

## ORIGINAL INVESTIGATION

## Accuracy of closed-loop and open-loop propofol delivery systems by bispectral index monitoring in breast surgery patients: a prospective randomized trial



Tian Xie , Yong Wang, Yuhua Liu, Junjie Li, Weijing Li, Hongmeng Xu \*

Forth Hospital of Hebei Medical University, Department of Anesthesiology, Hebei, China

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**KEYWORDS**

Anesthesia;  
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Infusion pump;  
Intravenous;  
Propofol

**Abstract**

**Background:** This randomized and controlled prospective study tested the hypothesis that closed-loop Target-Controlled Infusion (TCI) of propofol would be associated with better system performance when compared with open-loop controlled delivery of propofol.

**Methods:** Patients scheduled for elective breast surgery were randomly assigned to two groups: a closed-loop group, in which propofol infusion was performed by a closed-loop TCI system that used the Bispectral Index (BIS) as a feedback parameter to titrate the rate of propofol infusion, and an open-loop group, in which propofol infusion was performed manually and guided by the bispectral index.

**Results:** A total of 156 patients were recruited for this study (closed-loop group  $n = 79$ ; open-loop group  $n = 77$ ). The Global Score (GS) of the closed-loop group was lower than that of the open-loop group (34.3 and 42.2) ( $p = 0.044$ ). The proportions of time with a BIS value between 40 and 60 were almost identical in the closed-loop group and the open-loop group ( $68.7 \pm 10.6\%$  and  $66.7 \pm 13.3\%$ ) ( $p = 0.318$ ). The individuals in the closed-loop group consumed more propofol compared with those in the open-loop group ( $7.20 \pm 1.65 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  vs.  $6.03 \pm 1.31 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ,  $p < 0.001$ ). No intra-operative recall, somatic events or adverse events occurred. No significant difference in heart rate was observed between the two groups ( $p = 0.169$ ).

**Conclusion:** The closed-loop protocol was associated with lower BIS variability and lower out-of-range BIS values, at the cost of a greater consumption of propofol when compared to the open loop group.

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\* Corresponding author: Hongmeng Xu  
E-mail: [xuhongmeng66@aliyun.com](mailto:xuhongmeng66@aliyun.com) (H. Xu).

## Introduction

Total Intravenous Anesthesia (TIVA) has been widely used in clinical anesthesia management. Continuous constant-speed infusion and Target-Controlled Infusion (TCI) are the two most common methods of propofol infusion. When performing target-controlled infusion of propofol, the anesthesiologist adjusts the plasma concentration of propofol according to the bispectral value. Nevertheless, there are considerable individual variations in the sedation effect, despite using the same pharmacokinetic model. Closed-loop TCI has attracted widespread attention as a new approach to modulate anesthesia depth.

Closed-loop TCI of propofol was first described in the 1980s.<sup>1-3</sup> Recent developments in the field of electronic science and technology have led to a renewed interest in closed-loop TCI. Delivery of anesthetics by means of closed-loop control can overcome the limitations of TCI by compensating for the impacts associated with individual variations and therefore enable more rational and reliable administration of anesthetics. Additionally, previous findings have indicated that closed-loop controlled infusion could decrease the workload of anesthesiologists.<sup>4</sup>

In the closed-loop system, certain operational parameters need to be specified. Hypnotic depth, a pivotal variable in the closed-loop system, is a key parameter emphasized by anesthesiologists. The Bispectral Index (BIS), Covidien Ltd., Dublin, Ireland) is considered the most widely reported parameter for monitoring hypnotic depth. Multiple attempts have been made to verify the validity, safety, and superiority of BIS-guided regulated closed-loop target-controlled propofol infusion during general anesthesia in adults<sup>5-12</sup> and children.<sup>13,14</sup> In the existing reports, however, the BIS monitor and TCI pump were connected by a data cable, and the BIS monitors were externally placed in relation to the system.

In this study, the TCI pump was equipped with an internal BIS monitor, and we aimed to determine whether BIS-guided regulated closed-loop target-controlled propofol infusion could be associated with better system performance in providing adequate sedation compared with manually-controlled propofol TCI.

## Methods

### Subjects

This study was approved by the Medical Ethics Committee of the Fourth Hospital of Hebei Medical University, China, and written informed consent was provided by all subjects. The trial was registered at the Chinese Clinical Trial Registry, with number ChiCTR-INTR-17010399. A total of 160 patients were recruited from 2017-2-1 to 2017-7-31. We used block randomization to randomly assign the patients to the closed-loop or open-loop group ( $n = 80$  each). The group assignment was enclosed in opaque envelopes before the operations. The included patients undergoing elective breast surgery were over 18 years old, female, and classified as ASA I or II. The exclusion criteria consisted of a history of psychiatric disorders and the use of a cardiac pacemaker.

## Protocol

The BIS-guided TCI system used in this study was developed by China Beijing SIGO Medical Technology Co., Ltd. The salient feature of this equipment was an internal BIS monitor, which facilitated the TCI pump to achieve stable and effective regulation. This improvement made it possible to monitor the BIS values in real time, to calculate the mean value every 5 seconds and to adjust the infusion speed according to the difference between the mean value and the target value every 15 seconds.

The closed-loop infusion system can be used for both the induction and maintenance of total intravenous anesthesia. The bispectral index served as the control variable, while a standard syringe infusion pump was the control actuator. The system can be used to deliver propofol and achieve a target BIS value set in advance by the operator for induction and maintenance. There are two kinds of working modes. When choosing the manual mode, the operator can adjust different plasma concentrations of propofol through target-controlled infusion to achieve different sedation levels from the panel of this system. In the automatic mode, this controller can adjust different plasma concentrations of propofol TCI by itself in accordance with the control variable BIS. Before infusing, the operator is requested to input age, gender, weight, and height into the system, and a target BIS value is also set. In the automatic mode, the system updates the electroencephalographic data of the patients per 5 seconds and determines the BIS error (disparity between the target and actual BIS value). This value is transferred to the control algorithm, which plays a role in counting an adjustment in the infusion rate in order to achieve the target value. It does not change the propofol infusion rate at intervals less than 15 seconds, keeping in view the time interval for it to produce any effect on the BIS. In fact, we set the target goal of  $BIS = 50 \pm 10$ , and the maximal allowable rate of 1% propofol infusion of this system is  $1200 \text{ mL} \cdot \text{h}^{-1}$ .

### Training of the researchers

Before the formal start of this study, a standard training for closed-loop control system operation was performed for 1 month. The anesthesiologists were admitted for this study only when they were skilled for the entire research process and performed at least 10 successful closed-loop target-controlled infusion total intravenous anesthesia procedures. The operators in this research all had considerable experience in TCI anesthesia.

### Anesthesia management

Without premedication, the patients were monitored with non-invasive blood pressure, pulse oximetry, electrocardiogram, capnography, and BIS. The BIS electrode was positioned on the patient's forehead and connected to the BIS guided TCI system. Investigators had considerable clinical experience in titrating intravenous anesthesia using the BIS guided TCI system.

All patients received total intravenous anesthesia in TCI mode using the population pharmacokinetic sets of Marsh et al.<sup>15</sup> for propofol.

In the open-loop group, after intravenous administration of  $0.25 \mu\text{g}\cdot\text{kg}^{-1}$  sufentanil, propofol was infused automatically, and the initial target plasma concentration of propofol was  $4 \mu\text{g}\cdot\text{mL}^{-1}$ . Then,  $0.2 \text{ mg}\cdot\text{kg}^{-1}$  cisatracurium was intravenously administered. Endotracheal intubation was performed when the BIS value reached 50. As soon as we finished the intubation, the maintenance phase begun, and propofol and remifentanil were infused immediately. The infusion speed of remifentanil was  $0.2\text{--}0.8 \text{ mg}\cdot\text{h}^{-1}$ , aiming at adequate heart rate and arterial pressure (an adequate level is approximately 20% of the basic level). The target concentration of propofol was manually regulated according to the BIS value by experienced anesthesiologists. The target range of the BIS value was from 40 to 60.

In the closed-loop group, after intravenous administration of  $0.25 \mu\text{g}\cdot\text{kg}^{-1}$  sufentanil, propofol was infused automatically, and the initial target plasma concentration of propofol was  $4 \mu\text{g}\cdot\text{mL}^{-1}$ . Then,  $0.2 \text{ mg}\cdot\text{kg}^{-1}$  cisatracurium was intravenously administered. Endotracheal intubation was performed when the BIS value reached 50. Propofol and remifentanil were infused immediately after intubation. During the maintenance phase, the infusion speed of remifentanil was  $0.2\text{--}0.8 \text{ mg}\cdot\text{h}^{-1}$ , aiming at adequate heart rate and arterial pressure (an adequate level is approximately 20% of the basic level). The target concentration of propofol was regulated automatically based on the BIS value, and the target range of the BIS value was  $50 \pm 10$ .

For both groups, with the exception of the propofol infusion, all other anesthesia management procedures were performed by the anesthesiologists in accordance with the currently recommended guidelines. No other hypnotics were allowed. For all patients, body movements were not allowed during anesthesia, as the movements could increase the BIS value and induce unwanted propofol delivery; therefore, cisatracurium was administered intermittently.

Upon the completion of the surgery, the infusions of propofol and remifentanil were terminated simultaneously in both groups. The endotracheal tube was removed when the patient responded to instructions from the physician and was able to breath spontaneously.

## Measurements

In this study, we set the global score as the primary outcome, we included the proportion of time with the BIS value between 40 and 60, and the consumption of propofol and intraoperative adverse events in the analysis, as well.

The Global Score (GS)<sup>10,16</sup> is a measure of the overall effectiveness of the closed-loop system and accounts for median absolute performance error, wobble value and the proportion of time with the BIS value within 40–60.<sup>17</sup>

- i. Performance Error (PE) represents the difference between the set value and the actual BIS value.

$$PE_{ij} = \left( \frac{BIS_{actualij} - BIS_{set}}{BIS_{set}} \right) \times 100$$

- ii. Median Performance Error (MDPE)

$$MDPE_i = \text{Median}\{PE_{ij}, j = 1, 2, \dots, N_i\}$$

- iii. Median Absolute Performance Error (MDAPE)

$$MDPE_i = \text{Median}\{|PE_{ij}|, j = 1, 2, \dots, N_i\}$$

- iv. The intraindividual variability of PE was reflected by the wobble value.

$$\text{Wobble}_i = \text{Median}\{|PE_{ij} - MDPE_i|, j = 1, 2, \dots, N_i\}$$

- v. GS was calculated with the following expression.

$$GS = \frac{MDAPE + \text{Wobble}}{\% \text{ of time BIS between 40 and 60}}$$

GS was set as the primary outcome measure of this study. Lower MDAPE and the wobble value, as well as a higher percentage of time with a BIS value between 40–60, were associated with lower GSs, which demonstrated the excellent performance of the closed-loop system.

Otherwise, the consumption of propofol in the maintenance period, somatic events (movements and grimacing), adverse events (hypersensitivity reactions and restlessness in the recovery period), blood loss of more than 500 mL, and the application of vasoactive agents during anesthesia were recorded in detail. Recall of intraoperative events was assessed with a standardized interview performed on the third postoperative day. The heart rate and MAP of the patients were documented at several time points. T1 was the baseline, T2 was the time point of intubation, T3 was the moment of skin incision, T4 was 20 minutes after the incision, and T5 was the time at which the surgeon started to suture.

## Statistical analysis

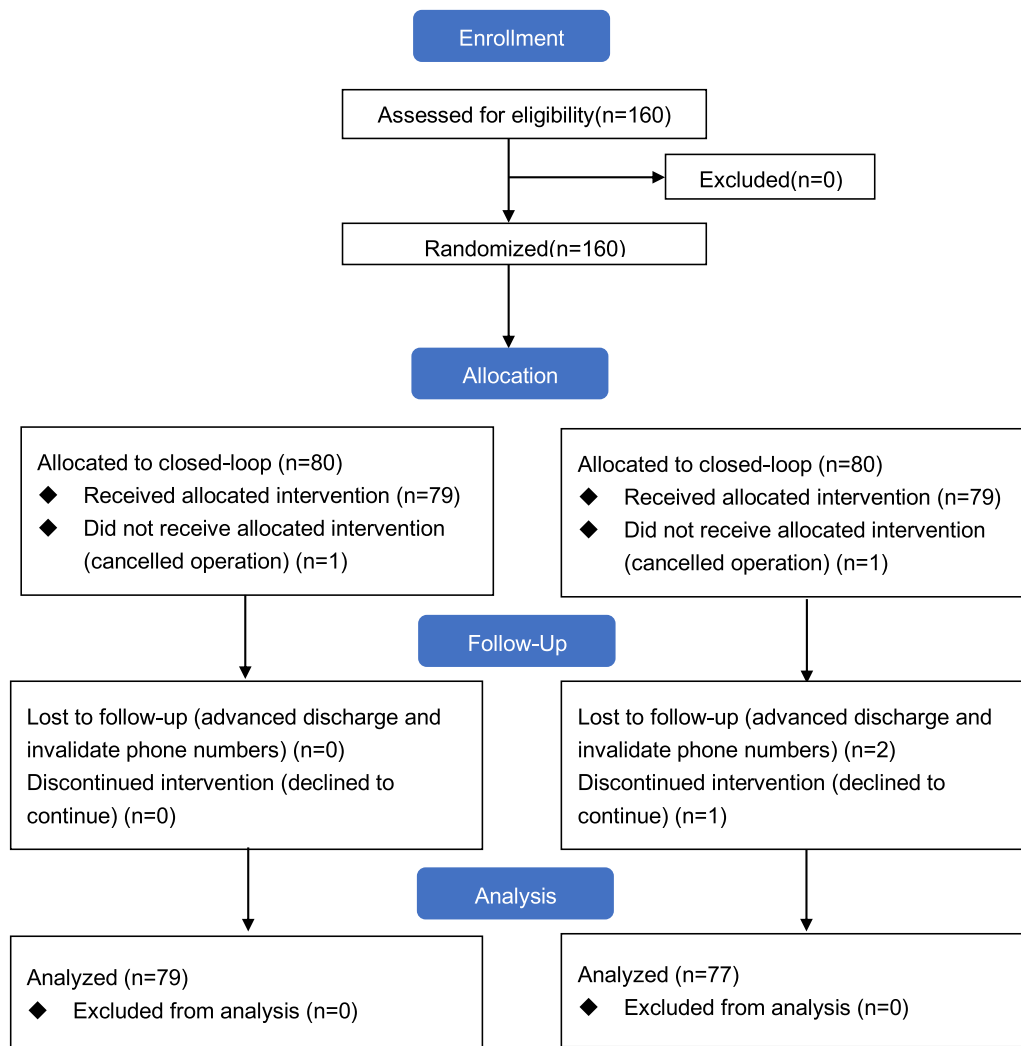
A pilot study was done, comprising a total of 30 patients, and following the same study protocol. This pilot study indicated a GS of approximately  $50 \pm 33$  in the manual group and  $38 \pm 16$  in the closed-loop group. Based on these values, we estimated that a total of 148 patients (74 per group) would provide an 80% power with a 5% two-side type I error. We thus planned to recruit 80 patients to allow for dropouts.

The statistical analysis was performed with SPSS 20.0;  $p < 0.05$  was considered statistically significant.

The  $\chi^2$  test was used, as appropriate, to compare categorical variables expressed as numbers and frequencies. The Mann-Whitney U test was used to compare continuous variables, which were presented as the mean  $\pm$  SD or median and interquartile range. Comparisons of repeated measurements were performed using repeated-measure ANOVA.

## Results

This study included 160 patients with informed consent. In the closed-loop group, one patient was excluded due to cancellation of operation. In the open-loop group, two patients failed to participate in the follow-up, and one patient declined to continue after consenting. Thus, 79 and 77 patients were subjected to analysis in the two groups, respectively (Fig. 1).



**Figure 1** CONSORT flow diagram illustrating the flow of patients. CONSORT, Consolidated Standards of Reporting Trials.

No significant group differences in the demographic variables were observed (Table 1). Furthermore, there were no significant differences in preoperative comorbidities, i.e., hypertension, diabetes, arrhythmia, Coronary Heart Disease (CHD) and cerebral infarction (Table 1).

The mean GS values were remarkably lower in the closed-loop group (34.3, with a range of 27.7–47.7) in comparison with those of the open-loop group (42.2, with a range of 31.2–58.5), and the difference was statistically significant ( $p = 0.044$ ) (Table 3).

Individuals in the closed-loop group consumed more propofol than those in the open-loop group, exhibiting a significant difference ( $7.20 \pm 1.65$  vs.  $6.03 \pm 1.31$  mg.kg<sup>-1</sup>.h<sup>-1</sup>,  $p < 0.001$ ) in the maintenance period. In addition, the proportions of time with BIS values between 40 and 60 were  $68.7 \pm 10.6\%$  in the closed-loop group and  $66.7 \pm 13.3\%$  in the open-loop group, exhibiting no significant difference ( $p = 0.318$ ) (Table 2). No significant difference in anesthesia maintenance time or the use of vasoactive drugs was found between the two groups. No cases of adverse events, intraoperative recall or massive hemorrhage were observed (Table 3). MAP and heart rate of the patients changed with the deepening of anesthesia, and MAP and heart rate in T2,

T3, T4, T5 significantly differed from MAP and heart rate in T1 ( $p < 0.001$ ). A similar MAP trend was identified in the two groups ( $p = 0.694$ ). No significant difference in heart rate was observed between the two groups ( $p = 0.169$ ) (Fig. 2).

## Discussion

This randomized and controlled prospective study showed that the proportion of time with BIS values between 40 and 60 during anesthesia in the closed-loop group was similar to that in the open-loop group; the closed-loop group also had lower BIS variability and lower out-of-range BIS values and consumed more propofol. It is noteworthy that the pharmacokinetics and pharmacodynamics, as well as the response to propofol, varied among individual patients. Typically, anesthesiologists integrate their assessment of these factors with the clinical status of patients to determine the method of anesthetic delivery. The human factors associated with the decision-making process were also subjected to individual variations. In contrast, the closed-loop control system responds in real time to changes in the BIS value and achieves precise patient-individualized anesthetic administration.

**Table 1** Medical and demographic characteristics of patients in the closed-loop group and the open-loop group.

		Closed-loop (n = 79)	Open-loop (n = 77)
<b>Gender</b>	Female (%)	79 (100)	77 (100)
<b>Age</b>	(years)	53.7 ± 11.9	56.6 ± 12.2
<b>Height</b>	(cm)	159.06 ± 5.75	159.05 ± 5.03
<b>Weight</b>	(kg)	64.7 ± 9.3	62.7 ± 9.1
<b>BMI</b>		25.59 ± 3.71	24.83 ± 3.76
<b>Comorbidities</b>	Hypertension (%)	11 (13.9)	11 (14.3)
	Diabetes (%)	2 (2.5)	3 (3.9)
	CHD (%)	2 (2.5)	2 (2.6)
	Arrhythmia (%)	2 (2.5)	3 (10.4)
	Cerebral infarction (%)	1 (1.3)	2 (2.6)
<b>Neoadjuvant chemotherapy before surgery</b>	(%)	1 (1.3)	5 (6.5)

Data are presented as mean ± SD or number (%).

Closed-loop, Group with automated control of propofol infusion guided by the bispectral index; Open-loop group, Group with manual control of propofol infusion guided by the bispectral index; CHD, Coronary Heart Disease.

**Table 2** Accuracy of the closed-loop and open-loop propofol control systems.

	Closed-loop (n = 79)	Open-loop (n = 77)	<i>p</i>
BIS 40–60 (%)	68.7 ± 10.6	66.7 ± 13.3	0.318
SR	0 (0)	0 (0)	1.000
GS	34.3 (27.7–47.7)	42.2 (31.2–58.5)	0.044
MDPE	−4.26 (−8.51~−2.13)	2.13 (−4.16~10.64)	<0.001
MDAPE	12.77 (10.64–14.9)	14.9 (12.8–17.0)	0.004
WOBBLE	12.0 ± 3.9	13.4 ± 4.6	0.042

Data are presented as the mean ± SD, median (interquartile range) or number (%).

Closed-loop, Group with automated control of propofol infusion guided by the bispectral index; Open-loop group, Group with manual control infusion of propofol guided by the bispectral index; BIS 40–60; Percentage time in which the BIS value was between 40 and 60; SR, Burst suppression ratio was calculated as SR > 10% lasting at least one minute; GS, Global Score; MDPE, Median Performance Error; MDAPE, Median Absolute Performance Error; Wobble, The intraindividual variability in PE.

**Table 3** Comparison of the anesthetic procedures between the two groups during the maintenance phase.

		Closed-loop (n = 79)	Open-loop (n = 77)	<i>p</i>
<b>Maintenance time</b>	(h)	1.30 ± 0.43	1.44 ± 0.49	0.052
<b>Propofol dose</b>	(mg.kg <sup>-1</sup> .h <sup>-1</sup> )	7.20 ± 1.65	6.03 ± 1.31	<0.001
<b>Induction time</b>	(min)	1.79 ± 0.71	1.59 ± 0.51	0.05
<b>Recovery time</b>	(min)	8.4 ± 4.0	9.0 ± 4.0	0.581
<b>Blood loss ≥ 500 mL</b>	n (%)	0 (0)	0 (0)	1.000
<b>Vasoactive drug use</b>	n (%)	13 (16.5)	16 (20.8)	0.541
<b>Somatic events</b>	n (%)	0 (0)	0 (0)	1.000
<b>Adverse events</b>	n (%)	0 (0)	0 (0)	1.000
<b>Intraoperative recall</b>	n (%)	0 (0)	0 (0)	1.000

Data are presented as the mean ± SD or number (%).

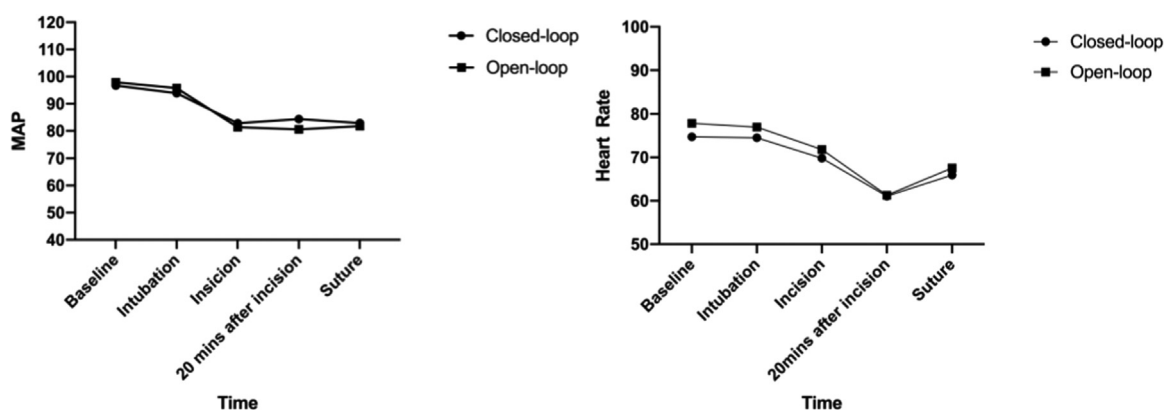
Closed-loop, Group with automated control of propofol infusion guided by the bispectral index; Open-loop group, Group with manual control of propofol infusion guided by the bispectral index.

Therefore, modulating the hypnosis depth according to pharmacodynamic feedback reduces intraindividual differences and facilitates more reliable attainment and maintenance of adequate hypnosis depth.

The closed-loop group maintained sufficient anesthesia depth with remarkably higher precision and stability than the open-loop group. A lower GS in the closed-loop group

(34.3, with a range of 27.7–47.7) than in the open-loop group (42.2, with a range of 31.2–58.5) indicated superior overall performance (*p* = 0.044). Moreover, the MDAPE of the closed-loop group (12.77, with a range of 10.64–14.9) was significantly lower (*p* = 0.004) than that of the open-loop group (14.9, with a range of 12.8–17.0). The lower MDAPE indicated that the closed-loop group target-





**Figure 2** The trends of MAP and heart rate values in both groups during anesthesia.

controlled anesthesia maintained the sedation level more precisely than the open-loop group. Furthermore, a lower wobble value, which describes the intraindividual variability, was observed in the closed-loop group ( $12.0 \pm 3.9$  vs.  $13.4 \pm 4.6$ ,  $p = 0.042$ ), suggesting that dose adjustments were more subtle and frequent, thus leading to a reduced tendency to wobble around the target. Taken together, these results suggest that the control of propofol infusion was more precise and stable in the closed-loop group, and the closed-loop TCI of propofol provided a more intelligent method for the control of anesthesia depth. These results are consistent with those of other studies and suggest that the closed-loop target-controlled system is a preferable alternative to the conventional infusion systems.<sup>4,8,11,12,14,18</sup>

Though demonstrating precise and stable propofol infusion, the proportions of time with BIS values between 40 and 60, which was indicative of adequate anesthesia depth, were almost identical in the two groups. In fact, in most of the existing studies, the proportions of time with BIS values between 40 and 60 were higher in the closed-loop studies.<sup>4,7,12,14</sup> Liu N et al. found that the percentages of time spent in the BIS range of 40–60 were similar in the manual TCI and closed-loop groups during bronchoscopy.<sup>19</sup> The results of our study might indicate that, to some extent, the manually-controlled infusion of propofol according to the bispectral index could be equivalent to feedback-controlled infusion in maintaining adequate anesthesia depth. A possible explanation for this finding is that the anesthesiologists had accumulated substantial experience in the manual control of adequate sedation depth according to the BIS value. Therefore, it was not surprising that the manually controlled TCI according to the BIS value in this study achieved such a high proportion of time with BIS values between 40 and 60, similar to the closed-loop group. Another possible explanation for this finding is the lag handling of technology. The infusion system facilitates the plasma concentration of propofol according to the BIS value, and a feedback-controlled system is a kind of lag handling system. Existing technology could make it possible to respond to situations in real time but it has no predictive power. The human brain is more efficient in making complex decisions. We are very good at prevention and processing in advance. Hence, it could conceivably be hypothesized that the experience and proficiency of the operators have critical influences on the comparison of manually controlled systems and automatically controlled systems.

Interestingly, the consumption of propofol for the patients under closed-loop target-controlled infusion was  $7.20 \pm 1.65 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  in comparison to  $6.03 \pm 1.31 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for those patients in the open-loop group ( $p < 0.001$ ) in the maintenance period. Some related studies that compared closed-loop and manual target-controlled propofol infusion showed that the consumption of propofol was comparable with the two methods.<sup>12,14</sup> Wang et al. reported that a closed-loop target-controlled infusion system can reduce the amount of propofol.<sup>20</sup> Another randomized controlled trial detected a significant reduction in excessive depth of anesthesia and lower intraoperative propofol requirement in the closed-loop group.<sup>21</sup> Similar outcomes were found in thoracic patients.<sup>22</sup> One possible explanation for the difference was that the closed-loop TCI system regulated the infusion speed more frequently. This closed-loop system allowed monitoring of the BIS value in real time; the system allowed adjustment of the infusion rate every 15 seconds, which was more frequent than the systems used in other studies.<sup>7,13</sup> In one study, the system updated the data every 5 seconds and adjusted the infusion rate of propofol every 30 seconds to reach the target BIS value.<sup>7</sup> In addition, the amplitude of the accommodation may have been larger in the closed-loop group owing to the internal feedback system.

One study found that closed-loop TCI of propofol provided satisfactory control of arterial blood pressure and heart rate.<sup>7</sup> However, this experiment did not detect any evidence for a more stable hemodynamic state in the closed-loop group, which was consistent with another trial.<sup>23</sup> Although the hemodynamic parameters changed during anesthesia, MAP and heart rate in T2, T3, T4, T5 differed significantly from MAP and heart rate in T1 ( $p < 0.001$ ), and no significant difference was identified between the two groups. This finding may be attributed to the various factors that influence MAP and heart rate. Some of the patients in both groups were reported to use vasoactive drugs, but no one experienced great blood loss or allergy reactions. Some of them were treated by vasoactive drugs for temporary low MAP ( $< 60 \text{ mmHg}$ ) after induction, especially patients with multiple complications or elderly. Moreover, adequate sedation levels were achieved in both groups.

Our research found that the closed-loop system could modulate the hypnosis depth according to pharmacodynamic feedback and maintain adequate hypnosis in surgery with a lower global score, MDAPE and Wobble. These surrogate measures described the accuracy of the closed-loop system,

though not clinical outcomes. However, according to our findings, the effectiveness and stability of the closed-loop system alleviated the workload of the practitioners and reduced intraindividual differences. The anesthesiologists could be more attentive to the surgery process and other aspects.<sup>4,12</sup> Considering the increasing consumption of propofol, practitioners should pay more attention to the surgery process when using the closed-loop system. Maybe flexible application of the closed-loop system and taking over at the right time could help to attain and maintain more adequate sedation control in the future. Moreover, there was no difference in intraoperative recall between the two groups. Considering the extremely low incidence rate of recall (0.1–0.2%),<sup>24</sup> the sample size might be insufficient to detect this problem. Adequate sedation was achieved in both groups, which possibly helped to prevent intraoperative recall. This hypothesis was not tested in this research, however.

There are some limitations in this research. First of all, we did not calculate the period of BIS lower than 40, which might explain the difference of propofol consumption between the two groups. In this study, however, we compared burst suppression as a measure of excessive depth of anesthesia. Secondly, use of sufentanil and remifentanil might influence Bis to some extent. In our study, we controlled the dosage of sufentanil in order to minimize this impact. However, we did not compare the difference of remifentanil between groups, and we did not utilize TCI for remifentanil administration, which may waken our findings in a sense. Thirdly, this study focused on breast cancer patients, and they were all female. With the large population of female surgery patients in the whole world, however, we believe that our findings play a part in providing better sedation management during anesthesia for this particular population. The results cannot be generalized to males or other types of surgery. Further studies should include a larger population.

## Conclusion

The closed-loop protocol was associated with lower BIS variability and lower out-of-range BIS values, at the cost of a greater consumption of propofol when compared to the open-loop group.

## Funding

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## Declaration of Competing Interest

The authors declare no conflicts of interest.

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