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Hyperoxia therapy for prevention of postoperative nausea and vomiting after breast cancer surgery

Terapija hiperoksijom u prevenciji postoperativne mučnine i povraćanja nakon operacije karcinoma dojke

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Abstract

Background/Aim. Postoperative nausea and vomiting (PONV) are one of the most common causes of patient dissatisfaction in the postoperative period after general anesthesia. Hyperoxia may prevent PONV after abdominal surgery, but the effectiveness of intraoperative and early postoperative hyperoxia in preventing PONV after breast cancer surgery has not been fully elucidated. The aim of this study was to assess if the application of intraoperative hyperoxia during surgery could prevent PONV. **Methods.** Forty female patients with breast cancer were recruited for the study, all of whom underwent surgical treatment of breast cancer with axillary sentinel node sampling or axillary lymph node dissection. A balanced general anesthesia was conducted, which was induced with propofol and maintained with sevofluran. Out of the 40 patients, 20 (intervention group) received a volatile gas mixture with a fraction of inspired oxygen (FiO_2) of 0.8 L/min intraoperatively and, afterward, 3 L/min of oxygen *via* face mask for two hours after surgery. The other 20 patients (control group) received a FiO_2 of 0.4 L/min during the surgery without further administration of oxygen in the early postoperative period. The presence and severity of PONV were assessed at 30 min, 4, 24, 32, 48, and 56 hrs after surgery with the use of the PONV numerical Intensity Scale by Wengritzky for evaluating clinically significant PONV in the first six hours after surgery. Data were collected in an Excel spreadsheet and analyzed using the independent Student's *t*-test. **Results.** The overall incidence of PONV during the 30 min after the surgery was 17.5% (15% in the group of patients receiving FiO_2 of 0.8 L/min and 20% in the group of patients receiving FiO_2 of 0.4 L/min intraoperatively). There was no statistically significant difference between the two groups in the frequency of PONV, as well as in the severity of PONV, measured with the PONV Intensity Scale by Wengritzky ($p \geq 0.05$). **Conclusion.** We found no benefit of intra- and post-operative hyperoxia in reducing the incidence of PONV. The data do not support routine administration of hyperoxia, in addition to antiemetics, for the prevention of PONV in patients undergoing breast cancer surgery.

Key words:
anesthesia, general; breast neoplasms; hyperoxia; nausea; oxygen inhalation therapy; postoperative period; surgical procedures, operative; vomiting.

Apstrakt

Uvod/Cilj. Postoperativna mučnina i povraćanje (*postoperative nausea and vomiting* – PONV) su jedan od najčešćih razloga nezadovoljstva bolesnika u postoperativnom periodu posle opšte anestezije. Hiperoksija može sprečiti PONV posle abdominalne hirurgije, međutim, efikasnost intraoperativne i rane postoperativne primene hiperoksije u prevenciji PONV posle operacije karcinoma dojke nije do kraja razjašnjena. Cilj rada bio je da se proceni da li primena hiperoksije tokom operacije može sprečiti PONV. **Metode.** U studiju je bilo uključeno 40 bolesnica sa karcinomom dojke, podvrgnutih operativnom lečenju, kojima su uzorkovani aksilarni limfni čvorovi "stražari" ili disektovani aksilarni limfni čvorovi. Sprovedena je balansirana opšta anestezija, koja je indukovana propofolom, a održavana sevofluranom. Od 40 bolesnica, njih 20 (grupa sa intervencijom) je intraoperativno primilo inhalacionu smešu gasova sa udahnutom frakcijom kiseonika (*fraction of inspired oxygen* – FiO_2) od 0,8 L/min i zatim još 3 L/min kiseonika putem maske za lice, tokom dva sata nakon operacije. Drugih 20 bolesnica (kontrolna grupa) primilo je FiO_2 od 0,4 L/min tokom operacije, bez dalje primene kiseonika u ranom postoperativnom periodu. Prisustvo i težina PONV bili su procenjivani 30 min, 4, 24, 32, 48 i 56 sati nakon operacije primenom Wengritzky-jeve PONV numeričke skale za procenu inteziteta klinički značajne PONV, tokom prvih šest sati nakon intervencije. Podaci su bili prikupljeni u *Excel* tabeli i analizirani pomoću nezavisnog Studentovog *t*-testa. **Rezultati.** Ukupna incidenca PONV tokom

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30 min nakon intervencije iznosila je 17,5% (15% u grupi bolesnica koje su primale FiO_2 od 0,8 L/min i 20% u grupi bolesnica koje su primale FiO_2 od 0,4 L/min intraoperativno). Nije bilo statistički značajne razlike između dve grupe ispitanica u učestalosti PONV i težini PONV, merenih pomoću Wengritzky-jeve numeričke skale za procenu intenziteta PONV ($p \geq 0,05$). **Zaključak.** Nije dokazana korist od intraoperativne i rane postoperativne primene hiperoksije u prevenciji PONV. Dobijeni rezultati ne podržavaju rutinsku primenu hiperoksije pored antiemetskih lekova, u cilju smanjenja učestalosti PONV kod bolesnica posle hirurškog lečenja karcinoma dojke.

Ključne reči:
anestezija, opšta; dojka, neoplazme; hiperoksija; mučnina; lečenje inhalacijom kiseonika; postoperativni period; hirurgija, operativne procedure; povraćanje.

Introduction

The subjective feeling of nausea or vomiting in the first 48 hrs after surgery (postoperative nausea and vomiting – PONV) represents one of the most common reasons for patient dissatisfaction in the postoperative period. Vomiting is assumed to be the most undesirable outcome after anesthesia [1], and many patients would prefer pain over PONV postoperatively [2]. The overall incidence of PONV is approximately 30% after balanced general anesthesia [3, 4]; however, in high-risk patient populations, it can be as high as 80% [5]. Although PONV seldom leads to any serious medical conditions (such as aspiration pneumonia, wound dehiscence, or even anastomotic leak formation due to emetic strains) in the modern clinical setting, severe vomiting can cause dehydration, electrolyte imbalance and negatively impact patient satisfaction with anesthesia care providers, as well as generate increased hospital costs (delayed postsurgical mobilization and longer hospital stay, restricted ambulatory surgery) [6].

Numerous drugs (e.g., opioid analgesics, volatile anesthetics, nitrous oxide) applied during general anesthesia affect the release of neurotransmitters (e.g., acetylcholine, dopamine, histamine, substance P, serotonin) contributing to the development of nausea and vomiting and the function of receptors in the central emetogenic areas (*area postrema*, *nucleus* in the solitary tract). Opioids also determine the gastrointestinal tract mechanics by decreasing gastric emptying, intestinal motility, and peristalsis [7].

The results of several randomized controlled trials prove that volatile anesthetics and opioid analgesics potentiate the development of PONV [8–10]. Therefore, total intravenous (IV) and regional anesthesia (if applicable) are superior to balanced general anesthesia in the prevention of PONV. It is established that anesthesia (and surgery) duration plays an important role in inducing PONV. The most common patient-specific risk factors are female gender, younger age, non-smoking status, and history of PONV or motion sickness [5]. Moreover, intense preoperative anxiety, insufficient perioperative fluid administration [11], or obesity can also enhance the development of PONV [12]. Morita et al. [13] reported a significantly higher incidence of PONV in patients undergoing breast cancer surgery with desflurane anesthesia, especially in the early postoperative period. According to the Enhanced Recovery After Surgery – ERAS protocol [14, 15], all patients, even those with no existing risk factors for PONV, should receive monoprophylaxis; however, patients with the Apfel Simplified Risk Score (ASRS) of 1 or 2 should be administered two antiemetics, and patients with high-risk of developing PONV should receive three to four antiemetics for prophylaxis [16, 17]. In modern clinical settings, clinicians are encouraged to pay special attention to lowering the risk for PONV by preferring propofol-based, i.e., total IV anesthesia, avoiding volatile analgesics and nitrous-oxide exposure, or applying opioid-sparing analgesia. Nevertheless, for pharmacologic prevention, a multimodal approach with drugs that act differently is recommended [18] (Figure 1).

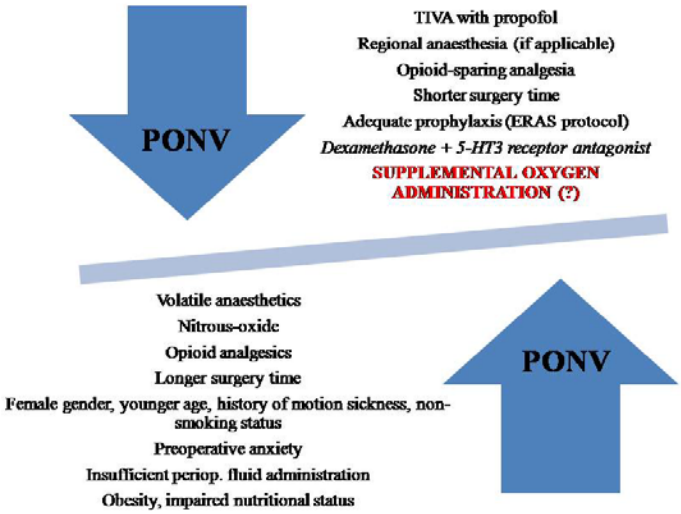

Fig. 1 – Summary of factors contributing to postoperative nausea and vomiting (PONV) and preventing PONV.
TIVA – total intravenous anesthesia; ERAS – enhanced recovery after surgery; 5-HT3 – 5-hydroxytryptamine (serotonin) 3 receptor.

According to the recommendations of the World Health Organization (WHO), supplemental oxygen administration in the intraoperative and early postoperative period may reduce the occurrence of surgical site infection (SSI) and the incidence of PONV [19]. Although the routine use of hyperoxia in the anesthesiology practice is controversial because of the possible adverse effects (increased oxidative stress, lung atelectasis, and hyperoxia-related vasoconstriction in the coronary arteries, with a sequential decrease in myocardial perfusion), the results of a recently published meta-analysis show, that the administration of fraction of inspired oxygen (FiO_2) of 0.8 L/min in the perioperative setting is free of complications [20]. Intestinal tissue is highly metabolically active and has poor tolerance for hypoxia; therefore, even short periods of insufficient perfusion in the intestinal tract can lead to the release of serotonin – an emetogenic substance [21]. It is supposed that supplemental oxygen administration may prevent intestinal hypoxia and reduce the incidence of PONV; thus, hyperoxia is a potentially highly available and cost-effective alternative treatment modality for the prevention of PONV.

In some highly vulnerable patient populations, more tremendous PONV prevention is required. In the cases of oncological patients' nutritional status may be modified due to chemotherapy-induced nausea and vomiting, decreased caloric intake, malabsorption, or even cachexia [22]. These factors lead to a higher incidence of PONV in cancer surgery and the patients undergoing balanced general anesthesia frequently require an intense multimodal approach for the prevention of PONV. Therefore, the aim of this study was to assess whether the intraoperative and early postoperative administration of supplemental oxygen reduces the incidence of PONV and thus evaluate the potential of hyperoxia as an alternative additional treatment modality in cancer patients.

Methods

The study was conducted between February and June 2022 at the Department of Anesthesiology with Reanimatology of the tertiary referral, high-volume center for cancer treatment in Vojvodina, Serbia. Ethical approval of the study protocol was obtained from the institutional Ethics Committee of the Oncology Institute of Vojvodina (approval No. 4/21/2-2611/2-3, from September 08, 2021). Written informed consent was obtained from all patients.

Forty female patients older than 18 years undergoing breast cancer surgery (quadrantectomy, segmentectomy, amputation, or mastectomy) with axillary sentinel node sampling or axillary lymph node dissection were approached for this study. Exclusion criteria were the following: patients receiving neoadjuvant chemotherapy prior to this surgery, the impossibility of completing the surgical procedure (metastasis, neighboring organ infiltration), anesthesia time shorter than 60 min, and patients who declined study participation. The Revised Cardiac Risk Index (RCRI) [23] was used to assess the patient's risk of developing perioperative cardiac complications. All potential subjects who had more than one risk factor and, hence, risk for cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest greater than 6% were excluded from the study. According to the non-cardiac surgery guidelines of the European Society of Cardiology and European Society of Anesthesiology, the surgical procedures conducted in this study are associated with a low risk of developing major adverse cardiac events (30-day risk of cardiovascular death and myocardial infarction lower than 1%) [24].

Balanced general anesthesia with propofol induction (1.5–2.5 mg/kg) and sevoflurane maintenance (1.2%–1.4% end-tidal concentration or minimum alveolar concentration of 1–1.2) was conducted. Non-depolarizing muscle relaxant rocuronium was administered with the induction dose of 0.6 mg/kg IV and boluses of 0.1–0.3 mg/kg IV according to clinical requirements. Analgesia was provided with boluses of fentanyl (50–100 μg IV) – first dose at anesthesia induction (50 μg IV) and intraoperative boluses according to hemodynamic response to pain. At the end of the surgery, all the patients received metamizole (2.5 g IV) and ondansetron (4 mg IV), and the 8-hour dosing of these analgesic and antiemetic drugs was continued for two days. A laryngeal mask was used for airway management, and pressure-regulated volume control ventilation was ensured in all examined patients.

The patients were randomly assigned to one of the two investigated groups. In the intervention group, the patients received intraoperatively a volatile mixture with FiO_2 of 0.8 (80%) and 3 L/min of oxygen *via* face mask in the post-anesthesia care unit and the surgical ward for two hours after the surgery. Patients assigned to the control group received a volatile mixture with FiO_2 of 0.4 (40%) during surgery without further administration of oxygen in the early postoperative period. Except for the FiO_2 in the volatile mixture administered intraoperatively and the early postoperative administration of oxygen in patients in the intervention group, the entire perioperative and intraoperative treatment and administered medications (anesthesia drugs, muscle relaxants, antimicrobial, analgesic, antiemetic drugs, and thromboprophylaxis) were identical in the two groups.

The following intraoperative monitoring was conducted in all patients: electrocardiogram (leads II and V_5), non-invasive blood pressure measurement in 5-minute intervals, pulse oximetry, monitoring of ventilation parameters, capnography, and anesthesia gas monitoring. Non-invasive blood pressure monitoring and pulse oximetry were conducted in the postanesthetic care unit as well as in the surgical ward three times a day.

The ASRS [5] was used to estimate the patient's risk for developing PONV. It includes four risk factors: female gender, non-smoking status, history of PONV or motion sickness, and postoperative use of opioid analgesics. Patients with ASRS of 2 are considered medium-risk patients for developing PONV, and ASRS ≥ 3 is associated with a high risk of PONV.

The presence and severity of PONV were assessed at 30 min, 4, 24, 32, 48, and 56 hrs after surgery, using a five-grade scale, which was earlier applied [25] for estimating PONV in cancer surgical patients. The grading system was used as follows: grade 1 – no signs of PONV; grade 2 – minor nausea; grade 3 – mild nausea and vomiting; grade 4 –

severe nausea and vomiting; grade 5 – incoercible vomiting. A numerical PONV Intensity Scale [26] was applied to evaluate clinically significant PONV in the first six hours after surgery. The key scored features were intensity, pattern and duration of nausea, as well as the number of vomiting. A clinically important PONV is defined as a total score ≥ 50 at any time throughout the study period. PONV scores, patient's vital parameters, and eventually observed postoperative complications were recorded in the examination sheet.

Sample size calculation was used in order to determine the adequate total number of included patients. The confidence level was set to 95% and the margin of error to 5%. The incidence of PONV is 20% in patients treated according to institutional standards at our clinic who have not received neoadjuvant chemotherapy, undergoing general anesthesia for breast cancer surgery; therefore, the expected population proportion was set to 20%. We applied the adjusted sample size calculation, taking into consideration the examined population size. The total number of patients fulfilling the inclusion criteria during the study period in our hospital was 48. Hence, according to the adjusted sample size calculation, the adequate number of included subjects for obtaining statistical relevance was 40.33. This sample size was divided into two equal proportions, and the included patients were randomly assigned into one of the two groups (intervention group and control group). Forty female patients undergoing breast cancer surgery were recruited for this study – 20 (50%) patients were assigned to the intervention group and 20 (50%) to the control group. The total number of eligible patients to enter the investigation after screening was 48; however, one patient was excluded because of canceled surgery. Five patients were not included in the investigation because of rejection to participate in the study or because of the temporary absence of the investigators at the time of the surgery. The total number of randomized patients was 42, but two patients were excluded because of intraoperative hemodynamic instability and deviation from the study protocol through additional nitrous-oxide administration; therefore, the total number of included patients was 40 (Figure 2).

Data was collected in Excel and SPSS Software (IBM, Chicago, USA) was used for data analysis. Categorical data were analyzed with Pearson's Chi-square test or Fisher's exact test and quantitative data were analyzed using the independent Student's *t*-test for significance. Data were presented as numbers (percentages) or median (interquartile range – IQR) and statistical significance was set at $p \leq 0.05$.

Results

The median age of the included patients was 60 (IQR:19.5) years; most of them (90%) were classified as physical status II according to the American Standards Association (ASA), and 10% were in status ASA III. The most common comorbidities were arterial hypertension (n = 21; 52.5%), hypothyroidism (n = 8; 20%), and varicose veins of the lower extremities (n = 6; 15%). The most frequently performed surgical procedure was quadrantectomy with axillar sentinel node sampling (n = 27; 67.5%) or with axillar lymph node dissection (n = 5; 12.5%) and subcutaneous mastectomy (n = 6, 15%). The median duration of the surgical procedure was 60 (IQR:17.5) min, with a median anesthesia time of 75 (IQR:20) min. The median length of hospital stay was 4 (IQR:1) days. There were no statistically significant differences ($p \geq 0.05$) in surgery time, anesthesia time, and length of hospital stay between the intervention group and the control group (Table 1). In the postoperative period, 85% of the subjects had no complications, but 7.5% of the patients experienced pain, 5% somnolence, and 2.5% vertigo in the first four hours after surgery.

The median value of the RCRI was 3.9 (IQR:0) in both groups. Most (92.5%) of the patients had no existing risk factors for the development of perioperative cardiac complica-

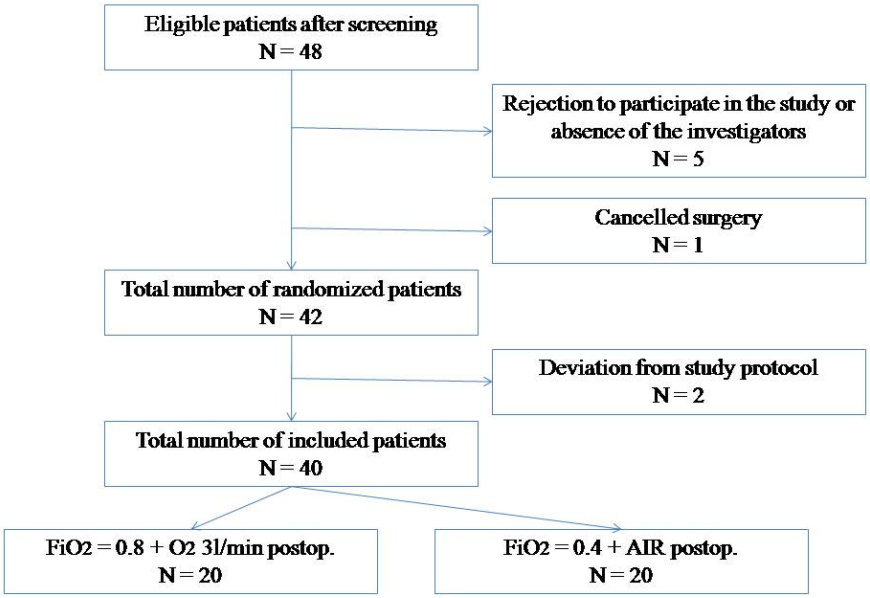

Fig. 2 – Flowchart of patient recruitment.
FiO_2 – fraction of inspired oxygen; AIR – patients without supplemental oxygen administration postoperatively; N – number of patients.

tions (estimated risk is 3.9%); nevertheless, one person in the intervention group and two people in the control group reported the presence of one risk factor (the estimated risk for developing cardiac death, nonfatal myocardial infarction or nonfatal cardiac arrest is 6%). According to the ASRS, 87.5% of the subjects had two risk factors for the development of PONV; hence, they were considered medium-risk patients. Ten percent of the patients (two people in each group) were classified as low-risk, and 2.5% (one person in the control group) as high-risk patients for the development of PONV. There were no statistically significant differences ($p \geq 0.05$) in the values of RCRI and ASRS between the two groups of patients (Table 1).

The median value of Wengritzky score was 0 (IQR:0) in both groups. As clinically important PONV was defined as a total Wengritzky score ≥ 50, there was only one person in the control group who developed clinically significant PONV. There was no statistically significant difference ($p \geq 0.05$) in the Wengritzky score between the two groups of patients.

The overall incidence of PONV was 17.5% during the first 30 min after surgery: two (10%) patients in each group experienced severe nausea and vomiting, two (5%) patients in the control group reported mild nausea, and one (2.5%) per-son in the intervention group developed minor nausea. Fifteen percent of the examined subjects reported the presence of PONV four hours after surgery: severe nausea and vomiting occurred in one (2.5%) person in the control group, two (10%) people in each group developed mild nausea, and one (2.5%) patient in the control group reported minor nausea. Twenty-four hours after the surgery, four (10%) patients experienced PONV: one (2.5%) person in the control group re-ported mild nausea, but two patients in the control group and one person in the intervention group (7.5%) experienced minor nausea. Thirty-two hours after surgery, only one (2.5%) person in the control group developed minor nausea. All the patients were without any signs of PONV 48 and 56 hrs after the surgery. There was no statistically significant difference ($p \geq 0.05$) in the incidence and severity of PONV between the two investigated groups of patients at any time point during the study period (Figures 3 and 4).

Table 1

Demographic and clinical characteristics of patients

Parameters	Intervention group	Control group	*p*-value
Age (years), median (IQR)	60 (14)	60 (21.5)	> 0.05
Physical status, n (%)			
ASA II	18 (45)	18 (45)	> 0.05
ASA III	2 (5)	2 (5)	> 0.05
Comorbidities, n (%)			
Arterial hypertension	12 (30)	9 (22.5)	> 0.05
Hypothyroidism	5 (12.5)	3 (7.5)	> 0.05
Varicose veins of lower extremities	3 (7.5)	3 (7.5)	> 0.05
Obesity	2 (5)	1 (2.5)	> 0.05
Depressive disorder	2 (5)	3 (7.5)	> 0.05
Surgery time (min), median (IQR)	62.5 (22.5)	60 (15)	> 0.05
Anesthesia time (min), median (IQR)	75 (27.5)	72.5 (17.5)	> 0.05
Hospital stay (days), median (IQR)	4 (1)	4 (0.5)	> 0.05
RCRI, median (IQR)	3.9 (0)	3.9 (0)	> 0.05
Apfel Simplified Risk Score, n (%)			
1	2 (5)	2 (5)	> 0.05
2	18 (45)	17 (42.5)	> 0.05
3	0 (0)	1 (2.5)	> 0.05

IQR – interquartile range; ASA – American Standards Association; RCRI – Revised Cardiac Risk Index; n – number of patients.

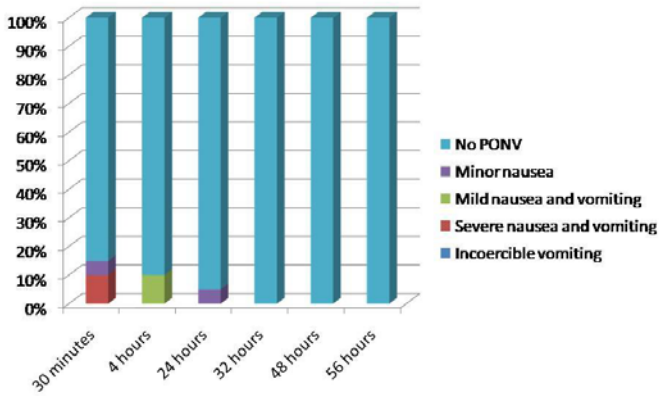

Fig. 3 – Incidence of postoperative nausea and vomiting (PONV) in the intervention group.

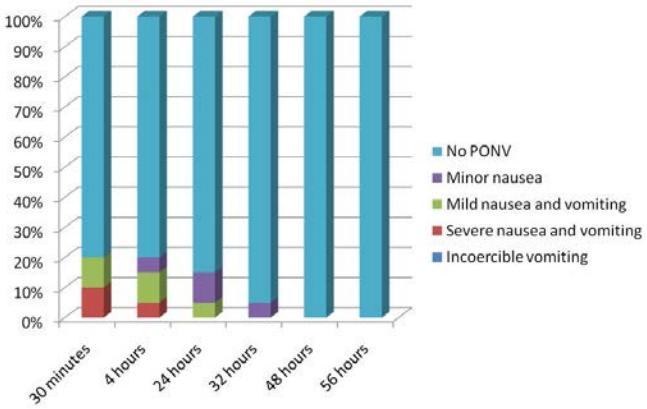

Fig. 4 – Incidence of postoperative nausea and vomiting (PONV) in the control group.

Discussion

The results of our study showed no statistically significant difference in the incidence and severity of PONV between the two groups of investigated patients. There was one person in the control group who developed clinically remarkable PONV according to the Wengritzky score, and that person was the only high-risk patient with an ASRS of 3. The incidence of PONV was the highest 30 min after surgery, and, in most of the cases, the symptoms did not persist longer than 24 hrs. There were no cardiovascular or respiratory adverse effects due to supplemental oxygen administration reported during the entire study period.

So far, no generally accepted agreement about the optimal FiO_2 concentration during general anesthesia has been made. However, in 2016, the WHO recommended that adult patients undergoing general anesthesia be ventilated intraoperatively using a volatile mixture with FiO_2 of 80%. It was supposed that hyperoxia may contribute to lowering the incidence of SSI and play an important role in the prevention of PONV [19]. The results of a recently conducted large-scale meta-analysis were heterogeneous, but the most wide-reaching included clinical trial failed to prove the effectiveness of hyperoxia in reducing the incidence of SSI. Therefore, numerous highly actual literature sources do not support the routine administration of high concentrations of FiO_2 intraoperatively, and the impact of hyperoxia on the prevention of PONV also remained unjustified [27]. Interestingly, another meta-analysis examining the hyperoxia-induced impact on SSI and PONV suggests that high FiO_2 has a beneficial effect on PONV and does not increase the risk of postoperative atelectasis. Analyzing the results of 11 trials, it was concluded that the incidence of PONV was reduced from 24.8% in patients receiving normal FiO_2 to 19.5% in patients undergoing abdominal, gynecological, breast, and thyroid surgery in high FiO_2 conditions. In patients receiving volatile anesthetics without prophylactic antiemetic drugs, hyperoxia seemed to have a strong protective effect against PONV. Moreover, the incidence of SSI also decreased in patients who, besides prophylactic antibiotics, also received high concentrations of FiO_2 [28]. According to the findings of the mentioned studies and currently available literature, the role of supplemental oxygen in the prevention of PONV remained controversial.

There are numerous meta-analyses conducted to observe the effect of perioperative administration of hyperoxia, and some of them, first of all, focus on reducing the PONV incidence. Orhan-Sungur et al. [29] found no clear benefit of the administration of high FiO_2 during general anesthesia in reducing the occurrence of PONV. On the other hand, Rincón and Valero [30] reported a decrease in the incidence of PONV due to the perioperative administration of high FiO_2, and they concluded that supplemental oxygen therapy has the potential to reduce PONV incidence but cannot replace the currently available pharmacologic treatment modalities. The largest meta-analysis, including 12 clinical trials and 5,583 patients, found no clear difference in PONV incidence between the groups of patients undergoing surgery in high (FiO_2 = 0.8) vs. low (FiO_2 = 0.3) fraction of oxygen in the inspired gas mixture. However, according to the subgroup analysis, there was a reduced incidence of PONV in patients having abdominal surgery, in contrast to the group of subjects undergoing laparoscopic gynecological intervention or some other type of non-abdominal surgery [31]. Our results correlate with the results of the newest meta-analysis, including all relevant previous trials on this topic, published in 2023. According to the findings of Markwei et al. [32], supplemental oxygen administration does not reduce the incidence of PONV after abdominal or non-abdominal surgery. Furthermore, it does not affect the severity of PONV, the number of rescue antiemetic doses given, or the time to the first rescue antiemetic drug administration.

Some earlier conducted case-control studies emphasize the impact of hyperoxia on the reduction of PONV incidence in cancer patients [33–35]. According to these studies, the incidence of nausea and vomiting was significantly lower in the group of patients with various oncological diseases who received 80% of oxygen intraoperatively and six hours after surgery, compared to the control group, and these results are in contrast to our findings. We can suppose that the main reason for the difference in the outcomes between the previous studies and our study is the relatively short exposure time in our patients' cases. Moreover, the patients in our study received a single dose of ondansetron intraoperatively, which

represents a standard treatment in our hospital. The administration of an antiemetic drug may have interfered with the results, but because of ethical issues, it was not justified to withdraw the best standard treatment. Nevertheless, Chiu et al. [36] highlight the effectiveness of a combined approach in cancer patients, i.e., total IV anesthesia with regional anesthesia (paravertebral and pectoral nerve blocks), in reducing opioid consumption and lowering the incidence of PONV after total mastectomy. Tripathy et al. [37] reported equally prolonged postoperative analgesia and low intra- and postoperative opioid requirements in the groups of patients undergoing breast cancer surgery receiving isoflurane-maintained anesthesia with pectoral or paravertebral nerve block.

According to the enhanced recovery after surgery protocol, all patients with existing risk factors for the development of PONV should receive a combination of two antiemetics for PONV prophylaxis [14]. The most commonly applied first-line treatment is a combination of dexamethasone and 5-hydroxytryptamine 3 receptor antagonist. Still, the routine administration of dexamethasone in cancer patients is controversial, as the effect of dexamethasone on the long-term oncological outcome has not been fully studied yet; therefore, a single treatment was applied in our study. Tabrizi et al. [38] reported a lower incidence of PONV following gynecological and breast surgery after routinely assessing the ASRS for PONV and implementing PONV guidelines. However, Krieser et al. [39] showed in their retrospective cohort study that female patients undergoing general anesthesia are affected by failure to adhere to PONV prevention guidelines to a disproportionately greater extent than male patients.

Several factors could affect the results of our study. Most importantly, the routine administration of ondansetron has probably highly interfered with the results. As we mentioned, we could not withdraw a single dose of antiemetic medication from our patients due to ethical issues. That being the case, we could examine if hyperoxia could be an effective additional treatment modality to the routine administration of ondansetron, but the antiemetic potential of supplemental oxygen without the usage of any other pharmacologic agent could not be assessed. Second, intraoperative analgesia was provided with boluses of fentanyl, according to the hemodynamic response to pain. This is a relatively subjective method, which, to some extent, depends on the individual practice of the anesthesia care providers. On that account, there could appear differences in opioid administration between the included subjects based on patient age, body constitution, pain response, and subjective evaluation of the anesthesiologist. Third, preoperative anxiolysis and fluid administration could affect the results. All patients received a single dose of an anxiolytic drug (bromazepam 3 mg *per os*) the evening prior to surgery; however, that is a standardized dose, which cannot reduce anxiety to the same extent in all patients. Moreover, after admission to the hospital, patients were allowed to eat until evening and drink water until midnight prior to surgery. Therefore, there were individual differences in preoperative hydration between the included patients, which could affect the incidence and severity of PONV. Fourth, anesthesia time, and thus the exposure time to volatile anesthetics, was slightly different between the included subjects, which could influence the study outcome. Fifth, neostigmine in a dose of 2.5 mg IV was administered to all patients at the end of the procedure for reversal of neuromuscular blockade. Neostigmine has a parasympathomimetic effect, increasing intestinal motility and secretion, thus potentially contributing to the development of PONV [40].

Our study has some limitations. First of all, the sample size and the occurrence of the examined phenomenon were low. According to the sample size calculation based on the prevalence of the examined clinical condition in our institution, the number of patients was sufficient, but the incidence of PONV was not high enough. Hence, to obtain stronger statistical evidence, a greater sample size is required. Furthermore, only patients were trial-blinded, but trial personnel were not. Third, the administration of a single dose of an antiemetic drug represents an indispensable part of the best standard treatment in our hospital, which could highly affect our results. Fourth, the anesthesia time and overall exposure time to hyperoxic conditions was relatively short.

Taking into consideration the systemic effects of oncological disease, cancer treatment, and a higher incidence of PONV in this population, we aimed to investigate PONV in a specific, highly sensitive patient population – breast cancer patients. Our study is unique in patient selection, and the strength of our study is in obtaining a relatively homogenous patient population with a specific disease undergoing surgical intervention and general anesthesia under identical conditions. We included only low-risk patients for the development of postoperative cardiovascular or respiratory complications as a consequence of supplemental oxygen administration. Summarizing our results and the findings of the previous years, we can suggest that supplemental oxygen should not be routinely administered intraoperatively with the expectation of reducing PONV incidence. Most of the studies reporting a favorable effect of hyperoxia in the prevention of PONV were conducted a decade ago [28, 30, 33–35]. Bearing in mind that anesthesia practice has been remarkably changed since that time, our results provide up-to-date information about the perioperative use of hyperoxia in the current clinical setting.

Conclusion

We found no benefit of intra- and postoperative hyperoxia in reducing the incidence of PONV. Results obtained do not support routine administration of hyperoxia in addition to antiemetics for the prevention of PONV in patients undergoing breast cancer surgery. For that reason, we can suggest that supplemental oxygen should not be administered routinely during general anesthesia for breast cancer surgery to prevent PONV.

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R E F E R E N C E S

1. *Macario A, Weinger S, Carney S, Kim A.* Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg 1999; 89(3): 652–8.
2. *Sizemore DC, Singh A, Dua A, Singh K, Grose BW.* Postoperative Nausea [updated 2022 Nov 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500029/
3. *Franck M, Radtke FM, Apfel CC, Kuhly R, Baumeyer A, Brandt C,* et al. Documentation of post-operative nausea and vomiting in routine clinical practice. J Int Med Res 2010; 38(3): 1034–41.
4. *Pierre S, Whelan R.* Nausea and vomiting after surgery. Cont Edu Anaesth Crit Care Pain Med 2013; 13(1): 28–32.
5. *Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N.* A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999; 91(3): 693–700.
6. *Elvir-Lazo OL, White PF, Yumul R, Cruz Eng H.* Management strategies for the treatment and prevention of postoperative/postdischarge nausea and vomiting: an updated review. F1000Res 2020; 9: F1000 Faculty Rev-983.
7. *Stoops S, Kovac A.* New insights into the pathophysiology and risk factors for PONV. Best Pract Res Clin Anaesthesiol 2020; 34(4): 667–79.
8. *Vari A, Gazzanelli S, Cavallaro G, De Toma G, Tarquini S, Guerra C,* et al. Post-operative nausea and vomiting (PONV) after thyroid surgery: a prospective, randomized study comparing totally intravenous versus inhalational anesthetics. Am Surg 2010; 76(3): 325–8.
9. *Apfel CC, Kranke P, Katz MH, Goepfert C, Papenfuss T, Rauch S,* et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth 2002; 88(5): 659–68.
10. *Gecaj-Gashi A, Hashimi M, Sada F, Baftiu N, Salihu S, Terziqi H,* et al. Propofol vs isoflurane anesthesia-incidence of PONV in patients at maxillofacial surgery. Adv Med Sci 2010; 55(2): 308–12.
11. *Jewer JK, Wong MJ, Bird SJ, Habib AS, Parker R, George RB.* Supplemental perioperative intravenous crystalloids for postoperative nausea and vomiting. Cochrane Database Syst Rev 2019; 3(3): CD012212.
12. *Gan TJ.* Risk factors for postoperative nausea and vomiting. Anesth Analg 2006; 102(6): 1884–98.
13. *Morita T, Yamamoto M, Sakamoto A.* What are the factors affecting postoperative nausea and vomiting following breast cancer surgery with inhalation anesthesia? J Nippon Med Sch 2020; 88(5): 418–22.
14. *Temple-Oberle C, Shea-Budgell MA, Tan M, Semple JL, Schrag C, Barreto M,* et al. Consensus Review of Optimal Perioperative Care in Breast Reconstruction: Enhanced Recovery after Surgery (ERAS) Society Recommendations. Plast Reconstr Surg 2017; 139(5): 1056e–71e.
15. *Xie J, Huang X, Gao M, Wei L, Wang R, Chen J,* et al. Surgical Pharmacy for Optimizing Medication Therapy Management Services within Enhanced Recovery after Surgery (ERAS®) Programs. J Clin Med 2023; 12(2): 631.
16. *Rajan N, Joshi GP.* Management of postoperative nausea and vomiting in adults: current controversies. Curr Opin Anesthesiol 2021; 34(6): 695–702.
17. *Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS,* et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesth Analg 2020; 131(2): 411–48. Erratum in: Anesth Analg 2020; 131(5): e241.
18. *Kienbaum P, Schaefer MS, Weibel S, Schlesinger T, Meybohm P, Eberhart LH,* et al. Update on PONV-What is new in prophylaxis and treatment of postoperative nausea and vomiting? Summary of recent consensus recommendations and Cochrane reviews on prophylaxis and treatment of postoperative nausea and vomiting. Anaesthesist 2022; 71(2): 123–8. (German)
19. *Wenk M, Van Aken H, Zarbock A.* The new World Health Organization recommendations on perioperative administration of oxygen to prevent surgical site infections: A dangerous reductionist approach? Anesth Analg 2017; 125(2): 682–7.
20. *Weenink RP, de Jonge SW, van Hulst RA, Wingelaar TT, van Ooij PAM, Immink RV,* et al. Perioperative Hyperoxyphobia: Justified or Not? Benefits and Harms of Hyperoxia during Surgery. J Clin Med 2020; 9(3): 642.
21. *Akça O, Sessler DI.* Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Minerva Anesthesiol 2002; 68(4): 166–70.
22. *Mercadante S.* Nutrition in cancer patients. Support Care Cancer 1996; 4(1): 10–20.
23. *Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF,* et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100(10): 1043–9.
24. *Norderud K, Egholm G, Thim T, Olesen KKW, Madsen M, Jensen LO,* et al. Validation of the European Society of Cardiology and European Society of Anaesthesiology non-cardiac surgery risk score in patients treated with coronary drug-eluting stent implantation. Eur Heart J Qual Care ClinOutcomes 2019; 5(1): 22–7.
25. *Motamed C, Weil GG, Bourgain JL.* Impact of extending prevention of postoperative nausea and vomiting for cancer surgical patients in the PACU: a before and after retrospective study. Braz J Anesthesiol 2022; 72(6): 762–7.
26. *Wengritzky R, Mettho T, Myles PS, Burke J, Kakos A.* Development and validation of a postoperative nausea and vomiting intensity scale. Br J Anaesth 2010; 104(2): 158–66.
27. *Fasquel C, Huet O, Ozier Y, Quesnel C, Garnier M.* Effects of intraoperative high versus low inspiratory oxygen fraction (FiO_2) on patient's outcome: A systematic review of evidence from the last 20 years. Anaesth Crit Care Pain Med 2020; 39(6): 847–58.
28. *Hovaguimian F, Lysakowski C, Elia N, Tramér MR.* Effect of intraoperative high inspired oxygen fraction on surgical site infection, postoperative nausea and vomiting, and pulmonary function: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2013; 119(2): 303–16.
29. *Orhan-Sungur M, Kranke P, Sessler D, Apfel CC.* Does supplemental oxygen reduce postoperative nausea and vomiting? A meta-analysis of randomized controlled trials. Anesth Analg 2008; 106(6): 1733–8.
30. *Rincón DA, Valero JF.* Supplemental oxygen for the prevention of postoperative nausea and vomiting: a meta-analysis of randomized clinical trials. Rev Esp Anestesiol Reanim 2008; 55(2): 101–9. (Spanish)
31. *Holst JM, Klitholm MP, Henriksen J, Vallentin MF, Jessen MK, Bolther M,* et al. Intraoperative respiratory and hemodynamic strategies for reducing nausea, vomiting, and pain after surgery: Systematic review and meta-analysis. Acta Anaesthesiol Scand 2022; 66(9): 1051–60.
32. *Markwei MT, Babatunde IO, Kutlu-Yalcin E, Essber HA, Mascha EJ, Liu L,* et al. Perioperative Supplemental Oxygen and Postoperative Nausea and Vomiting: Subanalysis of a Trial, Systematic Review and Meta-analysis. Anesthesiology 2023; 138(1): 56–70.
33. *Greif R, Laciny S, Rapf B, Hickle RS, Sessler DI.* Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology 1999; 91(5): 1246–52.
34. *Purhonen S, Niskanen M, Wüstefeld M, Mustonen P, Hynynen M.* Supplemental oxygen for prevention of nausea and vomiting after breast surgery. Br J Anaesth 2003; 91(2): 284–7.

35. *Zhou Q, Cai M, Gou J, Ning N*. Effect of Postoperative High-Concentration Oxygen on Recovery After Thyroid Surgery: A Prospective, Open, Randomized, Controlled Study. Front Endocrinol (Lausanne) 2021; 12: 595571.
36. *Chiu C, Aleshi P, Esserman LJ, Inglis-Arkell C, Yap E, Whitlock EL*, et al. Improved analgesia and reduced post-operative nausea and vomiting after implementation of an enhanced recovery after surgery (ERAS) pathway for total mastectomy. BMC Anesthesiol 2018; 18(1): 41.
37. *Tripathy S, Mandal I, Rao PB, Panda A, Mishra T, Kar M*. Opioid-free anesthesia for breast cancer surgery: a comparison of ultrasound guided paravertebral and pectoral nerve blocks. A randomized controlled trial. J Anaesthesiol Clin Pharmacol 2019; 35(4): 475–80.
38. *Tabrizi S, Malhotra V, Turnbull ZA, Goode V*. Implementation of postoperative nausea and vomiting guidelines for female adult patients undergoing anesthesia during gynecologic and breast surgery in an ambulatory setting. J Perianesth Nurs 2019; 34(4): 851–60.
39. *Krieser KA, Riley JB, Baus JE, Hoffman JT, Sullivan JN, Lobato RL*. PONV Prophylaxis failure disproportionately affects female patients, despite intraoperative computerized decision support guidance. Graduate Med Edu Res J 2020; 2(1): 6.
40. *Jin Z, GanTJ, Bergese SD*. Prevention and Treatment of Postoperative Nausea and Vomiting (PONV): A Review of Current Recommendations and Emerging Therapies. Ther Clin Risk Manag 2020; 16: 1305–17.

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