Neoadjuvant Chemotherapy Can Decrease the EC50 of Propofol with Effect-Site for Inducing the Loss of Consciousness in Patients with Breast Cancer: A Prospective Study

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Abstract
Background: Neoadjuvant chemotherapy has many advantages, including shrinking the tumor volume, reducing the scope of operation, decreasing the degree of trauma and providing evidence for postoperative chemotherapy. However, a certain degree changes of physiological are associated with neoadjuvant chemotherapy. Therefore, we suspect that the sensitive to general agents would be also changed after neoadjuvant chemotherapy. This study aimed to determine the minimum effective concentration represented by the EC50 of propofol for inducing loss of consciousness (LOC).

Methods: Sixty patients with breast cancer were enrolled in this study. Patients with or without neoadjuvant chemotherapy were allocated into Group NC and Group C respectively. The concentration of propofol was decided by using the up-down method with an initial concentration of 2.5 µg/mL and concentration change of 0.3µg/mL. An effective induction of LOC was defined as the disappear of eyelash reflex and no response to language stimulation. The Dixon and Massey formula was applied to calculate the EC50 for both groups.

Results: The EC50 of propofol for inducing LOC were 4.1µg/mL (95%CI, 3.7-4.5µg/mL) and 3.3µg/mL (95%CI, 2.8-3.8µg/mL). There was significant difference between the two groups.

Conclusion: Neoadjuvant chemotherapy can increase the sensitive of propofol, can decrease the EC50 of propofol for inducing of LOC in patients with breast cancer.

Keywords: Neoadjuvant Chemotherapy, Ec50, Propofol, Loss of Consciousness, Breast Cancer.

Introduction
Neoadjuvant chemotherapy has many advantages, including shrinking the tumor volume, down-staging the tumor, reducing the scope of operation, decreasing the degree of trauma, providing evidence for postoperative chemotherapy and even avoiding mastectomy [1]. However, a certain degree changes of physiological are associated with neoadjuvant chemotherapy, such as immune function and hepatic function [2]. Moreover, studies reported that cognitive function declined after neoadjuvant chemotherapy in patients with breast cancer. Therefore, we suspect that the sensitive to general agents would be also changed of patients after neoadjuvant chemotherapy. This study aimed to determine the minimum effective concentration represented by the median effective concentration (EC50), which means the concentration that would be necessary to provide effective induction for 50% of the patients treated) of propofol for inducing loss of consciousness (LOC), using up-down allocation method.

Materials and Methods
Subjects and setting
Following Institutional Ethics Committee approval (Jiaxing University Affiliated Women and Children Hospital) and patient written informed consent from all patients, sixty patients with the statue of American Society of Anesthesiologists’ physical class I or II, scheduled for elective modify radical mastectomy, were enrolled in this study. Exclusion criteria were as follows: body mass index (BMI) greater than 30 kg/m², age <20 years or >60 years, chronic hypertension, and patients with a history of cardiac, respiratory, renal or hepatic failure. Based on a computer-generated grouping number sheets using EXCEL (Microsoft Office software), patients with or without neoadjuvant chemotherapy were allocated into Group NC and Group C respectively (n =30). In Group NC, patients received TEC protocol for neoadjuvant chemotherapy: epirubicin 75 mg/m²
and cyclophosphamide 500 mg/m² on day 1, docetaxel 75 mg/m² on day 2, at 21-day intervals. Ten to fifteen days after neoadjuvant chemotherapy (all the patients received four to six times of course of treatment), patient underwent elective modify radical mastectomy.

Induction and maintenance of general anesthesia
All patients received no premedication. After arriving in Operation Theater, each patient had an intravenous cannula inserted into a peripheral arm vein and received an infusion of 500 mL 37°C Ringer’s solution before the induction of anesthesia. Standard monitoring including non-invasive blood pressure (NIBP), pulse oximetry (SpO₂) and electrocardiogram (ECG), and all patients were also monitored with the Bispectral Index (BIS) and train-of-four stimulation (TOF) (TCI-III-B, Weili Fangzhou Guangzhou, China).

Anaesthesia was induced with effect-site of 2.5 µg/mL of propofol (target control injection, TCI) (TCI-III-B, Weili Fangzhou Guangzhou, China) with the pharmacokinetic and pharmacodynamic (PK-PD) model introduced by Schneider and colleagues for propofol [3]. An effective induction of LOC was defined as the disappear of eyelash reflex and no response to language stimulation. Otherwise it was regarded as an ineffective induction of LOC. The concentration of propofol for subject was according to the response (effective or ineffective) of previous patient. In brief, If the response of the previous patient was effective, the concentration of propofol for the next patient was decreased by 0.3 µg/mL in that group. Conversely, if the response of the patient was ineffective, the concentration of propofol for the next patient was increased by 0.3 µg/mL in that group.

If it was an ineffective concentration, 2 mg/kg intravenous propofol was rescued to help the induction of LOC. After an effective induction of LOC, 4.0 mg/mL of remifentanil also via a TCI bump (TCI-III-B, Weili Fangzhou Guangzhou, China) with the pharmacokinetic and pharmacodynamic (PK-PD) model introduced by Minto and colleagues [4]. And 0.6mg/kg rocuronium was administrated to facilitate tracheal intubation. Anaesthesia was also maintained with propofol and remifentanil. The concentration of propofol was adjusted in steps of 0.5µg/mL according to the value of BIS which was controlled between 40 and 60. But the concentration of propofol should not less than 2.0µg/mL in order to avoiding intraoperative awareness. Similarly, the concentration of remifentanil was adjusted in steps of 0.5 ng/mL based on the variation of blood pressure and heart rate which was kept the variation changed less than 10 percentages than the former record of blood pressure or heart rate. Hypotension was defined as systolic blood pressure (SBP) less than 90 mmHg or a 20% decrease from baseline level. Baseline blood pressure of the patient was recorded in the preoperative room as the average of 3 readings taken 1 min apart. Ephedrine 5 mg was given intravenously if necessary. Bradycardia was defined as heart rate less than 60 beats per minute. Atropine 0.5 mg was intravenously administered when bradycardia occurred.

Data collecting
The primary outcome of this study was the effective and ineffective concentration of propofol for inducing LOC. Patients’ demographic data including age, body weight, height and duration of surgery were recorded. The onset time and dose of LOC was also studied.

Statistical analysis
According to Tyagi and our previous study, a sample size of 30 patients for each group was determined in the current study, because sample size is regarded as adequate when 6 pairs of reversal of sequence are achieved [5,6]. The Dixon and Massey formula was applied to calculate the EC50 for both groups [7]. Demographic data were collected and are presented as count or mean ± SD as appropriate. Nominal data were analyzed using the Chi-square test, and continuous data were analyzed using Student t test for intergroup comparison. Statistical analysis was performed with Graphpad Prism 5 (Version 5.01). Statistical significance was defined as P < 0.05 (two-sided).

Results
The CONSORT diagram of the present study is showed in (Figure 1). A total of 60 patients were assessed for eligibility, and all of them were enrolled and assigned into the Group NC (n = 30) or Group C (n = 30).

Data are presented as mean ± SD. *Student t test
The EC50 of propofol for inducing LOC were 4.1µg/mL (95%CI, 3.7-4.5µg/mL) and 3.3µg/mL (95%CI, 2.8-3.8µg/mL) in Group NC and Group C respectively. There was significant difference between the two groups. The individual responses (effective or ineffective induction) to the corresponding propofol concentration are showed in (Figure 2).

Figure 1: CONSORT Diagram.

Figure 2: Individual response to propofol at corresponding concentration. Unfilled rhombus (♦) represents an ineffective response to the corresponding concentration of propofol for inducing LOC. Filled rhombus (●) represents an effective response to the corresponding concentration of propofol for inducing LOC.
The time to LOC was significantly shorter in patients with an effective induction of LOC in Group NC than in Group C (252 ± 22 seconds vs. 344 ± 35 seconds, P< 0.001) (Figure 3). The dose of propofol was lower in patients with an effective induction of LOC in Group NC than in Group C (84 ± 15 vs. 102 ± 18, P< 0.001).

Discussion
In the current study, we found that the EC50 of propofol for inducing the LOC was lower with neoadjuvant chemotherapy than without neoadjuvant chemotherapy in patients with breast cancer. The onset time of LOC was shortened and the dose of propofol for inducing LOC was reduced after neoadjuvant chemotherapy.

It can be argue that EC95, which is more relevant to clinical experience than EC50, may be a better choice as a minimum effective concentration to determine the effect of neoadjuvant chemotherapy on the requirement of concentration of propofol for inducing the LOC. Nevertheless, we chosen EC50 as an assessment standard for the following reasons. Firstly, up-and-down method is the classic way to evaluate the efficiency of drug, and its advantage is to save sample size. Secondly, it was not difficult to rescue the ineffective induction via intravenous injection propofol.

In this study, patients in the Group NC received the same chemotherapy regimens and chemotherapy drugs, and patients are in good conditions without any complications. Therefore, any factors of the subjects, which may influence the results, can be excluded from our study.

To interpret the possible mechanism of the finding in this study, the following explanations should be taken into account. To begin with, evidences showed that patients with breast cancer accepted chemotherapy were associated with fatty liver, toxic hepatitis and hepatic dysfunction. The liver is a main site of metabolism for intravenous anesthetics and chemotherapeutics, and an injury to the liver may affect their metabolism. Therefore, we would speculate that the lowering of EC50 of propofol with effect-site for inducing LOC after neoadjuvant chemotherapy related to the hepatic injury. Secondly, chemotherapy drug may play a role of decreasing the EC50 of propofol. Study has reported 17% of patients with breast cancer suffered cognition impairment after chemotherapy treated [8]. Therefore, we conjectured that there would be partial chemotherapy drug permeated the blood brain barrier and enhanced the action of propofol. And further studies are needed to verify this suspicion. Finally, study has demonstrated that upregulation of estrogen receptor and progesterone receptor expression in patients with breast cancer after neoadjuvant chemotherapy. Chen et al. reported that a lower propofol effect-site concentration induces LOC in the luteal phase, and the requirement of propofol for inducing LOC was associated with the level of hormone [9]. Therefore, neoadjuvant chemotherapy may decrease the EC50 of propofol via the different level of sex hormone caused by neoadjuvant chemotherapy. And further studies are needed to verify this suspicion.

In this study, we found that the time to LOC was shorter and the dose requirement of propofol was lower in Group NC than in Group C. The following factors may contribute to this phenomenon. Firstly, neoadjuvant chemotherapy may more or less result in damage of hepatic function. Although, patients received sorts of treatments to prevent the damage of hepatic function before surgery, ingestion of propofol was decreased caused by the disorder and the decreasing of hepatic blood flow associated with neoadjuvant chemotherapy. Secondly, decreasing of activity of hepatic microsomal enzymes caused by neoadjuvant chemotherapy would lead to a lower removal rate and efficiency of drug clearance. Thirdly, protein binding ratio may reduced after neoadjuvant chemotherapy, which can lead to more free drug and sequently shorten the onset time and enhance the pharmacological effects.

Limitations existed in this study. Firstly, elder patients were excluded from this study. Further studies are needed to explore the effect of neoadjuvant chemotherapy on general anesthetics of elder people with breast cancer. Secondly, although we have demonstrated that neoadjuvant chemotherapy can decrease the EC50 of propofol for inducing LOC, the EC95 of propofol for inducing LOC is still unknown and further studies are needed. Thirdly, the plasma concentration in this study was calculated by the TCI machine system and not inspected by laboratory. A certain difference may be existed between the measured value and calculated value.

Conclusion
Neoadjuvant chemotherapy can decrease the EC50 of propofol for inducing the loss of consciousness in patients with breast cancer.

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Reference


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