

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

Zhao Zhao

Shenzhen Second People's Hospital

Junjie Li

Shenzhen Second People's Hospital <https://orcid.org/0000-0003-1226-5404>

Yang Fang

Shenzhen Second People's Hospital

Luo Nanbo

Shenzhen Second People's Hospital

Yang Han

Shenzhen Second People's Hospital

Yang Xinping

Shenzhen Second People's Hospital

Peng Liangquan

Shenzhen Second People's Hospital

Lu Wei

Shenzhen Second People's Hospital

Guangguang Fang

Shenzhen Second People's Hospital

Wang Daping

Shenzhen Second People's Hospital

Zhiheng Liu (✉ zhiheng_liu_tongji@163.com)

Shenzhen Second People's Hospital <https://orcid.org/0000-0002-2823-543X>

Research article

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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 an anesthetic drug delivery system that can automatically adjust infusion rate of propofol guided by BIS, and the proportional-integral-derivative (PID) controller is the most widely used component in Closed-loop TCI system of propofol[2]. It can reduce errors during system operation and automatically regulate infusion of propofol, to maintain BIS within a set target range. Based on PID controller, this automatic infusion system of propofol infusion is better than manual adjustment of propofol TCI during general anesthesia[3, 4].

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. Whether the same story might happen on the operations in beach chair position remains unknown.

Beach chair position is a deformation of the supine surgical position. After placement of beach chair position, the patient's head and neck form an angle of $90^{\circ}\sim 110^{\circ}$ with the horizontal position. Danilo et al. [5] found cerebral perfusion decreased in the beach chair position by using a multiparameter transcranial Doppler-derived approach in patients underwent shoulder surgery. Changes in intracranial blood flow may cause changes in EEG signals and EEG waveform. According to previous research[6], although the probability of brain ischemia under beach chair position during perioperative period is small, it is still unavoidable.

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 beach chair position. In addition, we aimed to study if different propofol infusion system had some effects on the incidence of postoperative cognitive dysfunction with its liable biomarkers as well as on intraoperative hemodynamic fluctuations.

Materials And Methods

Study design

This is a prospective randomized controlled study, which was approved by the Ethics Committee of Shenzhen University First Affiliated Hospital/Shenzhen Second People's Hospital 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 beach chair position were randomized into either group C or group O, described below, 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

All 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). These data were automatically collected and recorded in our electronic medical record

system (Medicalsystem, Co. Ltd., Suzhou, China). At the same time, patients were monitored with BIS (A-2000XP BIS, Aspect Medical system, Dublin, Ireland).

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 mcg ml⁻¹) by BCP-100 infusion system and remifentanyl (the initial target concentrations in the effect-side was 4ng/ml) by normal TCI pump 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.[7] and Minto et al.[8] were used for propofol and remifentanyl, respectively.

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

The patients were randomized into two groups, namely group O and group C, according to methods to adjust propofol TCI target concentration during maintenance phase of general anesthesia. In group O, the target concentration of propofol was regulated manually by anesthesiologists based on their clinical experience, and in group C it was regulated automatically by the closed-loop infusion system (BCP-100, Beijing Silugao Medical Technology Co. Ltd., Beijing, China), in order to maintain BIS value at about 50 (40 to 60). The system used in this study was based on PID control as described above. It would judge the average value of BIS within 5 seconds in closed-loop mode. If the average value exceeded the set range, the system referred to the trend of the average value to decide whether to increase or decrease the concentration. And in the process of increasing or decreasing the concentration, the system referred to the trend of propofol concentration to determine whether to stop or accelerate the procedure. Both groups were treated with remifentanyl, and the target concentration (3 to 5 ng ml⁻¹) was determined by the clinical judgment of the anesthesiologists.

Surgery was performed in beach chair position. 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 20~40mcg or 0.02~0.1mcg kg⁻¹ 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 50bpm. 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

[Please see the supplementary files to view this section.]

Statistical analysis

SPSS 17.0 was used for statistical analysis. . 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. P-value <0.05 was considered statistically significant.

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⁻¹ and 15.25 ± 5.11 mg kg⁻¹ 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 h⁻¹) than in group O (7.33 ± 3.11 times h⁻¹) ($p < 0.05$). 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[9]. It means that patient's position during anesthesia may affect the BIS values, which may be related to decrease cerebral blood flow[5]. Brain ischemia and transient visual loss caused by decreased cerebral blood flow have been documented in patients who have undergone shoulder surgery in the beach chair position[10-15]position. Although the cause was unclear, intraoperative cerebral hypoperfusion may be considered to be a high-risk factor.

Our study wanted to avoid over-shoot anesthesia caused by over-dosage of propofol in shoulder arthroscopy in the beach chair position, to minimize 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.[16] 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.[17], 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 h^{-1} in group C, which is impossible to perform manually.

Over-shoot anesthesia has been reported to cause a significant decrease in cerebral blood flow due to the overdosage of propofol[18], which maybe cause brain ischemia. Then an MMSE was performed on each patient, and the serum samples were collected to measure cerebral ischemic biomarkers, including S100B protein and GFAP. In the present study, the concentration of S100B protein temporarily increased after extubation, and returned to the baseline the day after operation. The previous study[19] has shown that the concentration of S100B protein in patients with brain ischemia would peak after 24h. The trend of S100B concentration in this study was inconsistent with the performance of brain ischemia. Similarly, the trend of GFAP concentration was inconsistent with the brain ischemia. The increase of S100B concentration after extubation in this study may be related to the increase secretion of extracranial tissue caused by surgical trauma[20]. And the results of MMSE shown that no patient had postoperative cognitive dysfunction. With the advantages of close monitoring and rapid adjustment, closed-loop could reduce the mean dose of propofol during the maintenance phase, but closed-loop system had no advantage in reducing complications. It may be because only ASA I/II patients were selected, and underwent surgery for no more than 3 hours under BIS monitoring in our study.

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, $11.14 \pm 3.08 \text{ mcg kg}^{-1} \text{ h}^{-1}$ in group C and $11.05 \pm 3.30 \text{ mcg kg}^{-1} \text{ h}^{-1}$ in group O in Liu's study[21]; the doses of remifentanyl in our study was $0.11 \pm 0.03 \text{ mcg kg}^{-1} \text{ min}^{-1}$ in both groups), which is conducive to rapid and stable recovery of patients.

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

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

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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Author's 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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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) | |
| <p>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.</p> <p>BMI = Body Mass Index</p> | | | | |

| Table 2 Effectiveness of the closed-loop control system. | | | | |
|---|--|-----------------|-------------------|----------|
| | | Open-loop(n=58) | Closed-loop(n=58) | P-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 |
| <p>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 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.</p> | | | | |

| 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 <i>t</i> -tests or ManneWhitney U-tests as appropriate. | | | | |

Figures

CONSORT 2010 Flow Diagram

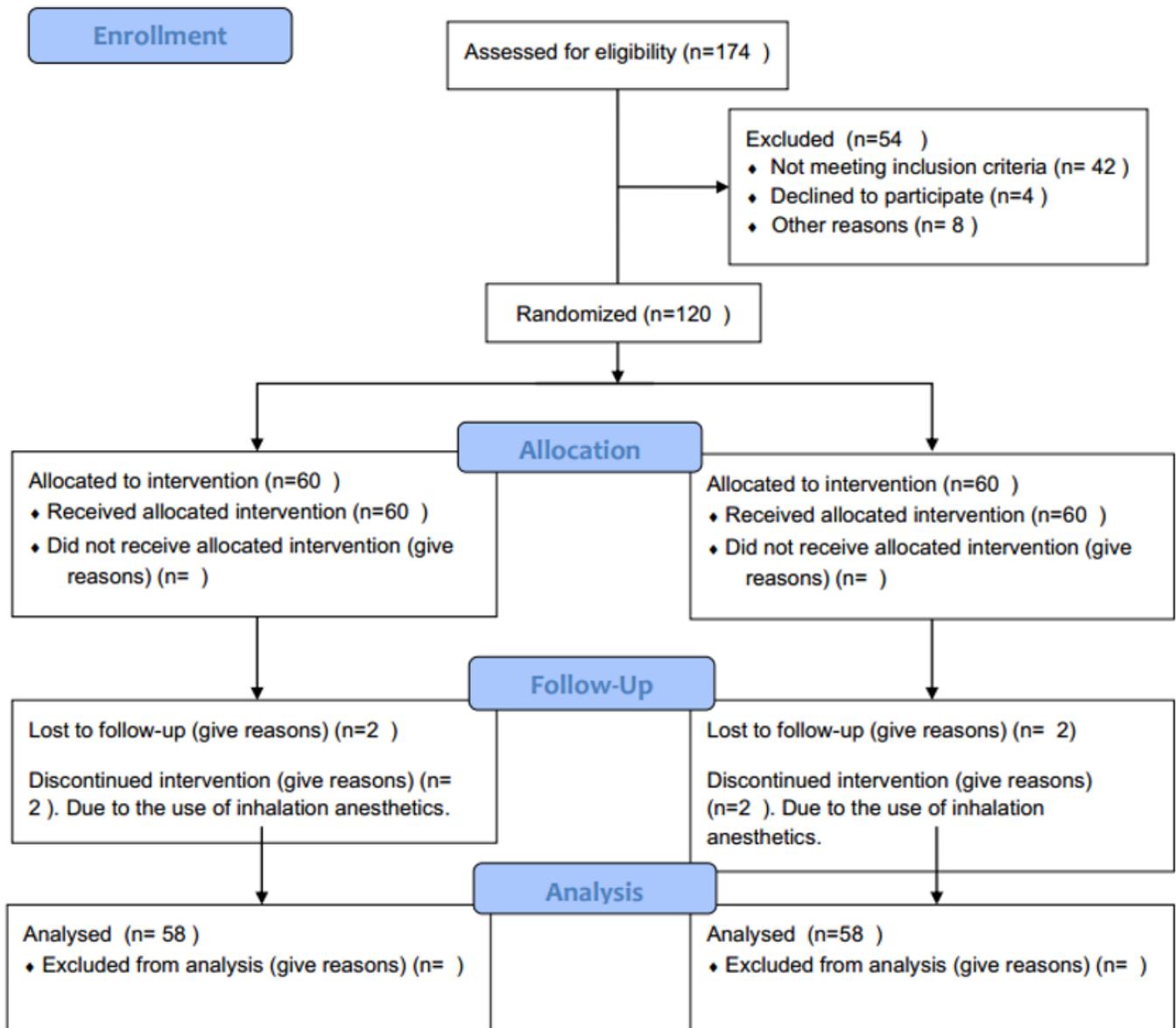


Figure 1

Study flowchart

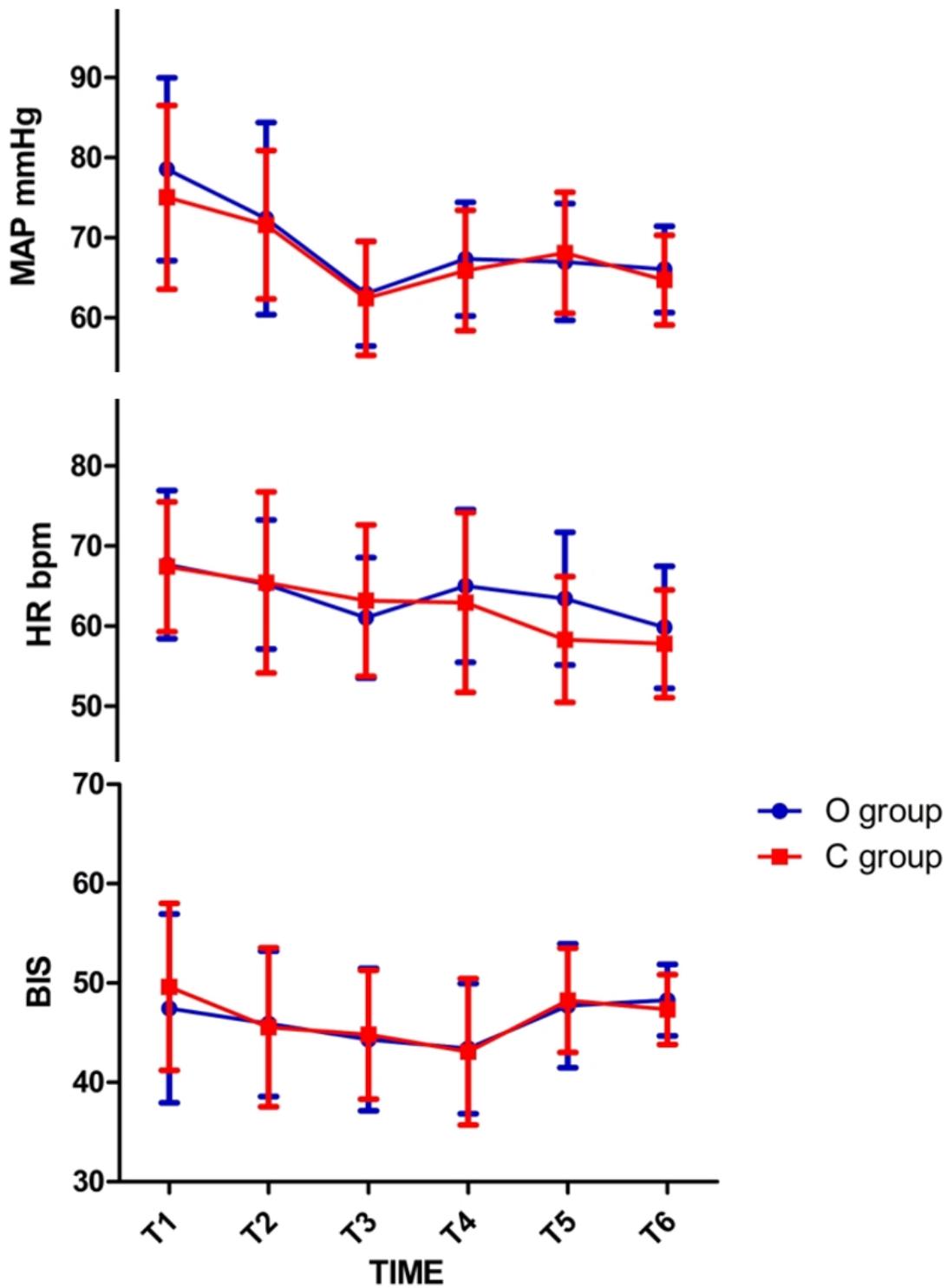


Figure 2

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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- [Appendix.docx](#)
- [CONSORT2010Checklist.doc](#)