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Research Article

Neoadjuvant Chemotherapy Does Not Decrease the Dose Requirement of Propofol for Inducing the Loss of Consciousness in Patients with Breast Cancer: A Prospective Study

Guangfa Xia[1], Fei Xiao[2], Liu Lin[2], Xiaoping Zhu[1] and Juanyin Zhu[1*]

[1]Department of Galactophore, Jiaxing University Affiliated Women and Children Hospital, Jiaxing City, China
[2]Department of Anesthesia, Jiaxing University Affiliated Women and Children Hospital, Jiaxing City, China

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ABSTRACT

Background: Neoadjuvant chemotherapy can cause certain damage to patients' physiological function. Therefore, we suspected that the sensitivity to propofol would also be altered by neoadjuvant chemotherapy. We aimed to compare the ED50 for inducing loss of consciousness (LOC) in patients with and without preoperative neoadjuvant chemotherapy.

Methods: Sixty-two patients were randomized to receive neoadjuvant chemotherapy (group N) or not (group C) 10 to 15 days before elective modify radical mastectomy. The up-down method was used to determine the ED50 of propofol. Patients in each group received an initial dose of 4.0 μg/mL of propofol and a variable dose (increments or decrements) of 0.4 μg/mL of propofol based on the effective or ineffective response of the prior patient. The effective dose of propofol for induction of LOC in 50% patients was calculated and compared.

Results: The EC50 and 95% confidence intervals (95%CI) of propofol in the two groups were 3.27 μg/mL (95%CI, 3.09～3.43 μg/mL) and 3.33μg/mL (95%CI, 3.19～3.47 μg/mL) for patients undergoing elective modified radical mastectomy with and without neoadjuvant chemotherapy respectively. Thus, there was no difference in the EC50s between the two groups, $P = 0.55$.

Conclusions: Under the condition of this study, we found the EC50s of propofol for induction of LOC were 3.27 and 3.33 μg/mL for patients undergoing elective modified radical mastectomy in the presence or absence of neoadjuvant chemotherapy. We do not recommend reducing the dose of propofol for induction of LOC in patients with neoadjuvant chemotherapy.

Introduction

Preoperative neoadjuvant chemotherapy can reduce the clinical stage of malignant tumor and narrow the surgical scope [1]. Therefore, it is increasingly being used in the preoperative treatment of malignant tumor patients in recent years. However, chemotherapy causes certain damage to the patients' physiological function [2]. Therefore, we hypothesized that the sensitivity to propofol might be also altered by neoadjuvant chemotherapy. This study aimed to compare the minimum effective concentration represented by the median effective concentration (EC50) of propofol for inducing loss of consciousness (LOC) in patients with or without preoperative neoadjuvant chemotherapy, using the up-down allocation method.

Methods

After getting the approval from the Institutional Ethics Committee of Jiaxing University Affiliated Women and Children Hospital and getting the patients' written informed consent from the study subjects, sixty-two patients with American Society of Anesthesiologists' physical status I or II, scheduled for elective modify radical mastectomy, were recruited in

Correspondence to: Juanyin Zhu, Department of Galactophore, Jiaxing University Affiliated Women and Children Hospital, East Zhonghuan Rd, 2468#, Jiaxing, China; E-mail: tiaopidaodi@163.com

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this clinical trial. The exclusion criteria were as follows: subjects with body mass index (BMI) >35 kg/m^2, age <20 years or >60 years, chronic hypertension, or with hepatic dysfunction after neoadjuvant chemotherapy were excluded from this study. According to the different treatment strategies, patients were allocated into group N (with neoadjuvant chemotherapy) and group C (without neoadjuvant chemotherapy). In group N, patients were treated with TEC chemotherapy regimen, as follows: 6 cycles of 75 mg/m^2 epirubicin, 600 mg/m^2 cyclophosphamide and 75 mg/m^2 docetaxel at an interval of 3 weeks. The patients underwent elective modified radical mastectomy after 10 to 15 days following the treatment. No premedication was delivered to patients. After arrival in the operating room, patients then had an IV 18-G cannula inserted into an upper limb vein and received an infusion of 300 mL of 37°C Ringer's solution prior to the induction of anesthesia. Standard monitoring, including arterial blood pressure, pulse oximetry (SpO2) and electrocardiogram (ECG) was done. Bispectral Index (BIS) was applied to guide the depth of anesthesia and the train-of-four stimulation (TOF) (TCI-III-B, Weili Fangzhou Guangzhou, China) was used to guide the degree of relaxant.

Only propofol was used for the induction of LOC with an initial effect-site concentration of 4.0 μg/mL (target control injection, TCI) (TCI-III-B, Weili Fangzhou Guangzhou, China) using the pharmacokinetic and pharmacodynamic (PK-PD) model [3]. Then the effect-site concentration of propofol for the next patient was adjusted by the method of up-down allocation. For example, if the current propofol dose (n μg/mL) succeeded in induction of LOC, which was regarded as an effective dose, the subsequent dose for the following patient will be (n–0.4) μg/mL. Conversely, if the current propofol dose (n μg/mL) failed in induction of LOC, which was regarded as an ineffective dose, the subsequent dose for the following patient will be (n+0.4) μg/mL. An effective dose was regarded as the loss of eyelash reflex, no response to language stimulation and a BIS value of less than 60. Otherwise it was defined as an ineffective dose. After the patient's losing of consciousness, 4.0 ng/mL of remifentanil then delivered via the TCI pump with the pharmacokinetic and pharmacodynamic (PK-PD) model [4]. Then rocuronium (0.6 mg/kg) was given to facilitate tracheal intubation. Anaesthesia was also maintained with propofol and remifentanil. The concentration of propofol was adjusted according to the value of BIS which was controlled between 40 and 60. But the concentration of propofol should not less than 2.0 μg/mL in order to avoid intraoperative awareness. Similarly, the concentration of remifentanil was adjusted according to the variation of blood pressure so as to keep it within 10% of the formerly recorded value. 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 to treat hypotension if necessary. Bradycardia was defined as heart rate less than 60 beats per minute. Atropine 0.5 mg was intravenously administrated when bradycardia occurred.

The primary outcome of this study was the effective and ineffective dose 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. 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 mean ± SD. Nominal data were analyzed using the Chi-square test, and continuous data were analyzed using the 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).

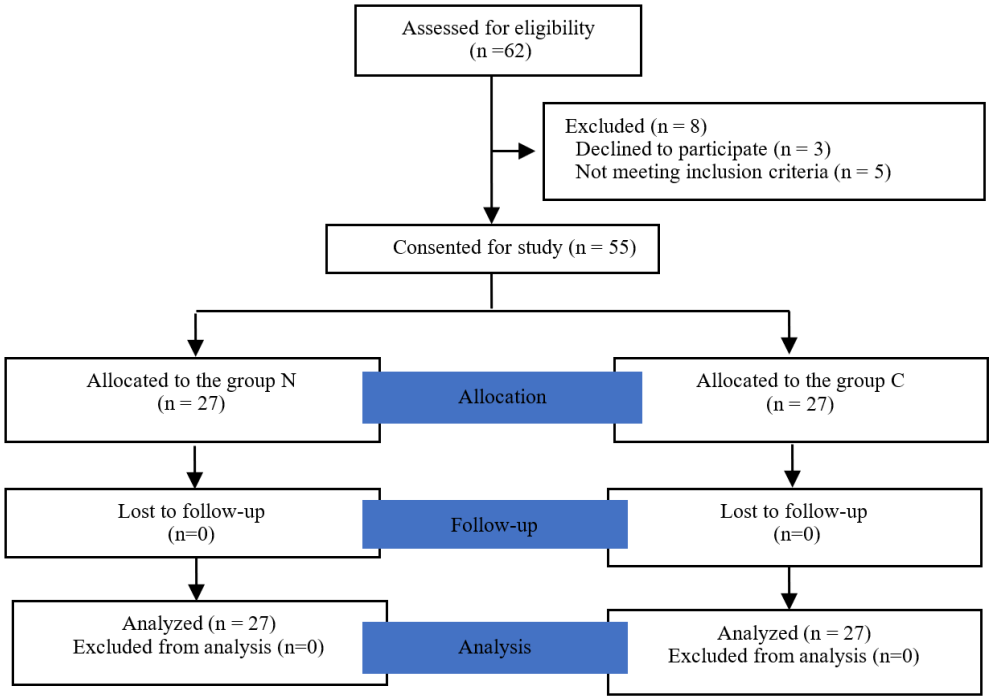

Figure 1: CONSORT Diagram.

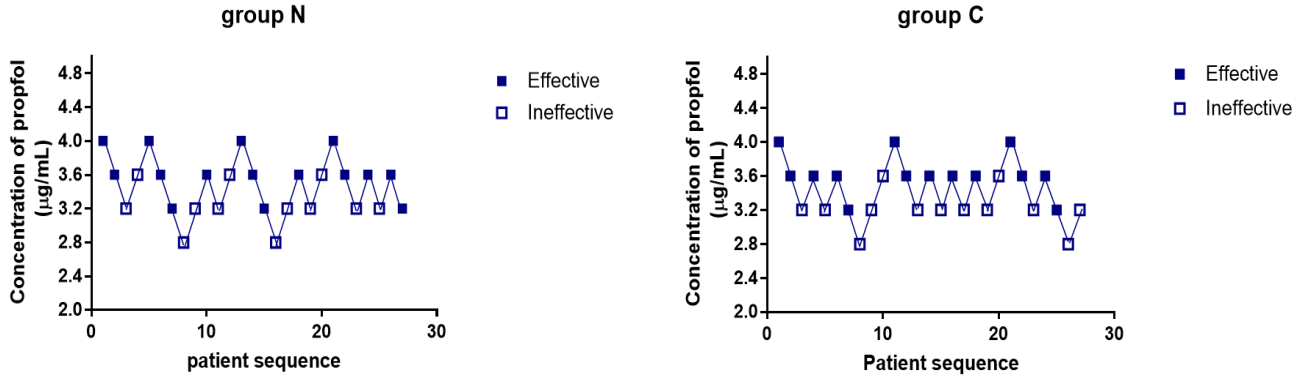

Figure 2: Dose-response of patients to propofol in the two groups. Filled square (■) represents as an effective response to the corresponding concentration. Unfilled square (□) represents an ineffective response to the corresponding concentration. The EC50 and 95% confidence intervals (95%CI) of propofol in the two groups were 3.27 μg/mL (95%CI, 3.09～3.43 μg/mL) and 3.33μg/mL (95%CI, 3.19～3.47 μg/mL). Thus, there was no difference in the EC50s between the two groups, $P = 0.55$.

Results

The CONSORT diagram of the present study is showed in (Figure 1). A total of 62 patients were assessed for eligibility, 55 of them were enrolled and assigned into the group N (n = 28) or group C (n = 27) and no patient was lost in the final analysis. There was no significant difference in the population characteristics including age, height and weight, $P > 0.05$ (Table 1). The EC50 and 95% confidence intervals (95%CI) of propofol in the N and C groups were 3.27 μg/mL (95%CI, 3.09～3.43 μg/mL) and 3.33μg/mL (95%CI, 3.19～3.47 μg/mL) for patients undergoing elective modified radical mastectomy with and without neoadjuvant chemotherapy respectively. There was no difference in the EC50s between the two groups, $P = 0.55$. The effective or ineffective loss of consciousness and the corresponding concentration of propofol are presented in (Figure 2). The time to LOC was similar in patients with an effective induction of LOC in Group N with that in Group C (326 ± 22 seconds vs. 344 ± 35 seconds, $P > 0.05$) The dose of propofol was lower in patients with an effective induction of LOC in Group N than in Group C (98 ± 15 vs. 102 ± 18, $P > 0.05$).

Table 1: Patients' demographic characteristics, surgical time.

Characteristic	group N	group C	P value
Age	48± 5	46± 7	.27
Height	162 ± 11	163 ± 9	.45
Weight	60 ± 7	58 ± 79	.73
BMI	23 ± 3	23 ± 3	.47
Duration of surgery	113 ± 16	119 ± 21	.38

Presented as mean ± SD, using Student t test.

Discussion

In this study, we found The EC50 and 95%CI of propofol in the N and C groups were 3.27 μg/mL (95%CI, 3.09～3.43 μg/mL) and 3.33 μg/mL (95%CI, 3.19～3.47 μg/mL) respectively. Our results suggested that in patients with neoadjuvant chemotherapy undergoing elective modified radical mastectomy, the dose of propofol for induction of losing of consciousness should not be reduced. Vuyk et al. used the linear regression method to study the loss of consciousness in female patients induced by propofol alone and found that the EC50 of the loss of consciousness in female patients induced by propofol alone was 3.4 μg/mL, which was similar to that in our study [8]. The greatest advantage of up-down allocation is to save sample size. However, it might be debated that the EC50 of propofol determined by the up-down allocation method in this study could not be completely exact as the sample size in this study was small. Fortunately, the aim of this study is to compare the difference in EC50 in presence and absence of neoadjuvant chemotherapy for patients undergoing elective modified radical mastectomy. And this allocation method is competent for the comparison of the difference in this context.

Studies have shown that 17% of patients with breast cancer suffered cognitive impairment after chemotherapy treatment [9]. Therefore, we suspected that the chemotherapeutic drugs could partially permeate the blood-brain barrier and enhance the action of propofol. However, in this study we failed to validate our suspicion and found that the chemotherapy drugs may not affect the pharmacodynamics of propofol in this population. The following two factors may contribute to this finding: 1. Patients in this study were in good condition and patients with hepatic dysfunction were excluded from the study. 2. Patients underwent elective modified radical mastectomy after ten to fifteen days following neoadjuvant chemotherapy. Perhaps the chemotherapy drug may have been completely metabolized and does not affect the patient's sensitivity to propofol.

Limitations exist in this study. First, we did not measure the plasma concentration of propofol by laboratory; it was only deduced by the TCI machine system. There could be certain differences between the two. Second, we only assessed the EC50 of propofol in this population; the dose-response studies are needed in future. In summary, under the conditions of this study, we found the EC50s of propofol for inducing of LOC were 3.27 and 3.33 μg/mL for patients undergoing elective modified radical mastectomy in the presence and absence of neoadjuvant chemotherapy. We do not recommend reducing the dose of propofol for inducing of LOC in patients with neoadjuvant chemotherapy.

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