant with Ondansetron for Preventing Postoperative Vomiting and Nausea in Patients at Moderate to High Risk

Arun Kumar Kulshreshtha[1], Aruna Mahanta[2]

[1]Associate Professor, Department of Anaesthesiology, Krishna Mohan Medical College & Hospital, Pali Dungra, Sonkh Road, Mathura U.P.
[2]Associate Professor, Department of Anaesthesiology, Krishna Mohan Medical College & Hospital, Pali Dungra, Sonkh Road, Mathura U.P.

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Corresponding author: Dr. Aruna Mahanta,
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Abstract

Background: A uncomfortable and dangerous side effect of anesthesia and surgery is postoperative nausea and vomiting (PONV). PONV affects 30–50% of patients undergoing general anesthesia and up to 70–80% of those at high risk for PONV, including female patients, nonsmokers, people who have experienced PONV or motion nausea in the past, and people who are getting opioids postoperatively. PONV affects 30–50% of patients undergoing general anesthesia and up to 70–80% of those at high risk for PONV, including female patients, nonsmokers, people who have experienced PONV or motion nausea in the past, and people who are getting opioids postoperatively. Antiemetics are advised for patients at a moderate to high risk of PONV, according to the "Consensus guidelines for the management of postoperative nausea and vomiting." Additionally, in patients receiving selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists as preventative therapy for PONV, such as ondansetron, up to 30–40% of patients develop PONV on the first postoperative day.

Aim: Chemotherapy-related nausea and vomiting can be avoided with the help of the neurokinin antagonist aprepitant. For the purpose of preventing nausea and vomiting during surgery, we contrasted aprepitant with ondansetron.

Material and Method: This investigation was a randomized, double-blinded clinical control trial. It was completed in a tertiary care hospital's anesthesiology department. Before the study was conducted, it was approved by our institution's ethics and research committee. Between the ages of 18 and 65, all female American Society of Anesthesiologists physical status 1 or 2 patients scheduled for thyroid or breast procedures were enrolled in the study. Those already on antiemetics, steroids, or any other medication known to produce emesis were excluded, as were patients with known hypersensitivity to ondansetron or aprepitant, pregnant women, and nursing mothers. The best premedication and common anesthetic substances were used in the anesthesia approach. No regional anaesthetic of any kind was administered to any of the patients.

Results: After randomization, 100 patients were divided into two groups, with 50 patients placed in Group 1 and 50 patients in Group 2, respectively, because they needed unforeseen intensive care or high dependency unit admissions or needed intraoperative steroids, which would have an impact on how well the antiemetic medications under study worked. Patient demographics, PONV risk factors, anesthesia and operation time, blood loss, and fluid volume did not significantly differ across the groups.

Conclusion: This trial showed that in patients with moderate to high PONV risk, the NK1 receptor antagonist fosaprepitant was more effective than the 5HT-3 receptor antagonist ondansetron at preventing vomiting 0-2, 0-24, and 0-48 hours after surgery. However, there were no discernible differences between fosaprepitant and ondansetron in the frequency of PONV, the full response, the need for rescue antiemetics, or the severity of nausea at any time period studied.

Keywords: Aprepitant, Ondansetron, serotonin (5-hydroxy-tryptamine), antagonism, Mastectomy, NK-1 receptor antagonist and post-operative nausea

Introduction

A uncomfortable and dangerous side effect of anesthesia and surgery is postoperative nausea and vomiting (PONV). PONV affects 30–50% of patients undergoing general anesthesia and up to 70–80% of those at high risk for PONV, including female patients, nonsmokers, people who have experienced PONV or motion nausea in the past, and people who are getting opioids postoperatively. [1–4] Antiemetics are advised for patients at a moderate to high risk of PONV, according to the "Consensus guidelines for the management of postoperative nausea and vomiting." Additionally, in patients receiving selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists as preventative therapy for PONV, such as ondansetron, up to 30–40% of patients develop PONV on the first postoperative day. [5] In addition to causing the patient pain and discomfort, PONV hinders physical therapy, lengthens hospital stays, and raises the risk of pulmonary embolism or venous thrombosis. [6-7] As a result, more potent medicines are needed, especially for high-risk individuals, to prevent PONV. Up to 70-80% of patients have nausea and vomiting in the first 24 hours following surgery. [8–9] 30–40% of patients still develop postoperative nausea and vomiting despite receiving antiemetic prophylaxis with intravenous 5HT3 receptor antagonists (RAs) or other medications (PONV). [10] Therefore, there is a medical need for better PONV prevention. Non-peptide neurokinin1 (NK1) RAs are a novel class of drugs that have shown action against both peripheral and central emetic triggers in animal models. [11-12] Evidence supporting the potential effectiveness of NK1 RAs against PONV was found in clinical trials of two different medications in this class, [13–14] which were evaluated in patients undergoing major gynecological surgery, which is consistent with the idea that antagonism at the NK1 receptor could affect the response to emetic stimuli. [15] In one trial, an NK1 RA given either alone or in conjunction with a 5HT3 RA was found to dramatically reduce the incidence of vomiting in the first 24 hours following surgery. [16] Another trial found that an NK1 RA was more effective than a placebo at controlling vomiting in patients with established PONV. [17]

As a side effect of general anesthesia, postoperative nausea and vomiting (PONV) is the second most frequently reported. It is a complicated issue brought on by the interaction of surgical, anesthetic, and patient factors. In certain patient populations and following specific surgical procedures, such as gynecological, endocrine, and ocular procedures, the risk of PONV is increased. [18] Despite improvements in anesthetic techniques, 20–30% of cases of PONV still occur. [19] The archetypal 5HT3 receptor antagonist ondansetron is the

medication most frequently used in anesthetic practice for the prevention of PONV. [20] Despite its extensive use, PONV is remains highly common, particularly following thyroid or mastectomy. [21] In the postoperative phase, PONV is frequently mentioned as the most unpleasant concern, maybe even more disturbing than pain. Anesthesiologists are working toward a postoperative phase free of nausea and vomiting due to the increased awareness of the need to increase patient satisfaction. When given intravenously, fosaprepitant quickly changes into aprepitant, which is a highly selective neurokinin-1 (NK1) receptor antagonist. Fosaprepitant is a water-soluble, phosphorylated prodrug. [22] Two major trials found aprepitant to be superior to ondansetron in avoiding PONV. Aprepitant blocks NK1 receptors, exhibits antiemetic effectiveness, and has a long half-life. [23-24] Fosaprepitant is used to treat chemotherapy-induced nausea and vomiting (CINV), and research suggests that it prevents CINV better and for a longer period of time than other antiemetics. [25] We recently demonstrated that fosaprepitant prevented vomiting 0-24 and 0-48 hours after surgery better than ondansetron. [26] We used information from earlier studies to examine the effectiveness of fosaprepitant and ondansetron in preventing PONV in patients with moderate to high PONV risk.

Material and Methods

This investigation was a randomized, double-blinded clinical control trial. It was completed in a tertiary care hospital's anesthesiology department. Before the study was conducted, it was approved by our institution's ethics and research committee. Between the ages of 18 and 65, all female American Society of Anesthesiologists physical status 1 or 2 patients scheduled for thyroid or breast procedures were enrolled in the study. Those already on antiemetics, steroids, or any other medication known to produce emesis were excluded, as were patients with known hypersensitivity to ondansetron or aprepitant, pregnant women, and nursing mothers.

The best premedication and common anesthetic substances were used in the anesthesia approach. No regional anaesthetic of any kind was administered to any of the patients. Fentanyl and paracetamol up to 5 mcg/kg were used to provide intraoperative analgesia. Prior to moving to the ward following surgery, patients were monitored for an hour in the post-anesthesia care unit. For 24 hours following surgery, prophylactic antiemetic outside the parameters of the research protocol was banned. Rescue therapy was, however, provided at the patient's request or in cases of severe nausea or emetic episodes. The postoperative care provider made the decision on the type of rescue medication. The length of anesthesia, the timing of each bout of vomiting, and the postoperative administration of rescue drugs were all noted. An independent researcher who was not informed of the patient's randomization gathered the data. The incidence of postoperative vomiting was one of the study's main findings. The quantity of emetic episodes, the degree of postoperative nausea, the timing of the first episode of vomiting, the usage of rescue antiemetics, and patient satisfaction scores were secondary outcomes. Patients at 0-2, 2-12, and 12-24 h following surgery rated their nausea on an 11-point verbal rating scale from 0 ("no nausea") to 10 ("nausea as awful as it could be"). [27]

Remifentanil (0.3–0.5 μg/kg/min), propofol (1-2 mg/kg), and rocuronium (0.8 mg/kg) were used to produce anesthesia in order to make endotracheal intubation easier. Propofol (target-controlled infusion: 2-4 μg/ml) or volatile anesthetics (sevoflurane 1-2% or desflurane 3-4%) in oxygen with air mixture, remifentanil, and fentanyl were used to keep the patient unconscious. Rocuronium was administered in incremental dosages as

required to relax the muscles, and sugammadex 2 mg/kg was administered at the conclusion of surgery to undo this effect. On the patient's request, a rescue antiemetic (10 mg metoclopramide) and/or analgesic were given. Blinded observers assessed the incidence of nausea and vomiting, the complete response rate (no vomiting and no need for rescue antiemetics), the usage of rescue antiemetics, and the degree of nausea after 2-, 24-, and 48-hours following surgery. The nausea score was used to gauge the severity of the nausea (0, absence of nausea; 1–3 mild, moderate, and severe nausea, resp.). The highest scores for each survey session were selected by blinded observers who also documented all negative outcomes during the first 48 hours following surgery.

Statistical analysis

Skewed variables are presented with a median, while normally distributed values are shown with a mean (SD) (IQR). Numbers and percentages are used to present the category variables. To determine the relationship between two groups and categorical variables, the chi-square test, Fisher's exact test, and Yate's continuity correction were utilized. The nonparametric Mann-Whitney test was used to evaluate the other parameters between the two groups, including the length of anesthesia and the time of the first vomiting episode.

Result

After randomization, 100 patients were divided into two groups, with 50 patients placed in Group 1 and 50 patients in Group 2, respectively, because they needed unforeseen intensive care or high dependency unit admissions or needed intraoperative steroids, which would have an impact on how well the antiemetic medications under study worked. Patient demographics, PONV risk factors, anesthesia and operation time, blood loss, and fluid volume did not significantly differ across the groups.

Table 1: Postoperative parameters.

	NK1 group, $n = 50$	ONS group, $n = 50$
0–2 hours		
PONV	24 (41%)	20 (28%)
Complete response	54 (78%)	61 (80%)
Vomiting	1 (2%)	12 (17%)
Rescue antiemetic use	15	10
0–24 hours		
PONV	35 (55%)	33 (49%)
Complete response	47(71%)	40 (67%)
Vomiting	1(2%)	18 (28%)
Rescue antiemetic use	22	18
0–48 hours		
PONV	35 (55%)	37 (53%)
Complete response	48 (71%)	30 (67%)
Vomiting	1 (2%)	16 (29%)
Rescue antiemetic use	15	13

At 0-2 hours, 0-24 hours, and 0-48 hours following surgery, there was no appreciable change in the percentage of patients who had no vomiting and no rescue (complete response). However, at 0-2 hours, 0-24 hours, and 0–48 hours following surgery, the incidence of vomiting was considerably reduced in the NK1 group compared to the ONS group. Both groups used equal amounts of rescue antiemetics over the 0-48 h period when vomiting rates were adjusted for the use of

rescue antiemetics. When patients needed postoperative rescue antiemetics, 10 mg of metoclopramide was given to them. For any examined time period, there were no group-specific changes in PONV, rescue antiemetic use, or nausea score.

Table 2: Nausea and NRS.

	NK1 group, n = 50	**ONS group, n = 50**
0–2 hours		
Severity of nausea (0/1/2/3)	38/13/5/4	55/3/2/11
2–24 hours		
Severity of nausea (0/1/2/3)	52/7/3/2	47/5/7/8
24–48 hours		
0 Severity of nausea (0/1/2/3)	66/3/1/0	66/3/1

Discussion

The goal of this double-blinded, randomized, clinical control trial was to determine how well the NK1 antagonist aprepitant prevented PONV in a subset of patients having thyroid and breast operations. Since ondansetron, a 5HT3 antagonist, was the go-to antiemetic in our practice, we decided to contrast aprepitant with it. [28] Aprepitant 40 mg was administered orally as a single dosage, and ondansetron injection 8 mg was administered in 3 doses, separated by 8 hours, on the first postoperative day, in order to make the "pharmacological" medications equivalent. [29] Both of these medications have different elimination half-lives; ondansetron is provided every 5-7 hours, whilst aprepitant is administered once daily. [30]

The overall incidence of PONV in this study was roughly 30%, which is consistent to other studies on the subject. [31,32] The chance of PONV incidence increased to 60–80% in all 120 of the study's patients, all of whom had an Apfel's simplified risk score of 2-3, which indicates a high-risk score. Additionally, all of the patients had received volatile anesthetics. Similar rates have also been seen in earlier investigations of high-risk patients. [33-34] However, due to the anesthetic regimen in place at our institution, our patient subset showed decreased occurrences of PONV. One oral dose of aprepitant, either 40 mg or 125 mg, was found to be more effective than one intravenous dose of ondansetron, 4 mg, in avoiding vomiting at 24 and 48 hours following surgery by Diemunsch et al.17 in their study of 922 patients who underwent open abdominal surgery. As evidence, Gan et al. [27] found that aprepitant was superior than ondansetron in avoiding vomiting in the first 24-48 hours after studying similar doses of both medications.

Vomiting is a more objective endpoint, whereas nausea can be harder to quantify. The much reduced spread of VRS scores with aprepitant indicates that it had greater antinausea efficacy than ondansetron according to the VRS employed in this cohort. The profiles of VRS scores between groups further confirmed the greater anti-nausea efficacy of aprepitant, as more patients taking aprepitant reported no nausea or no noticeable nausea, whereas those taking ondansetron reported the most severe level of nausea more frequently. [28] While rescue can affect vomiting, nausea can affect the need for rescue and is subject to patient-to-patient variations in both the severity of the nausea itself and the point at which a patient calls for help. The evaluation of PONV's overall control is particularly difficult due to the complexity of these relationships. According to Diemunsch et al. [17], aprepitant is much more effective than ondansetron at preventing vomiting. In the first 24 and 48 hours following surgery, aprepitant was shown by Gan et al. [27] to be more effective at preventing vomiting than ondansetron at lowering

nausea. Additionally, results of two clinical studies' data analysis23 showed that aprepitant prevented PONV better than ondansetron.

The incidence of PONV in untreated patients in this study is unknown, but the use of a placebo group was not justified in light of the previously established effectiveness of aprepitant in the postoperative setting and the potential unethicality of assigning patients in a high-risk population to receive a placebo instead of an effective treatment. Thus, when compared to a 5HT3 RA in similar situation with known efficacy, the study showed improvements in protection against vomiting and nausea provided by aprepitant. [35,36]

Total medical expenses could, however, go down as antiemetics can lessen PONV-related problems and shorten hospital stays. It is still unknown whether the fosaprepitant-induced decrease in postoperative vomiting enhances postoperative outcomes or offers patients additional advantages because long-term results were not assessed in this study. To determine how fosaprepitant therapy affects postoperative outcomes, more research is needed. [37] Particularly in high-risk patients, the role of dosages more than 40 mg in PONV therapy should be taken into consideration. We were only able to utilize oral aprepitant 40 mg because it is the dosage that the Drug Controller General of India has allowed for PONV. [38] Therefore, it might be wise to restrict its use to patients at high risk for PONV, such as those undergoing risky surgeries, at risk for serious complications from PONV, who have a hypersensitivity to opioids or anesthetics, have tried and failed to treat their PONV with inexpensive antiemetics, or who have previously experienced severe PONV despite receiving multimodal antiemetic therapy. [39]

Conclusion

This study demonstrated that the NK1 receptor antagonist fosaprepitant was superior to the 5HT-3 receptor antagonist ondansetron at preventing vomiting 0-2, 0-24, and 0-48 hours after surgery in patients with moderate to high PONV risk. At any time period under study, there were no appreciable differences between ondansetron and fosaprepitant in terms of the frequency of PONV, the full response, the need for rescue antiemetics, or the severity of nausea. In the 24 hours following surgery, a single dosage of oral aprepitant offers equivalent advantages to eight-hourly injections of ondansetron in terms of reducing PONV, the severity of nausea, the requirement for rescue antiemetics, and the length of time until the first episode of vomiting. To determine the best dose of aprepitant for PONV prophylaxis and treatment, suitable rescue techniques, its interactions with other anti-emetics, and its cost-effectiveness, more research is needed.

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