Closed-loop target-controlled infusion system for propofol guided by bispectral index applied in patients undergoing shoulder arthroscopy in the beach chair position- a randomized controlled trial

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Abstract

Background To compare the efficacy of anesthetic depth control using closed-loop and open-loop target controlled infusion (TCI) system of propofol guided by BIS in patients undergoing shoulder arthroscopy in the beach chair position (BCP).

Methods 120 patients underwent shoulder arthroscopy surgery in the BCP were randomized into two groups, the open-loop (O) group and the closed-loop (C) group. During the maintenance phase, BIS value was used as the feedback variable for TCI system of propofol in both groups. The Global score (GS) and the percentage of adequate anesthesia, the frequency of propofol regulation, and consumption of propofol were calculated. The MMSE scores of the day before and 1 day after surgery, serum GFAP and S100B proteins before anesthesia, after extubation and 1 day after surgery were compared.

Results The GS and the proportion of appropriate anesthesia time were better in the group C. The percentage of overshoot time was lower in the group C. The frequency of propofol regulation was observed higher in the group C. Propofol consumption in the group C was significantly lower than that in the group O. The MMSE scores, the GFAP and S100B protein concentrations had no significant difference between the two groups.

Conclusion Propofol administration using close-loop TCI system guided by BIS may increase the percentage of adequate anesthesia and shorten the percentage of overshoot time compared with open-loop TCI model in anesthesia maintenance phase in patients undergoing shoulder arthroscopy in the BCP, and do not increase the risk of POCD.

Background

Electroencephalographic (EEG) activity can provide a reliable basis for a substitute measurement of hypnosis, thus the Bispectral Index (BIS), an EEG monitor, has been proven helpful to titrate hypnotic drugs. The basis for EEG-based depth-of-anesthesia monitoring is the behavioral correlates and EEG changes occurring with increasing anesthetic depth[1]. Closed-loop target controlled infusion system is a closed loop anesthesia delivery system guided by BIS and automatically regulates the propofol infusion to maintain BIS within the set target range[2]. It has been reported to allow the automated delivery of propofol and maintain BIS values in predetermined range better than manual administration during general anesthesia[3].

Although closed-loop TCI systems for propofol guided by BIS has many advantages for depth-of-anesthesia maintenance, those results were obtained in the supine position, and whether the same story might happen on the operations in BCP remains unknown.

Beach chair position is a deformation of the supine surgical position. After placement of BCP, the patient's head and neck form an angle of $90^{\circ}\sim 110^{\circ}$ with the horizontal position. Alperin et al[4] monitored the blood flow and cerebrospinal fluid in the supine position and head high positions by MRI, and the

patients in this special position could cause a significant decrease in intracranial blood flow and cerebrospinal fluid. Changes in intracranial blood flow may cause changes in EEG signals and EEG waveform.

Therefore, the main aim of this study was to compare BIS profiles (percentage of time with desired values) between the closed-loop TCI systems of propofol guided by BIS and the open-loop TCI guided by BIS in BCP. In addition, we aimed to study if different propofol infusion system have any effects on the incidence of postoperative cognitive dysfunction and intraoperative hemodynamic fluctuations.

Materials And Methods

Study design

This is a prospective randomized controlled study, which was approved by the Ethics Committee of the Second People's Hospital of Shenzhen in August 2017, and was registered at Chictr.org.cn. (ID: ChiCTR- INR-17012557). Informed written consent was obtained from all patients, and the study was based on the principles of the Declaration of Helsinki for medical research involving human subjects.

Participants

From Sept. 2017 to March 2018, 120 patients were included in this study. ASA I/II patient aged 16–65 years scheduled for shoulder arthroscopy in BCP were randomized equally into either the group C or the group O using computer generated random numbers. The random allocation sequence was conducted by a team member who was not related to operation and patient assessment. And the same member prepared opaque envelopes in which the intervention information was concealed. Before interscalene brachial plexus block, these envelopes were opened. Patients were excluded from the study if with a cardiac pacemaker, communication difficulties, history of mental illness, craniocerebral surgery, coagulation dysfunction, diabetes mellitus with peripheral neuropathy, or participating in other clinical trials.

Interventions

Patients were monitored in the operating room as per standard procedure, with non-invasive blood pressure (NIBP), heart rate (HR), electrocardiogram (ECG), pulse oximetry (SpO₂) and invasive blood pressure (IBP) and BIS (A-2000XP BIS, Aspect Medical system, Dublin, Ireland) with electrodes placed on patients' forehead. Ultrasound-guided interscalene brachial plexus block was performed before anesthesia induction. All patients received TCI propofol (the initial target concentrations in the plasma was 3 to 4 ug/ml) and remifentanyl (the initial target concentrations in the effect-side was 4 ng/ml) until the BIS maintained at < 60 for 30 seconds, followed by propofol administration either by open-loop in the group O or closed-loop in the group C. The parameters of TIVA-TCI described by Marsh et al.[5] and Minto et al.[6] were used for propofol and remifentanyl, respectively.

The rocuronium was used after the loss of consciousness, and the induction dose was 0.6 mg/kg. Endotracheal intubation was performed after muscle relaxation.

During the maintenance phase, in order to maintain the BIS at about 50 (40 to 60), the target concentration of propofol was regulated manually in the group O and automatically by the system in the group C. Both groups were treated with remifentanyl, and the target concentration (3 to 5 ng/ml) was determined by the clinical judgment of the anesthesiologists.

Surgery was performed in BCP. Intraoperative blood pressure was controlled within 30% of the base value. When the blood pressure was lower than 30% of baseline value, phenylephrine was administered at 20 ~ 40ug or $0.02 \sim 0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Nitroglycerin was administered when blood pressure was higher than 30% of the base value. Atropine 0.5 mg was administered when heart rate was below 50 bpm. No inhalation anesthetic was used and 5 mg tropisetron was administered at about 15 minutes before the end of the operation.

The infusion of intravenous anesthetics was stopped at the end of the operation in both groups. When the patient established regular breathing with adequate ventilation, and be able to obey commands, extubation was performed.

An MMSE was assessed at the preoperative patient's visit and the day after surgery by a blinded anesthesiologist.

Blood samples were taken before anesthesia, after extubation and the day after operation, respectively. After centrifugation (15 minutes at 2000 rpm), serum samples were stored at -70 °C for long-term storage. Serum GFAP and S100B levels were measured in duplicate manner for each sample using a commercial ELISA.

Data collection

Outcomes

The global score (GS) can reflect the overall performances of the closed-loop infusion system, including the proportion of time of adequate anesthesia (BIS between 40 and 60), and the fluctuation of BIS.

Therefore, GS was selected as the primary outcome. The parameters were calculated as follows: performance error (PE) was defined as the difference between the actual value and the set value:

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

Median performance error (MDPE):

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

Median absolute performance error (MDAPE):

$MDAPE_i = \text{Median } [PE_{ij}, j = 1, \dots, N_i]$

Wobble reflects the intraindividual variability in PE:

$Wobbe_i = [PE_{ij} - MDPE_i], j = 1, \dots, N_i]$

i = subject number; j = jth (one) measurement of observation period; N = total number of measurements during the observation period.

Global score (GS) was calculated using the formula:

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

Lower MDAPE, lower Wobble, and higher proportion of time of BIS between 40 and 60, would result in a lower GS, which was represented better performances of the infusion system.

Other primary outcomes, which were collected automatically by the data-collecting software provided by Beijing slgo Medical Technology Co. Ltd, included: the percentage of adequate anesthesia (BIS between 40 and 60), overshoot (BIS < 40) and undershoot (BIS > 60) periods; the adjustment times per hour for control of adequate anesthesia.

Secondary outcomes included doses of propofol, remifentanyl, and the endotracheal tube removal time (from the end of the infusion of intravenous anesthetics to the removal of the endotracheal tube), patients' MAP, HR, BIS at T1 (5 minutes after intubation), T2 (10 minutes after intubation), T3 (5 minutes after adjusting to BCP), T4 (10 minutes after adjusting to BCP), T5 (15 minutes after adjusting to BCP), and T6 (20 minutes after adjusting to BCP), the MMSE scores of the day before operation and the day after operation, the serum concentration of GFAP and S100B protein.

Statistical analysis

SPSS 17.0 was used for statistical analysis. All statistical analyses were two-sided t test and a P-value < 0.05 was considered statistically significant. Categorical variables, expressed as numbers (frequencies), were compared using the χ^2 test or one-way ANOVA followed by Fisher test. Continuous variables were presented as means (standard deviation) or medians (25th percentile; 75th percentile). And comparisons between the two groups were performed using unpaired Student's t-tests or Mann-Whitney U-tests as appropriate.

Results

Of the 120 recruited patients, 2 patients were excluded from each group, due to the use of inhalation anesthetics (Figure 1). There was no significant demographic difference between the two groups (Table 1). And in the induction phase, patients' characteristics were also similar between the two groups.

The GS were 25.54 ± 9.94 in group C and 37.48 ± 16.31 in group O during the maintenance phase, respectively ($p < 0.05$) (Table 2). And the mean BIS were 47.31 ± 2.72 in group C and 48.95 ± 3.90 in group O during the maintenance phase, respectively ($p < 0.05$). As for the proportion of time of BIS between 40 and 60, the higher proportions were found in group C ($79.62 \pm 6.75\%$), while the lower were observed in group O ($72.02 \pm 13.15\%$) ($p < 0.05$). Meanwhile, the percentage of overshoot (BIS < 40) periods was lower in group C ($11.50 \pm 6.03\%$) than in group O ($14.54 \pm 10.53\%$). And the percentage time of undershoot (BIS > 60) periods was lower in group C ($8.87 \pm 6.02\%$) than in group O ($13.45 \pm 11.92\%$) (Table 2).

The mean consumption of propofol were 13.88 ± 3.76 mg/kg and 15.25 ± 5.11 mg/kg in group C and group O during the maintenance phase, respectively ($p < 0.05$) (Table 3). To maintain the BIS value in an appropriate range during anesthesia, propofol was regulated more frequently in group C (27.44 ± 9.56 times/hr) than in group O (7.33 ± 3.11 times/hr) ($p < 0.05$). The induction time, the maintenance time, the consumption of remifentanyl, rocuronium and vasoactive drugs were similar in the two groups. Tracheal extubation time (from the end of the infusion of intravenous anesthetics to the time of endotracheal tube removal) were 10.51 ± 2.72 and 11.01 ± 3.34 minutes in group C and group O, respectively ($p > 0.05$) (Table 3).

There was no statistically significant difference in the MAP, HR, and BIS between the two groups at any time point (Figure 2).

The MMSE scores were similar on the day before surgery and the day after surgery between the two groups, and no significant differences were found between the two groups at any time point when comparing the GFAP and S100B levels (Table 4).

Discussion

Previous studies have shown that there is a significant decrease in BIS values in head-up position compared with neutral position during general anesthesia[7]. It means that patient's position during anesthesia may affect the BIS values, which may be related to decrease cerebral blood flow [4]. Over-shoot anesthesia has been reported to cause a significant decrease in cerebral blood flow due to the overdosage of propofol[8]. Brain ischemia and transient visual loss caused by decreased cerebral blood flow have been documented in patients who have undergone shoulder surgery in the BCP^[9-14]. Although the cause was unclear, intraoperative cerebral hypoperfusion may be considered to be a high-risk factor.

Our study was that avoid over-shoot anesthesia caused by over-dosage of propofol in shoulder arthroscopy in the BCP, to minimizes the risk of cerebral hypoperfusion. Previous studies have shown that

low BIS may increase postoperative mortality. A prospective observational study of 1,046 non-cardiac surgery patients by Monk et al.[15] found that cumulative time of over-shoot anesthesia can predict mortality within 1 year, and the longer was the cumulative time of over-shoot, the higher the mortality rate was to be. A retrospective study of 4,352 cases by Lindholm et al.[16], similar to Monk et al., found that cumulative time of over-shoot anesthesia was predictive of mortality within 2 years in the absence of patients with malignant tumors. In our study, closed-loop TCI system reduced the incidence of over-shoot anesthesia period. At the same time, the proportion of time of BIS between 40 and 60, which was regarded as appropriate anesthesia, was longer in group C than in group O, though the mean BIS was lower in group C than in group O. Similarly, the GS of group C was observed lower than that in group O. Meanwhile, the less usages of propofol were observed in group C than in group O, suggesting that the regulation of propofol was more accurate in group C. Through the analysis of the infusion system, it was found that the regulation of propofol can be about 28.2 ± 9.6 times/hour in group C, which is impossible to perform manually.

Endotracheal extubation time is one of the parameters to measure the recovery quality of patients. In our study, endotracheal extubation time was not statistically significant, suggesting that the recovery quality was comparable in the two groups. Then, the brachial plexus nerve block in both groups may provide adequate analgesic effect, and the less dosages of opioids were used than other studies (for example, $11.14 \pm 3.08 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in group C and $11.05 \pm 3.30 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in group O in Liu's study[17]; the doses of remifentanyl in our study was $0.11 \pm 0.03 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in both groups), which is conducive to rapid and stable recovery of patients.

The mean dose of propofol in group C was less than group O during the maintenance phase, but the results of this study showed that none of the patients in the two groups had intraoperative awareness, postoperative cognitive dysfunction, or brain ischemia. It may be because only ASA I/II patients were selected, and underwent surgery for no more than 3 hours under BIS monitoring.

A weakness of this study was lack of intraoperative cerebral blood flow monitoring. Due to the limitation of surgical position placement, the probe of near infrared reflectance spectroscopy cannot be placed on the forehead. Therefore, the relationship between cerebral blood flow and BIS cannot be evaluated directly.

Conclusions

In the anesthesia maintenance stage, compared with open-loop TCI, the closed-loop TCI of propofol guided by BIS shortened the time of BIS < 40, reduce the dosage of propofol, and did not increase the incidence of postoperative cognitive dysfunction and intraoperative hemodynamic fluctuations. To verify the advantage of the close-loop of TCI for this kind of surgery reported in our study, researches with large sample size would be necessary.

Abbreviations

ASA
American Society of Anesthesiologists
BCP
Beach chair position
BIS
Bispectral index
ECG
Electrocardiogram
EEG
Electroencephalographic
ELISA
Enzyme linked immunosorbent assay
GFAP
Glial fibrillary acidic protein
GS
Global score
HR
Heart rate
IBP
Invasive blood pressure
MAP
Mean arterial pressure
MDPE
Median performance error
MDAPE
Median absolute performance error
MMSE
Mini-mental state examination
MRI
Magnetic resonance imaging
NIBP
Non-invasive blood pressure
PE
Performance error
SpO₂
Pulse oximetry
TCI
Target controlled infusion
TIVA
Total intravenous anesthesia

Declarations

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Contributions

Concept/design: J-jL, D-pW, Z-hL; Data analysis/interpretation: N-bL, FY, HY, L-qP; Drafting article: J-jL, ZZ; Critical revision of article: J-jL, ZZ, WL, Z-hL; Directing clinical research: G-gF; Approval of the article: J-jL, ZZ, N-bL, FY, HH, X-pY, L-qP, WL, G-gF, D-pW, Z-hL; Statistics: HH, X-pY; Data collection: N-bL, FY, L-qP. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second People's Hospital of Shenzhen (2017082203), and registered at Chictr.org.cn (ChiCTR-INR-17012557). Informed written consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1 Demographic characteristics of patients in the group C and the group O.				
		Open-loop(n=58)	Closed-loop(n=58)	P-values
Gender	Male(%)	30(52)	34(59)	0.577
Age	(years)	47(40.5;54)	45(30;52.25)	0.058
Height	(m)	1.67(0.08)	1.67(0.07)	0.909
Weight	(kg)	64(58.75;72.00)	67(60.75;75.50)	0.789
BMI	(kg/m ²)	22.86(2.45)	23.78(2.94)	0.567
ASA classification	I(%)	29(50)	25(43)	0.706
	II(%)	29(50)	33(57)	
Summary characteristics of intraoperative measurements presented as n (%) and means (standard deviation) or medians (25th percentile; 75th percentile). All P-values are for unpaired Student's t-tests or Manne Whitney U-tests as appropriate.				
BMI = Body Mass Index				

Table 2 Effectiveness of the closed-loop control system.			
	Open-loop(n=58)	Closed-loop(n=58)	<i>P</i> -values
GS	35(24.2;48.45)	25(18.48;31.5)	0.000
Mean BIS	49(47;52)	47(45.75;49)	0.005
BIS<40(%)	14.54(10.53)	11.5(6.03)	0.000
40<BIS<60(%)	74(65;81)	79.95(75.6;84.75)	0.001
BIS>60(%)	9.7(5.08;17.68)	7.6(3.85;13)	0.052
Summary characteristics of intraoperative measurements presented as means (standard deviation) or medians (25th percentile; 75th percentile). All <i>P</i> -values are for unpaired Student's t-tests or Manne Whitney U-tests as appropriate.GS = Global score of BIS; BIS<40(%) = percentage of time in which the BIS value was less than a value of 40; 40<BIS<60(%) = percentage of time in which the BIS value was between 40 and 60 during the maintenance; BIS>60(%) = percentage of time in which the BIS value was greater than a value of 60.			

Table 3. Comparison of anesthetic procedures between the two groups.				
		Open-loop(n=58)	Closed-loop(n=58)	P-values
Induction time	(min)	4.24(1.96)	5.18(2.25)	0.219
Maintenance time	(min)	159.13(43.72)	154.69(38.16)	0.649
Extubation time	(min)	11.13(8.07)	10.70(8.49;12.56)	0.386
Propofol				
Mean dose of induction time	(mg/kg)	1.82(0.45)	1.89(0.51)	0.296
Mean dose of maintenance time	(mg/kg)	15.25(5.11)	13.88(3.76)	0.026
Adjusted times	(/h)	7.21(5.55;9.42)	27.69(21.46;34.44)	0.000
Remifentanil				
Mean dose	($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	0.11(0.03)	0.10(0.03)	0.908
Adjusted times	(/h)	2.32(0.65)	2.45(0.84)	0.052
Mean dose of rocuronium	(mg/kg)	0.70(0.08)	0.69(0.08)	0.923
Phenylephrine	(%)	46(79)	48(83)	0.813
Atropine	(%)	24(41)	18(31)	0.334
Nitroglycerin	(%)	0	0	
Summary characteristics of intraoperative measurements presented as means (standard deviation) or medians (25th percentile; 75th percentile). All P-values are for unpaired Student's t-tests or ManneWhitney U-tests as appropriate.				

Table 4. Comparison of MMSE scores, GFAP and S100 β protein concentrations between the two groups.				
		Open-loop(n=58)	Closed-loop(n=58)	<i>P</i> -values
MMSE scores before surgery		26.64(1.82)	26.53(2.02)	0.684
MMSE scores after surgery		26.52(1.55)	26.28(1.50)	0.734
Intraoperative awareness rate		0	0	
GFAP[ng/ml]	T0	0.87(0.35)	1.00(0.39)	0.152
	T7	1.19(0.46)	0.92(0.45)	0.772
	T8	0.60(0.27)	0.92(0.30)	0.247
S100 β [pg/ml]	T0	32.08(16.13)	30.14(14.07)	0.327
	T7	71.20(24.94)	80.96(27.73)	0.242
	T8	32.16(13.02)	23.66(13.31)	0.863
Summary characteristics of intraoperative measurements presented as means (standard deviation) or medians (25th percentile; 75th percentile). All <i>P</i> -values are for unpaired Student's t-tests or ManneWhitney U-tests as appropriate.				

Figures

CONSORT 2010 Flow Diagram

Figure 1

Study flowchart

Figure 2

There was no statistically significant difference in the MAP, HR, and BIS between the two groups at any time point

Supplementary Files

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