Observational Study

Medicine®

OPEN

Effects of neoadjuvant chemotherapy on the depth of total intravenous anesthesia in patients with breast cancer undergoing unilateral modified radical mastectomy

A prospective observational study

Guisheng Wu, MD, Guanghua Fu, BM, Lei Zhang, BM, Zongwang Zhang, MD, Xuxiang Wang, BM*

Abstract

Toxic effects of neoadjuvant chemotherapy (NC) on nervous, hepatorenal, and pulmonary systems might affect general anesthesia depth. This study aimed to evaluate the effects of NC on depth of total intravenous anesthesia.

This prospective observational study enrolled 60 patients undergoing elective unilateral modified radical mastectomy during total intravenous anesthesia with propofol and remifentanil (January–June 2015; Liaocheng People's Hospital, China): the NC group (n=30) received NC, while the control group (n=30) did not. Propofol and remifentanil dosages were adjusted according to indexes of consciousness (IoC1: sedation; IoC2: analgesia) to control fluctuations of blood pressure and heart rate within 20% of baseline values. Parameters reflecting propofol/remifentanil dosages, intraoperative adverse events, and quality of anesthetic recovery were recorded.

The duration of propofol infusion (1.3±0.4 vs 1.8±0.5 hours, $P<.05$), mean propofol dosage (8.0±1.0 vs 9.3±1.5 mg kg^{-1} h^{-1}, $P<.05$), and adjustment frequency of target-controlled remifentanil infusion (2.9±1.8 vs 4.4±2.6 times/surgery, $P<.05$) were significantly lower in the NC group than in the control group; adjustment frequency of target-controlled propofol infusion was also numerically lower (2.0±1.1 vs 2.7±1.5 times/surgery, $P=.053$). Duration of remifentanil infusion, mean remifentanil dosage, voluntary eye opening, extubation time, and recovery score were not significantly different between groups. The incidence of tachycardia was lower in the NC group than in the control group (7.1% vs 37.0%, $P<.05$), but there was no significant difference in the incidence of total adverse events between groups.

NC can enhance the sensitivity of breast cancer patients to the anesthetic effect of propofol.

Abbreviations: BMI = body mass index, CNS = central nervous systems, EEG = electroencephalogram, GABA = gamma-aminobutyric acid, NC = neoadjuvant chemotherapy, $P_{ET}CO_2$ = pressure of end-tidal carbon dioxide, PNS = peripheral nervous systems.

Keywords: consciousness indexes, neoadjuvant chemotherapy, propofol, remifentanil, unilateral modified radical mastectomy

1. Introduction

Breast cancer, which occurs in the breast ductal epithelium, is the most common malignant tumor in women, and the worldwide incidence of this disease has increased year-on-year.[1] Breast cancer exerts a considerable burden not only on the women it affects, with notable impacts on both physical and mental health, but also on healthcare systems and society in general. Surgical resection is currently the mainstay of breast cancer treatment, with radiotherapy and chemotherapy playing an adjuvant role. Neoadjuvant chemotherapy (NC), which is administered before surgery, is a therapeutic technology that has been developed in the last few decades. Several clinical studies[2–4] have suggested that patients with stage II/III breast cancer are suitable for treatment with NC and that patients who desire not to have their breast removed but are not suitable for breast-conserving surgery can benefit from this treatment modality.

NC can decrease tumor size and clinical stage,[5] thereby increasing the chances of successful breast-conserving surgery, controlling subclinical metastasis, and improving patient survival.[6] Furthermore, NC can also prevent the accelerated development and metastasis of breast cancer caused by alterations in angiogenic factors after tumor resection.[7] Moreover, NC can also help clinicians and researchers to determine the sensitivities of different subtypes of breast cancer to chemotherapy drugs[8] and develop biological models to help our understanding of how this is influenced by biological and genetic factors,[9] thus potentially facilitating the future development of individualized therapies to improve the curative effect.

However, the toxicity of NC to healthy tissues can result in a variety of adverse effects on different systems of the body,[10–19] including the nervous, hepatorenal, and pulmonary systems.

Editor: Eric Bush.

This study was funded by the National Natural Science Foundation of China (grant no. 81471134).

The authors have no conflicts of interest to disclose.

Department of Anesthesiology, Liaocheng People's Hospital, Liaocheng, Shandong, China.

* Correspondence: Xuxiang Wang, Department of Anesthesiology, Liaocheng People's Hospital, No. 67, Dongchang West Road, Liaocheng 252000, Shandong, China (e-mail: wangxuxianglc@sohu.com).

Medicine (2018) 97:51(e13776)

Received: 18 January 2018 / Accepted: 29 November 2018

http://dx.doi.org/10.1097/MD.0000000000013776

Chemotherapy has been reported to have a neurotoxic action on both the central and peripheral nervous systems (CNS and PNS), with effects including peripheral and autonomic neuropathy, cerebral and cerebellar dysfunction, encephalopathy, seizures, and even coma.[20–22] Hepatic toxicity can manifest as elevated serum enzymes, fatty infiltration, cholestasis, reduced protein synthesis, coagulation abnormalities, and the development of cirrhosis and fibrosis.[20–22] Nephrotoxicity can result in renal tubular or/and glomerular damage and acute or chronic renal failure, while pulmonary abnormalities can include pneumonitis and fibrosis.[20–22]

The systemic toxicity of NC has important implications for general anesthesia.[20–22] Because the liver, kidneys, or/and lungs play important roles in the metabolism and elimination of general anesthetic agents, NC-induced dysfunction of these systems might influence the dosage of anesthetic needed to produce a given depth of anesthesia. In addition to potential effects on anesthetic drug metabolism, chemotherapy drugs also have toxic actions in the CNS[17,23,24] and can impair spatial learning and memory in mice,[25] thus raising the possibility that NC-induced neurotoxicity may also contribute to an altered sensitivity to general anesthetics. However, very few studies have examined the possibility that patients administered NC have an altered sensitivity to general anesthetic agents. Three previous investigations reported that the dosages of propofol and etomidate required for the induction of anesthesia were lower in patients who had received NC than in those who had not received NC.[26–28] As propofol and etomidate are predominantly metabolized in the liver, the authors of these studies suggested that chemotherapy-induced liver damage and nervous system injury might both contribute to an enhanced sensitivity to anesthetic agents. Nonetheless, despite the availability of some data regarding the induction of anesthesia, no previous studies have explored the effects of NC on the maintenance of and recovery from anesthesia.

In our previous study,[29] patients with breast cancer who received NC before surgery needed a higher dosage of anesthetic. And there was a faster clearance of muscle relaxants and quicker recovery of spontaneous respiration in these patients than those who did not receive NC. We hypothesized that patients with breast cancer who received NC would have a different sensitivity to general anesthetic agents than patients who did not. Therefore, this study aimed to measure the dosages of propofol and remifentanil administered to patients with breast cancer undergoing surgery and to compare the dosages needed to produce the same depth of anesthesia between those who received NC and those who did not. In addition, anesthesia-related complications were compared between groups. We anticipate that this study will provide useful information assisting anesthetists in administering general anesthesia to NC patients.

2. Methods

This prospective observational study enrolled consecutively patients undergoing modified radical mastectomy between January 1, 2015 and June 30, 2015 at the Breast Surgery Ward of Liaocheng People's Hospital, Liaocheng, China. This protocol was approved by the hospital ethics committee before commencement of the study (ethics approval document no. 2014065). Before inclusion in the study, all patients and their authorized relatives were provided with detailed information regarding the nature of the study and the possible benefits, risks, and discomfort, and written informed consent was obtained.

The inclusion criteria included: American Society of Anesthesiologists physical status class I (healthy person) or II (mild systemic disease); age 18 to 65 years; unilateral breast cancer; for the NC group: had appropriate indications for NC and were scheduled for surgery 3 weeks after receiving 4 to 6 courses of chemotherapy (docetaxel, epirubicin, and cyclophosphamide) in the breast surgery ward (to allow recovery of renal and hepatic function); for the control group: Breast Imaging Reporting and Data System classification of 4C or higher, a high degree of malignancy, and the planned extent of lesion resection (>3 cm) was comparable to that of patients in the NC group; laboratory investigations revealed no abnormalities of white blood cell count, hepatic function or renal function; and body mass index (BMI) 18 to 30 kg m^{-2}. The exclusion criteria included: pregnant patients; allergic to the medications used in this study; hypertension; hypotension; tachycardia; or bradycardia.

2.1. Anesthesia and monitoring

The induction and maintenance of anesthesia and the intraoperative monitoring protocol were the same for patients in both the NC and control groups. After entering the operate room, the patient was administered 8 mL kg^{-1} of Ringer's solution followed by a maintenance dose of 4 mL kg^{-1} h^{-1}. The blood pressure and heart rate of each patient 15 minutes after they entered the operate room were acquired as the baseline. The following parameters were monitored throughout anesthesia: conventional noninvasive blood pressure; electrocardiogram; pulse oxygen saturation (SpO_2); pressure of end-tidal carbon dioxide ($P_{ET}CO_2$); and indexes of consciousness (IoC1 and IoC2) (Angel-6000D Multiparameter Anesthesia Monitor, Shenzhen Weihaokang Medical Technology Co, Ltd, Guangdong, China). Anesthesia was induced using target-controlled infusion of propofol (Omnitest Medical [Shanghai] International Trade Co, Ltd, Shanghai, China) based on the Marsh pharmacokinetic model. The perfusion speed of propofol was set as plasma target concentration of 4.0 μg mL^{-1}. Remifentanil (Yichang Humanwell Pharmaceutical Co, Ltd, Yichang, China) was intravenously administrated at 3 μg kg^{-1} and cisatracurium at 0.2 mg kg^{-1}. Tracheal intubation was performed for mechanical ventilation when satisfactory muscle relaxation was achieved (about 3 minutes) according to train-of-4 stimulation (Veryark-TOF, Veryark Science and Technology Co, Ltd, Guangxi, China). The indexes of ventilation (Drägerwerk AG & Co KGaA, Lübeck, Germany) were set as tidal volume (8 mL kg^{-1}), respiratory rate (12 times min^{-1}), respiratory ratio (1:2), and $P_{ET}CO_2$ (35–45 mm Hg); 0.05 mg kg^{-1} of cisatracurium was administered to maintain the muscle relaxation at 45 minutes after the beginning of the surgery.

During the surgery, the anesthetist adjusted the infusion rate of propofol and remifentanil according to the values of IoC1 and IoC2. The target concentration of propofol was adjusted according to the sedative index IoC1 maintaining within 40 to 60. Every time the propofol target concentration was increased 0.5 μg mL when IoC1 was >60. Propofol was increased 1 μg mL when body movements were observed, and decreased 0.5 μg mL per adjustment when IoC1 was <40.[29] The analgesic index IoC2 was used to adjust the remifentanil target concentration (using the Minto remifentanil pharmacokinetic parameter set) and was maintained within the range 30 to 50. The remifentanil target concentration was increased 1 ng mL during every adjustment when IoC2 was >50 and decreased 1 ng mL when IoC2 was <30.

Adverse reactions to anesthesia were treated as follows: if the fluctuation in blood pressure or heart rate was <30% of the baseline value, ephedrine 6 mg or atropine 0.2 mg were administered, respectively; if the fluctuation in blood pressure or heart rate was >30% of the baseline value, urapidil 10 mg or esmolol 1 mg kg was given, respectively.

2.2. Collection of clinical data

Baseline clinical and demographic data including age, gender, weight, height, BMI, blood pressure, and heart rate were recorded for each patient. In addition, the following information was obtained regarding the anesthetic procedure: remifentanil dosage parameters (frequency of adjustment of the target concentration, duration of infusion, and mean dosage); propofol dosage parameters (frequency of adjustment of the target concentration, duration of infusion, and mean dosage); incidence of intraoperative adverse events (hypertension, hypotension, tachycardia, bradycardia, and body movements); and the quality of the patient's anesthetic recovery (time to voluntary eye opening, extubation time, awakening score [OAA/S score], and whether the patient showed awareness during surgery).

With regard to intraoperative adverse events, hypertension was defined as a systolic pressure >160 mm Hg, hypotension as a systolic pressure <90 mm Hg, tachycardia as heart rate >90 bpm, and bradycardia as heart rate <45 bpm.[30] The time to voluntary eye opening was defined as the interval from stopping the infusion of the anesthetic drugs to the time the patient showed voluntary eye movements when their name was called in a normal voice. The OAA/S score was estimated at the moment of extubation. Intraoperative awareness (using modified Brice questionnaires) was estimated after the patients had fully awakened.

2.3. Outcome measures

The outcome measures compared between the 2 groups were the dosage parameters (frequency of adjustment of the target concentration, duration of infusion, and mean dosage) for propofol and remifentanil, incidence of intraoperative adverse events (hypertension, hypotension, tachycardia, bradycardia, or body movements), and the quality of the patient's anesthetic recovery (time to voluntary eye opening, extubation time, awakening score, and whether awareness was shown during surgery).

2.4. Statistical analysis

According to the results of a previous study, the average dosage of propofol in patients undergoing unilateral modified radical mastectomy and not receiving NC was 8.8 ± 1.1 mg kg^{-1} h^{-1}, while that of remifentanil was 3.8 ± 1.9 μg kg^{-1} h^{-1}.[29] A significant difference in anesthetic dosage in the NC group was defined as a fluctuation more than 20% compared with the control group.[29] The sample size for each group was calculated to be 24 patients, based on a significance level $\alpha = 0.05$ and test power $1 - \beta = 0.80$. Assuming a dropout rate of 20%, a total of 60 patients (30 in the NC group and 30 in the control group) were enrolled.

Data analysis was performed using SPSS v17.0 statistical software (IBM, Armonk, NY). The Kolmogorov–Smirnov test of normality was conducted for continuous data. Continuous data are shown in the form of mean ± standard deviation. Comparisons between groups were performed by the independent sample *t*-test or the Wilcoxon rank-sum test. Categorical data are presented as n (%) and were compared using the chi-squared test. A *P* value <.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study participants

A total of 71 patients with breast cancer were screened for eligibility, resulting in 11 patients being excluded (did not meet inclusion criteria, n=6; declined to participate, n=3; surgery cancelled, n=2). Thus, 60 patients were enrolled in the study (30 each in the NC and control groups). Two patients were subsequently excluded from the NC group due to the surgical method change, and 3 patients were excluded from the control group due to noncompliance to the study protocol. Therefore, a total of 55 patients were included in the final analysis (NC group, n=28; control group, n=27).

There were no significant differences between the NC and control groups in age, height, weight, BMI, systolic pressure, diastolic pressure, or heart rate (Table 1).

3.2. Anesthetic dosage parameters and quality of anesthetic recovery

During the anesthesia, the sedative index IoC1 was maintained within the range 40 to 60 to adjust the propofol target concentration, and the analgesic index IoC2 was maintained within the range 30 to 50 to adjust the remifentanil target concentration. Data for the anesthetic dosage parameters and quality of anesthetic recovery are shown in Table 2. Compared with the control group, patients in the NC group had a significantly shorter duration of propofol infusion (1.3 ± 0.4 hours vs 1.8 ± 0.5 hours, $P < .05$), lower mean propofol dosage (8.0 ± 1.0 mg kg^{-1} h^{-1} vs 9.3 ± 1.5 mg kg^{-1} h^{-1}, $P < .05$), and a lower frequency of adjustment of remifentanil target concentration (2.9 ± 1.8 times/surgery vs 4.4 ± 2.6 times/surgery, $P < .05$); in addition, there was a trend toward a lower frequency of adjustment of propofol target concentration (2.0 ± 1.1 times/surgery vs 2.7 ± 1.5 times/surgery, $P = .053$). There were no significant differences between groups in the duration of remifentanil infusion, mean remifentanil dosage, voluntary eye opening, extubation time, or recovery score (Table 2).

3.3. Intraoperative adverse events

The incidence of tachycardia was significantly lower in the NC group than in the control group (7.1% vs 37.0%; $P < .05$), but

Table 1

Baseline demographic and clinical data for patients in the 2 groups.

Parameters	NC group (n=28)	Control group (n=27)	*P*
Age, y	48±7	49±7	.472
Weight, kg	63±7	62±8	.811
Height, cm	160±5	159±6	.212
Body mass index, kg m^{-2}	25±2	24±3	.742
Systolic pressure, mm Hg	128±9	127±10	.341
Diastolic pressure, mm Hg	75±8	73±7	.954
Heart rate, bpm	76±9	74±6	.321

Data presented as the mean ± standard deviation.
NC = neoadjuvant chemotherapy.

Table 2

Comparison of anesthetic dosage parameters and quality of anesthetic recovery between the 2 groups.

Items	NC group (n=28)	Control group (n=27)	P
Propofol			
Frequency of target concentration adjustment (times/surgery)	2.0±1.0	2.7±1.5	.053
Infusion duration, h	1.6±0.4	1.8±0.5	.049
Mean dose, mg kg^{-1} h^{-1}	8.0±1.0	9.3±1.5	.040
Remifentanil			
Frequency of target concentration adjustment (times/surgery)	2.9±1.8	4.4±2.6	.002*
Infusion duration, h	1.6±1.9	1.6±0.6	.361
Mean dose, μg kg^{-1} h^{-1}	4.9±2.8	5.2±2.5	.538
Quality of anesthetic recovery			
Time to voluntary eye opening, min	6.0±3.5	6.8±2.9	.745
Extubation time, min	12.1±3.4	12.8±3.7	.750
Awakening score	4.0±0.9	3.8±0.9	.811

Data presented as the mean±standard deviation.
NC=neoadjuvant chemotherapy.
* $P<.05$ (Wilcoxon rank-sum test).

there was no significant difference in the total incidence of adverse events between the 2 groups (Table 3).

4. Discussion

The main finding of the present study was that in Chinese patients with breast cancer undergoing modified radical mastectomy, those who received NC had a significantly shorter duration of propofol infusion, lower mean propofol dosage, and lower frequency of adjustment of remifentanil target concentration; in addition, there was a trend toward a lower frequency of adjustment of propofol target concentration. In addition, the quality of anesthetic recovery and overall incidence of adverse events did not differ between the 2 groups. These data indicate that NC can enhance the sensitivity of breast cancer patients to the anesthetic effect of propofol.

The indexes of consciousness (IoC1 and IoC2) are new indexes reflecting the state of the brain's electrical activity. To measure these indexes, 3 electrodes are fixed on the patient's forehead to record electroencephalogram (EEG) signals, and symbolic dynamics is used to divide the EEG signal into several partitions, each marked with a symbol; the time sequences are then transformed into symbolic sequences. The depth of sedation (IoC1) is determined by the beta ratio, burst suppression ratio, and symbolic sequences, and the depth of analgesia (IoC2) is determined by symbolic sequences and the depth of sedation (IoC1). Studies have indicated that pain can cause changes in the electrical activities of the brain.[31–33] A study by Jensen et al[34] determined that IoC1 (qCON) could reliably predict the disappearance of the eyelash reflex (loss of consciousness) during intravenous anesthesia with propofol and remifentanil, and that IoC2 (qNOX) could predict whether patients would exhibit body movements when they encountered noxious stimulation under a similar depth of anesthesia. In this study, the induction and maintenance of anesthesia was achieved using target-controlled infusion of propofol and remifentanil. These agents are widely used short-acting general anesthetic drugs that have the advantage of rapid onset and offset. The dosages of the drugs were reliably calculated based on the infusion duration and total dosage read on the intravenous infusion pump, and assessment of IoC1 and IoC2 enabled precise control of the depth of anesthesia: the dosage of propofol was adjusted according to the sedation index (IoC1) and the dosage of remifentanil was adjusted according to the analgesia index (IoC2).

Breast cancer is a systemic disease,[35] and NC administered before surgery is an important part of the comprehensive treatment of this disease.[5] NC can increase the rate of breast-conserving surgery, enhance the effect of surgical treatment, and improve the survival rate of patients.[5–7] However, NC can also cause liver and kidney dysfunction and nervous system damage.[13,14,17,23,24] Because general anesthetic drugs act mainly on the nervous system and most are eliminated by the liver and kidneys, it is possible that NC boosts the effects of anesthetic agents by reducing their metabolism by the hepatorenal system and enhancing the sensitivity of the CNS to their actions. This hypothesis is supported by the observations described in the present study: patients treated with NC exhibited a shorter duration of propofol infusion, lower frequency of adjustment of propofol target concentration (borderline result), lower mean propofol dosage, and lower frequency of adjustment of remifentanil target concentration. Owczuk et al report that in female patients pretreated with anthracyclines for breast cancer, the tendency to Q-T corrected (QTc) prolongation during isoflurane-containing general anesthesia was more strongly expressed than in patients without previous chemotherapy, indicating that chemotherapy may improve expressions associated with anesthesia.[15] Furthermore, our data are consistent with those obtained in our previous study,[29] which showed that patients with breast cancer who received NC needed a higher dosage of anesthetic and manifested a faster clearance of muscle relaxants and quicker recovery of spontaneous respiration than those who did not receive NC. Indeed, patients who had received NC exhibited higher IoC1 and IoC2 values than the reference ranges for about 75% of the duration of anesthesia; some patients underwent the light anesthesia with 73 to 88 of IoC1 and IoC2, indicating that they had almost regained consciousness. This was despite the fact that the effective concentrations of propofol and remifentanil were in the range 3.5 to 5.5 μg mL and 2 to 5 ng mL, respectively, and that the hemodynamic parameters were within the reference ranges.

The findings of this study are consistent with the results of observations made in previous investigations.[26–28,36] A study by He et al[26] revealed that patients who received paclitaxel or cyclophosphamide plus adriamycin and 5-fluorouracil before surgery showed a decreased EC50 for the target-controlled

Table 3

Comparison of intraoperative adverse events between the 2 groups.

Adverse events	NC group (n=28)	Control group (n=27)	P
Hypertension	6 (21.4)	2 (7.1)	.140
Hypotension	12 (42.9)	15 (55.6)	.346
Tachycardia	3 (10.7)	2 (7.1)	.670
Bradycardia	2 (7.1)	10 (37.0)	.007*
Total number of adverse events	23 (20.5)	29 (26.9)	.270
Number of patients with adverse events	16 (57.1)	20 (74.1)	.187
Intraoperative awareness	0	0	1.000

Data presented as n (%).
NC=neoadjuvant chemotherapy.
* $P<.05$.

infusion of propofol during the induction of total intravenous anesthesia. The authors speculated that this might be an effect of chemotherapy-induced liver damage[13] on the metabolism of propofol. Research by Tan et al[27] also found that chemotherapy in patients with breast cancer could enhance the sedative effect of propofol and shorten the onset time during the induction of anesthesia. He et al also reported that for propofol and etomidate, the median effective concentration of intravenous anesthetic required to cause loss of consciousness was lower in patients who had received NC.[28] As propofol and etomidate are predominantly metabolized in the liver, the authors suggested that chemotherapy-induced liver damage and nervous system injury might both contribute to the enhanced sensitivity to anesthetic agent.[28] Du et al found that NC reduced the minimum alveolar concentration of sevoflurane needed to produce 50% blockade of the adrenergic response to surgical incision in patients undergoing radical gastrectomy.[36] Jacquillat et al report that adjuvant chemotherapy is necessary, especially in young patients and those with extensive disease. Initial chemotherapy preceding any local or regional treatment is justified on the grounds that both surgery and anesthesia lead to immunodepression.[37]

Marcotte et al report that addition of suberoylanilide hydroxamic acid to taxane chemotherapy improves the therapeutic effect on triple-negative breast cancer while decreasing the detrimental effect of paclitaxel on wound healing. This may have substantial implications on improving outcomes in breast reconstruction following chemotherapy.[38] Sevoflurane is eliminated mainly by the lungs (with smaller contributions from the kidneys and skin), hence the authors proposed that the enhanced sensitivity to anesthetics in patients who had received NC was due to chemotherapy-induced nervous system damage.[36]

A study of 300 patients by Berliere et al showed that for breast cancer surgery and adjuvant therapy, hypnosis sedation exerts beneficial effects on nearly all modalities of breast cancer treatment. Furthermore, they suggest that benefits of hypnosis sedation on breast cancer treatment are very encouraging and they further promote the concept of integrative oncology.[39] The detailed mechanisms by which chemotherapy might influence the sensitivity to anesthesia remain to be elucidated.

Propofol is a short-acting intravenous anesthetic that is rapidly distributed around the body within 40 seconds after intravenous injection to produce a sedative effect. The mechanism of propofol's anesthetic action is to enhance the effect of gamma-aminobutyric acid (GABA) and facilitate its inhibitory effect on postsynaptic nerves.[40,41] Propofol has a rapid distribution (a half-time of 2–4 minutes) and elimination (a half-time of 30–60 minutes), is widely distributed, and is quickly eliminated from the body (an overall elimination rate of 1.5–2 L min^{-1}). Propofol is mainly metabolized in the liver,[42] with glucuronidation accounting for just over 60% of the metabolism and cytochrome P450 (predominantly P4502B6) accounting for nearly 40%;[43,44] the metabolites are excreted in the urine. Docetaxel, epirubicin, and cyclophosphamide are also transformed or metabolized in the liver, and the liver damage caused by chemotherapy agents[45,46] may influence the pharmacokinetics and pharmacodynamics of propofol. For example, liver dysfunction can result in reduced albumin synthesis, decreasing the binding of propofol to plasma proteins and thus increasing the free drug concentration. Although the patients in our study received anesthesia and surgery 3 weeks after NC, a previous study has reported that liver dysfunction can persist for up to 3 to 4 weeks after cyclophosphamide chemotherapy.[47] Thus, the patients in our study may have had residual liver dysfunction that impaired propofol metabolism or its binding to plasma proteins.

Chemotherapy-induced damage to the CNS and PNS[17,48,49] may also contribute to the enhancement of propofol's effects. Docetaxel, which belongs to the taxane family of antineoplastic compounds, acts to strengthen the polymerization of tubulin and inhibit the depolymerization of the microtubule.[30,50] The formation of a stable, nonfunctional microtubule bundle prevents mitosis of tumor cells, causing cell division to be blocked in the M phase. Two studies found that the stability and efficiency of the synaptic in the brain tissue were enhanced, and the transmission speed of the information of the neurons was increased.[30,50] Propofol interferes with synaptic transmission of neural information by activating the GABA receptor, thereby prolonging the inhibitory postsynaptic current and enhancing the inhibitory effect on the synapse. Some evidence shows that chemotherapeutic drugs can enhance the function of the $GABA_A$ receptor, in part due to the upregulated expression of estrogen and progesterone receptors.[51,52] This is a potential mechanism by which docetaxel may enhance the sedative effect of propofol.

In this study, the incidence of bradycardia was significantly higher in the control group than in the NC group, and this may be related to the higher dosages of propofol and remifentanil used in the control group. However, there were no significant differences between the 2 groups in the quality of anesthesia recovery and the incidences of hypertension, hypotension, tachycardia, number of patients with adverse events, and total incidence of adverse events during surgery. Therefore, compared with patients in the control group, patients in the NC group were able to achieve a similar depth of anesthesia with lower dosages of propofol and remifentanil.

This study has some limitations. First, as this was a prospective observational study rather than a randomized controlled trial, there may have been selection bias. Second, this was a single-center study, so the results may not be generalizable to other regions of China or other countries. Third, the sample size was small so the study may have been underpowered to detect some real differences between groups. Fourth, the possible sensitizing effects of NC on anesthetic agents other than propofol and remifentanil were not examined. Lastly, the mechanisms by which NC augmented the effects of general anesthesia were not explored.

In conclusion, for Chinese patients with breast cancer undergoing modified radical mastectomy, those who received NC had a significantly shorter duration of propofol infusion, lower mean propofol dosage, and lower frequency of adjustment of remifentanil target concentration; there was also a trend toward a lower frequency of adjustment of propofol target concentration. The quality of anesthetic recovery and overall incidence of adverse events did not differ between groups. These findings suggest that NC can enhance the sensitivity of patients with breast cancer to the anesthetic effect of propofol.

Acknowledgment

The authors gratefully acknowledge the study participants and the staff at Liaocheng People's Hospital for their cooperation.

Author contributions

Conceptualization: Zongwang Zhang, Xuxiang Wang.
Data curation: Guisheng Wu, Zongwang Zhang.
Formal analysis: Guisheng Wu.

Investigation: Guanghua Fu, Lei Zhang.
Methodology: Guanghua Fu, Lei Zhang.
Writing – original draft: Guisheng Wu.
Writing – review & editing: Xuxiang Wang.

References

[1] Surveillance, Epidemiology, and End Results (SEER) Program. SEER*-Stat Database: Incidence-SEER 9 Regs Research Data, Nov. 2010 Sub. (1973–2008). i. <Katrina/Rita Population Adjustment>- Linked to County Attributes—Total US, 1969–2009 Counties. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch; 2011. Released April 2011 based on the November 2010 submission.
[2] van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224–37.
[3] Broet P, Scholl SM, de la Rochefordiere A, et al. Short and long-term effects on survival in breast cancer patients treated by primary chemotherapy: an updated analysis of a randomized trial. Breast Cancer Res Treat 1999;58:151–6.
[4] Mauriac L, MacGrogan G, Avril A, et al. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. Institut Bergonie Bordeaux Groupe Sein (IBBGS). Ann Oncol 1999;10:47–52.
[5] Bonadonna G, Veronesi U, Brambilla C, et al. Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 1990;82:1539–45.
[6] Gianni L, Baselga J, Eiermann W, et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol 2009;27:2474–81.
[7] Bhalla K, Harris WB. Molecular and biologic determinants of neoadjuvant chemotherapy of locoregional breast cancer. Semin Oncol 1998;25(suppl 3):19–24.
[8] Vincent-Salomon A, Rousseau A, Jouve M, et al. Proliferation markers predictive of the pathological response and disease outcome of patients with breast carcinomas treated by anthracycline-based preoperative chemotherapy. Eur J Cancer 2004;40:1502–8.
[9] Petit T, Wilt M, Velten M, et al. Comparative value of tumour grade, hormonal receptors, Ki-67, HER-2 and topoisomerase II alpha status as predictive markers in breast cancer patients treated with neoadjuvant anthracycline-based chemotherapy. Eur J Cancer 2004;40:205–11.
[10] van Laar JA, Rustum YM, Ackland SP, et al. Comparison of 5-fluoro-2′-deoxyuridine with 5-fluorouracil and their role in the treatment of colorectal cancer. Eur J Cancer 1998;34:296–306.
[11] Horn CC, Kimball BA, Wang H, et al. Why can't rodents vomit? A comparative behavioral, anatomical, and physiological study. PLoS ONE 2013;8:e60537.
[12] Springer K, Brown M, Stulberg DL. Common hair loss disorders. Am Fam Physician 2003;68:93–102.
[13] van Outryve S, Schrijvers D, van den Brande J, et al. Methotrexate-associated liver toxicity in a patient with breast cancer: case report and literature review. Neth J Med 2002;60:216–22.
[14] Yao X, Panichpisal K, Kurtzman N, et al. Cisplatin nephrotoxicity: a review. Am J Med Sci 2007;334:115–24.
[15] Owczuk R, Wujtewicz MA, Sawicka W, et al. Is prolongation of the QTc interval during isoflurane anaesthesia more prominent in women pretreated with anthracyclines for breast cancer? Br J Anaesth 2004; 92:658–61.
[16] Bai M, Wang B, Wang X. Randomized trial of weekly docetaxel and cisplatin combined with concurrent 3DCRT in patients with locally advanced esophageal cancer. Chin-Ger J Clin Oncol 2013;12:361–4.
[17] Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. Cancer Chemother Pharmacol 2009; 63:761–7.
[18] Richardson G, Dobish R. Chemotherapy induced diarrhea. J Oncol Pharm Pract 2007;13:181–98.
[19] Halpern NA, Bettes L, Greenstein R. Federal and nationwide intensive care units and healthcare costs. Crit Care Med 1994;22:2001–7.
[20] Allan N, Siller C, Breen A. Anaesthetic implications of chemotherapy. Contin Educ Anaesth Crit Care Pain 2012;12:52–6.
[21] Gehdoo RP. Anticancer chemotherapy and it's anaesthetic implications (current concepts). Indian J Anaesth 2009;53:18–29.
[22] Maracic L, Van Nostrand J, Beach D. Update for nurse anesthetists. Anesthetic implications for cancer chemotherapy. Aana J 2007; 75: 219–26.
[23] Newton HB. Neurological complications of chemotherapy to the central nervous system. Handb Clin Neurol 2012;105:903–16.
[24] Schlegel U. Central nervous system toxicity of chemotherapy. Eur Assoc Neuro Oncol Mag 2011;1:25–9.
[25] Winocur G, Vardy J, Binns MA, et al. The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. Pharmacol Biochem Behav 2006;85:66–75.
[26] He ZJ, Li ZH, Hu YH. Effect of neoadjuvant chemotherapy on the half effective target concentration of propofol in patients with breast cancer at the time of loss of consciousness. Chin J Anesthesiol 2010;30:273–5.
[27] Tan JT, Xu HM, Jia L. The effect of chemotherapy on the sedative effect of propofol in patients with breast cancer. Chinese J Anesthesiol 2014;34:395–7.
[28] He ZJ, Hu YH, Fan ZY. Median effective effect-site concentration of intravenous anesthetics for loss of consciousness in neoadjuvant chemotherapy patients. Chin Med J (Engl) 2011;124:504–8.
[29] Wu G, Zhang L, Wang X, et al. Effects of indexes of consciousness (IoC1 and IoC2) monitoring on remifentanil dosage in modified radical mastectomy: a randomized trial. Trials 2016;17:167.
[30] Hoskison MM, Shuttleworth CW. Microtubule disruption, not calpain-dependent loss of MAP2, contributes to enduring NMDA-induced dendritic dysfunction in acute hippocampal slices. Exp Neurol 2006; 202:302–12.
[31] Nir RR, Sinai A, Moont R, et al. Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. Clin Neurophysiol 2012;123:605–12.
[32] Huber MT, Bartling J, Pachur D, et al. EEG responses to tonic heat pain. Exp Brain Res 2006;173:14–24.
[33] Garkavenko VV, Gorkovenko AV, Man'kovskaia EP, et al. Change in the power of EEG activity in the alpha range in response to tonic pain stimulation of the distal joint of the little finger. Fiziol Cheloveka 2005;31:77–84.
[34] Jensen EW, Valencia JF, Lopez A, et al. Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia. Acta Anaesthesiol Scand 2014;58:933–41.
[35] Fisher B, Saffer E, Rudock C, et al. Effect of local or systemic treatment prior to primary tumor removal on the production and response to serum growth-stimulating factor in mice. Cancer Res 1989;49:2002–4.
[36] Du W, Li C, Wang H, et al. Effect of neoadjuvant chemotherapy on sevoflurane MAC-BAR value of patients undergoing radical stomach carcinoma surgery. Int J Clin Exp Med 2015;8:5649–57.
[37] Jacquillat C, Baillet F, Auclerc G, et al. Neoadjuvant chemotherapy of breast cancer. Drugs Exp Clin Res 1986;12:147–52.
[38] Marcotte JH, Rattigan DA, Irons RF, et al. The effect of the histone deacetylase inhibitor suberoylanilide hydroxamic acid and paclitaxel treatment on full-thickness wound healing in mice. Ann Plast Surg 2018;81:482–6.
[39] Berliere M, Roelants F, Watremez C, et al. The advantages of hypnosis intervention on breast cancer surgery and adjuvant therapy. Breast 2018;37:114–8.
[40] Hara M, Kai Y, Ikemoto Y. Enhancement by propofol of the gamma-aminobutyric acid A response in dissociated hippocampal pyramidal neurons of the rat. Anesthesiology 1994;81:988–94.
[41] Orser BA, Wang LY, Pennefather PS, et al. Propofol modulates activation and desensitization of GABAA receptors in cultured murine hippocampal neurons. J Neurosci 1994;14:7747–60.
[42] Takizawa D, Sato E, Hiraoka H, et al. Changes in apparent systemic clearance of propofol during transplantation of living related donor liver. Br J Anaesth 2005;95:643–7.
[43] Favetta P, Degoute CS, Perdrix JP, et al. Propofol metabolites in man following propofol induction and maintenance. Br J Anaesth 2002; 88:653–8.
[44] Oda Y, Hamaoka N, Hiroi T, et al. Involvement of human liver cytochrome P4502B6 in the metabolism of propofol. Br J Clin Pharmacol 2001;51:281–5.
[45] Takamoto T, Hashimoto T, Sano K, et al. Recovery of liver function after the cessation of preoperative chemotherapy for colorectal liver metastasis. Ann Surg Oncol 2010;17:2747–55.
[46] Bosilkovska M, Walder B, Besson M, et al. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. Drugs 2012;72:1645–69.

[47] Zsigmond EK, Robins G. The effect of a series of anti-cancer drugs on plasma cholinesterase activity. Can Anaesth Soc J 1972;19: 75–82.
[48] Vardy J, Tannock I. Cognitive function after chemotherapy in adults with solid tumours. Crit Rev Oncol Hematol 2007;63: 183–202.
[49] Ocean AJ, Vahdat LT. Chemotherapy-induced peripheral neuropathy: pathogenesis and emerging therapies. Support Care Cancer 2004;12: 619–25.
[50] Kaech S, Parmar H, Roelandse M, et al. Cytoskeletal microdifferentiation: a mechanism for organizing morphological plasticity in dendrites. Proc Natl Acad Sci USA 2001;98:7086–92.
[51] Vearncombe KJ, Rolfe M, Wright M, et al. Predictors of cognitive decline after chemotherapy in breast cancer patients. J Int Neuropsychol Soc 2009;15:951–62.
[52] Jain V, Landry M, Levine EA. The stability of estrogen and progesterone receptors in patients receiving preoperative chemotherapy for locally advanced breast carcinoma. Am Surg 1996;62:162–5.