Previous chemotherapy can cause PONV

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Abstract

Background. Although the treatment and mechanisms of postoperative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting (CINV) are similar, the interactions between these 2 morbidities require more research.

Objectives. In our prospective observational study, we investigated whether previous chemotherapy has an effect on PONV in breast cancer surgery.

Materials and methods. One hundred and forty-eight female patients with the American Society of Anesthesiologists (ASA) physical status I or II, aged 18–65 years and with a scheduled breast cancer surgery were recruited into the study. After they completed preoperative follow-up questionnaires, anesthesia was induced with propofol (2 mg/kg), remifentanil (1.0 µg/kg) and rocuronium (0.6 mg/kg), and maintained with sevoflurane (1.5–2.0%), 45% oxygen/air mixture and infusion of remifentanil (0.1–0.2 µg/kg/min). After extubation, the intensity of PONV was assessed during the first 2 h and at 2–24 h after surgery. The symptoms of PONV were classified as mild (mild nausea, vomiting once, and nausea caused by an external stimulant (eating, drinking or motion)), moderate (vomiting twice, mild nausea without an external stimulant, and antiemetic medication required once) and severe (vomiting more than twice, severe nausea, antiemetic medication required more than once) by a different researcher. Preoperative interview forms, perioperative anesthetic follow-up forms and postoperative assessment forms were recorded and evaluated by different members of this research group.

Results. Data of 143 patients were analyzed. In the group of patients who received chemotherapy, the prevalence of nausea and vomiting within the postoperative period of 2–24 h significantly increased ($p < 0.05$).

Conclusions. Previous chemotherapy may be a risk factor for the presence of PONV.

Key words: breast cancer, PONV, CINV

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Background

Breast cancer is diagnosed more and more often. According to World Health Organization (WHO), the number of newly diagnosed breast cancer cases amounts to nearly 2 million all over the world. In Turkey in 2018, there were 22,500 new cases of this disease.[1,2]

Postoperative nausea and vomiting (PONV) can cause several problems such as early postoperative aspiration and pneumonia, dehydration, and electrolyte imbalance. Delayed recovery may increase the healthcare costs because of the usage of antiemetics and prolonged hospital stay.[3,4] Gender (female), a history of PONV and/or motion sickness, as well as non-smoking status are well-known patient-related risk factors for PONV. More risk factors have been added by Apfel et al. (use of postoperative opioids) and Koivuranta et al. (length of surgery).[5,6] Other papers report that some types of surgery may be associated with an increased risk of PONV, such as laparoscopic and gynecological operations or cholecystectomy.[3,5–7]

The pathophysiology and treatment of PONV is complex. Such symptoms may occur due to the release of different neurotransmitters (serotonin, dopamine, muscarine, acetylcholine, neurokinin-1, histamine, and opioids) or stimulation of the vestibular-cochlear, glossopharyngeal or vagus nerve.[8] Hesketh indicated that chemotherapy-induced nausea and vomiting (CINV) is observed in approx. 30–90% of patients.[9] Although the treatment methods of PONV and CINV are similar, patients' response to them may be different.[10]

Objectives

In our prospective observational study, we investigated whether previous chemotherapy had the effect on PONV in breast cancer surgery.

Materials and methods

Following the approval from the University of Health Sciences Istanbul Education and Training Hospital Institutional Ethics Committee (approval No. 28.06.2019/1890), signed informed consent was obtained from each patient. The study conforms with the tenets of Declaration of Helsinki of 1964 and its later amendments. One hundred and forty-eight female patients with the American Society of Anesthesiologists (ASA) physical status I or II, aged 18–65 years and with scheduled breast cancer surgery were recruited into the study. Before surgery, all patients were asked about their medical history, and had their Apfel score counted. The exclusion criteria were as follows: 1) a history of drug abuse or known prolongation of the QT interval on electrocardiogram (ECG); 2) obesity (body mass index (BMI) >31 kg/m^2); 3) antiemetic use 24 h before the study and presence of hepatic or renal disease; 4) patients who who had their last chemotherapy less than 1 month ago; 5) patients with presence of allergy; 6) operation time shorter than 60 min or longer than 120 min; and 7) additional opioid necessity in the postoperative period.

Before the operation, all patients were routinely assessed with basic monitoring (ECG, noninvasive blood pressure (NIBP) measurement and oxygen saturation (SpO_2) probe). Anesthesia was induced with propofol (2 mg/kg), remifentanil (1.0 µg/kg) and rocuronium (0.6 mg/kg), and maintained with sevoflurane (1.5–2.0%), 45% oxygen/air mixture, and the infusion of remifentanil (0.1–0.2 µg/kg/min). In the last 30 min at the end of the operation, meperidine (30 mg) was administered. After extubation, the intensity of PONV was assessed during the first 2 h and at 2–24 h after surgery. Patients who complained of PONV were classified as mild (mild nausea, vomiting once), moderate (vomiting twice or need antiemetic medication once) and severe (vomiting more than twice, severe nausea, antiemetic medication needed more than once) by another anesthesiologist who has not anesthetised the patient. None of the patients were routinely prescribed opioid or antiemetic medication during the postoperative period. Patients who had moderate and severe PONV were given 10 mg of metoclopramide for rescue treatment. Patients who suffered a pain score >4 according to NRSS (numeric rating scale score) were treated with infusion of paracetamol (1 g). If the paracetamol was deemed not enough, an opioid (tramadol or meperidine) was given and patients were excluded from the study. Preoperative interview forms, perioperative anesthetic follow-up forms and postoperative assessment forms were recorded and evaluated by different members of our research group.

Statistical analyses

Statistical analyses were performed using IBM SPSS v. 25.0 software (IBM Corp., Armonk, USA). The conformity of the variables to the normal distribution was examined with histogram graphics and the Kolmogorov–Smirnov test. Parametric values with normal distribution are shown as mean ± standard deviation (M ±SD). Parametric values without normal distribution and nonparametric values are presented as the median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages. Interactions between chemotherapy and demand of additional analgesic were compared with the χ^2 test or the Fisher's exact test according to the number of patients in each group. Values of $p < 0.05$ were deemed statistically significant.

Results

Initially, 148 patients had been enrolled, but 5 were excluded from the study: 1 patient because of delayed surgery and 4 because of missing patient data. Patients' characteristics are presented in Table 1.

Table 1. Characteristics of study population

Variable		n (%) or M ±SD or median (Q1–Q3)
Age		51.90 ±12.51[b]
BMI		28 (25–32)[c]
Apfel score	1 2 3 4	32 (22.37)[a] 81 (56.64)[a] 24 (16.78)[a] 6 (4.19)[a]
Additional disease		85 (59.44)[a]
Additional drug		82 (57.34)[a]
Non-smokers		48 (33.57)[a]
Previous operation		111 (77.62)[a]
PONV 0–2 h	mild moderate severe	44 (69.84)[a] 16 (25.40)[a] 3 (4.76)[a]
PONV 2–24 h	mild moderate severe	23 (54.76)[a] 14 (33.33)[a] 5 (11.90)[a]
Previous chemotherapy		51 (35.66)[a]
CINV		35 (68.63)[a]
Additional analgesic		129 (90.21)[a]

[a] n (%); [b] mean ± standard deviation (M ±SD); [c] median (1st quartile – 3rd quartile (Q1–Q3)); BMI – body mass index; CINV – chemotherapy-induced nausea and vomiting; PONV – postoperative nausea and vomiting.

Apfel score distribution was as follows: 1 – 32 patients (22.37%), 2 – 81 patients (56.64%), 3 – 24 patients (16.78%), and 4 – 6 patients (4.19%). The PONV at 0–2 h was mild in 44 patients (69.84%), moderate in 16 (25.40%) and severe in 3 (4.76%), while PONV at 2–24 h was mild in 23 patients (54.76%), moderate in 14 (33.33%) and severe in 5 (11.90%). Fifty-one patients (35.66%) received chemotherapy for at least 1 month. Thity-five patients (68.63%) experienced CINV, while 129 patients demanded additional analgesics. The PONV symptoms at 2–24 h significantly worsened in those who received chemotherapy ($p < 0.05$). There was no significant difference between PONV 0–2 and PONV 2–24 grades in patients with CINV (Table 2).

Discussion

Surgery, chemotherapy, radiotherapy, and various combinations of these are used in breast cancer treatment. Da Silva et al. compared different types of oncologic operations in their retrospective study and reported that the only surgical procedure in which PONV prevalence was significantly higher was mastectomy; however, when they compared the results of Apfel's model, they could not find a difference regarding PONV in different mastectomy cases. Their study included both male and female patients and they used different types of anesthesia (general anesthesia alone or combined with epidural or spinal anesthesia). Also, the treatment with antiemetics and postoperative opioids was dependent of the clinicians' preference, and patient-controlled analgesia was employed in some of the patients.[11] In our prospective study, only female patients were included, and general anesthesia was the dominating type of anesthesia; antiemetics and opioids were used only if necessary.

The expected results for PONV from Apfel's original study were 21%, 39%, 61%, and 79% for grades 1, 2, 3, and 4, respectively. In our study, the Apfel scores were grade 1 for 32 patients (22.37%), grade 2 for 81 patients (56.64%), grade 3 for 24 patients (16.78%), and grade 4 for 6 patients (4.19%).

The association between PONV and CINV has not been fully established. There are studies reporting that hereditary factors may play a role in both PONV and CINV susceptibility and resistance.[12] On the other hand, antiemetic medications which have an effect on CINV are not always protective against PONV.

Janicki and Sugino determined that genetic variations in the *HTR3A* and *HTR3B* genes could increase the risk of PONV, and the *HTR3C* gene polymorphisms could have a predictive role for CINV in patients who receive moderately emetogenic chemotherapy. The main conclusion of that study was that the incidence of CINV was very low after chemotherapy in people who did not experience PONV after surgery.[13] Therefore, in our study, we aimed to investigate whether the reverse situation is also possible.

Oddby-Muhrbeck et al. claimed that CINV is strongly related to PONV, and previous PONV has a predictive role for CINV.[10] However, in their study, chemotherapy was applied after surgery, and in patients who experienced PONV before chemotherapy, supraglottic airway devices were used instead of tracheal intubation.

Our patients were given anesthesia after chemotherapy. In other words, it was investigated whether nausea and

Table 2. Relationship between PONV and chemotherapy

Variable		PONV 0–2 h, n (%)		χ^2/p-value	PONV 2–24 h, n (%)		χ^2/p-value
		no	yes		no	yes	
Chemotherapy	no yes	51 (55.43) 29 (56.86)	41 (44.57) 22 (43.14)	0.027/0.869#	72 (78.26) 29 (56.86)	20 (21.74) 22 (43.14)	7.242/0.007#
CINV	no yes	12 (75) 17 (48.57)	4 (25) 18 (51.43)	3.127/0.127*	11 (68.75) 18 (51.43)	5 (31.25) 17 (48.57)	1.343/0.246#

χ^2 test; * Fisher's exact test; statistically significant p-values are in bold. CINV – chemotherapy-induced nausea and vomiting; PONV – postoperative nausea and vomiting.

vomiting was more common during the postoperative period in patients receiving chemotherapy.

Anesthesia-related pharmacologic risk factors for PONV include inhalation anesthetics, nitrous oxide and usage of postoperative opioids. The effects of volatile anesthetics on PONV demonstrate a dose-dependent manner and particularly appear in the first 2–6 h after surgery.[14] Opioids increase the risk for PONV in a dose- and time-dependent manner.[15] We administered sevoflurane, remifentanil and oxygen/air mix for the maintenance of anesthesia. The incidence of PONV is lower with opioid-free total intravenous anesthesia (TIVA). It is known that propofol and TIVA reduce the PONV risk by approx. 25%.[16] In our study, PONV at 2–24 h was significantly increased in patients who received chemotherapy, and there was no significant difference between PONV 0–2 or PONV 2–24 in those with CINV. We think that we eliminated or minimized the negative effects of anesthetic medications.

We used propofol only in induction of anesthesia, and we reversed the effect of muscle relaxant with neostigmine. We did not apply antiemetic drugs routinely to our patients because of their possible side effects, and infused 1 g of paracetamol intravenously for postoperative analgesia when necessary.

Limitations

We did not compare the Apfel score with PONV and CINV results. When we were planning the methods, we included only female patients, which invalidated the results of Apfel score. Another limitation of our study was the administration of inhalation anesthesia instead of TIVA and/or combination of opioid-free regional anesthesia with TIVA as a part of multimodal analgesia management plan.[17–21] We used inhalation anesthesia because of its cost efficiency and routine preference of our hospital policy.

Conclusion

We concluded that prior chemotherapy may be a risk factor for the occurrence of PONV.

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