

# Effects of different plasma target concentrations of remifentanil on the MACBAR of sevoflurane in children with laparoscopic surgery

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## Research Article

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# Abstract

## Background

To investigate the effects of different plasma target concentrations of remifentanyl on the minimum alveolar concentration (MAC) for blocking adrenergic response (BAR) of sevoflurane in children with laparoscopic herniorrhaphy.

## Methods

Seventy five children with 3–7 years old scheduled for laparoscopic herniorrhaphy were randomly divided into group R<sub>0</sub>, group R<sub>1</sub>, and group R<sub>2</sub> according to different remifentanyl plasma target concentration (0, 1, and 2 ng/ml), respectively. The MAC<sub>BAR</sub> of sevoflurane was determined by the up-and-down and sequential method in each group. The concentrations of epinephrine and noradrenaline were also determined at corresponding time points.

## Results

In groups R<sub>0</sub>, R<sub>1</sub>, and R<sub>2</sub>, the MAC<sub>BAR</sub> of sevoflurane was (3.29 ± 0.17)%, (2.12 ± 0.10)% and (1.29 ± 0.11)%, respectively, and a significant difference was found among the three groups ( $P < 0.05$ ). The changes of epinephrine and noradrenaline concentrations in each group before and after insufflation of carbon dioxide pneumoperitoneum showed no significant differences.

## Conclusion

Remifentanyl by target-controlled infusion can effectively reduce the MAC<sub>BAR</sub> of sevoflurane during laparoscopic surgery in children. At a similar effect of MAC<sub>BAR</sub>, both the changes of epinephrine and noradrenaline concentrations are not affected by the infusion of different remifentanyl target concentrations.

## Trial registration

The trial was registered in the China Clinical Trial Center(<http://www.chictr.org.cn>) in advance (the registry number is ChiCTR1800019393.).

# Background

Laparoscopic surgery has been widely used in pediatric surgery in recent years. Compared with the traditional surgery method, it possesses many advantages, such as slight trauma, rapid postoperative recovery, lower incidence of infection and less pain, etc <sup>[1]</sup>. Due to the complicated effect of carbon dioxide (CO<sub>2</sub>) pneumoperitoneum stimulus on children's hemodynamics<sup>[2]</sup>, it raises a higher requirement for anesthesiologists to use drugs reasonably and maintain hemodynamic stability skillfully. Previous studies have shown that anesthesia with sevoflurane alone requires a higher minimum alveolar

concentration (MAC) to block adrenergic response (BAR) in adult patients with CO<sub>2</sub>pneumoperitoneum stimulus<sup>[3, 4]</sup>. However, a high concentration of sevoflurane is usually associated with hemodynamic instability, myocardial depression, postoperative respiratory function depression, and delirium<sup>[5]</sup>. Therefore, it is often necessary to use other analgesics to reduce sevoflurane's concentration and its side effects. Remifentanyl is a strong short-acting opioid, does not rely on liver and kidney metabolism, and is suitable for target-controlled infusion. Therefore, this study aims to investigate the effects of different remifentanyl plasma target concentrations on the MAC<sub>BAR</sub> of sevoflurane in children with laparoscopic surgery.

## Methods

### Subjects

This study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Approved No. 2018ERR009). Written informed consents were obtained from all 75 children's guardian. All experiment procedures (consisted of invasive manipulation) and data collection were conducted with prior informed consents. This study adhered to the applicable CONSORT guidelines and was registered with the Chinese Clinical Trials Registry at <http://www.chictr.org.cn> (ChiCTR1800019393, principal investigator: Juan XU, date of registration: Nov 8, 2018) .

The research was conducted between November 2018 and June 2019. All children were American Society of Anesthesiologists (ASA) physical status I-II, aged between 3 and 7 years. Exclusion criteria included a history of cardiovascular, brain, liver, kidney, or hematological disease; a history of allergies to inhalation anesthetics or opioids; a history of recent upper respiratory tract infection. The flow of patients through the trial is shown in Fig. 1.

### Study design

All children were randomly assigned to three groups (R<sub>0</sub>, R<sub>1</sub>, R<sub>2</sub>) with 25 cases in each group according to computer-generated randomization. Children in the three groups were anaesthetized by inhalation of sevoflurane and intravenous infusion of remifentanyl with different plasma target concentrations (0, 1, 2, ng ml<sup>-1</sup>), respectively. During the creation of CO<sub>2</sub> pneumoperitoneum, the sympathetic adrenergic response was monitored in all patients. A positive response was defined as an increased heart rate (HR) or mean arterial pressure (MAP) of more than 20% of its baseline value. On the contrary, if the increase of HR and MAP was less than 20% of its baseline value, the sympathetic adrenergic response was defined as a negative response. The mean value of MAP or HR measured 3 and 1 min before pneumoperitoneum stimulus was defined as its baseline value. The mean value of HR or MAP measured 1 and 3 min after the pneumoperitoneum pressure maintained stable was defined as its changed value. Patients would be excluded from the experiment if the following occurred: Hypotension (systolic blood pressure, SBP) was less than (70 + 2 × age) mmHg and treated with intravenous ephedrine or bradycardia (HR < 80 bpm) was treated with intravenous atropine<sup>[6, 7]</sup>.

# Anesthesia administration

## Induction

All children were fasted for 6 h and not allowed to drink water for 2 h before the operation, and not received premedication routinely. Before induction of anesthesia, a venous channel was established and infused with compound sodium chloride solution at a rate of  $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . Electrocardiogram, pulse oxygen saturation, non-invasive blood pressure were routinely monitored with a PM-9000 express monitor (Mindray Medical International Limited, Shenzhen, China), and depth of anesthesia was monitored by using bispectral index (BIS) (Canwell Medical International Limited, Zhejiang, China). In each group, anesthesia was induced by inhalation of 7% sevoflurane with 100% oxygen. After children lost their consciousness, the inhaled sevoflurane concentration was reduced appropriately, and  $1 \mu\text{g}/\text{kg}$  remifentanil and  $0.6 \text{ mg}/\text{kg}$  rocuronium were intravenously injected. After tracheal intubation, the sevoflurane concentration was adjusted to a preset end-tidal concentration, which was monitored by a multifunctional monitor (Shenzhen Mindray Biomedical Co., Ltd., PM9000). At the same time, remifentanil was administered by target-controlled infusion in each group with the Bovil model using a micropump (TCH, ver 4.0, Guangxi VERYARK Technology Co., Ltd).

## Measurement of $\text{MAC}_{\text{BAR}}$

When the preset end-tidal sevoflurane concentration had maintained stable at least 20 minutes,  $\text{CO}_2$  pneumoperitoneum was established, and its pressure was set at 9 mmHg with a flow rate of 2 L/min. The first child's preset end-tidal sevoflurane concentration in each group was obtained from a preliminary test. The next child's end-tidal sevoflurane concentration for maintenance in each group would be adjusted based on the result of the previous child's cardiovascular response. If the response were positive (negative), the subsequent child's end-tidal sevoflurane concentration would be increased (decreased) by 0.2%. The person for recording the data was blinded to the plasma target-controlled remifentanil concentrations used in all groups.

The test was over in each group when six crossing points of a positive versus negative response or a negative versus positive response in the pre-and the next child had occurred. The  $\text{MAC}_{\text{BAR}}$  of sevoflurane in each group was calculated as the mean value of the end-tidal sevoflurane concentrations corresponding to the six crossing points. After the above test had been done,  $0.1 \text{ mg}/\text{kg}$  of midazolam was given intravenously to prevent a potential intraoperative awareness. All the children were received a routine intravenous and inhaled combined anesthesia. The BIS value was maintained between 40 and 60. The sevoflurane and remifentanil were discontinued 5 minutes before the end of the operation, and  $1.5 \mu\text{g}/\text{kg}$  of fentanyl was intravenously injected for analgesia. After the endotracheal tube was removed, each child was removed to the pediatric intensive care unit.

## Analysis of blood samples

Arterial blood samples (each for 3 ml) were collected 3 min before and after CO<sub>2</sub> pneumoperitoneum with sodium-heparin-containing tubes. Soon after, the plasma was separated and frozen at -70°C in a refrigerator until analysis. After the sample collection had been completed, the concentrations of epinephrine (E) and norepinephrine (NE) were measured using a method that has been described previously<sup>[3]</sup>.

## Statistical analysis

Statistical analysis was performed using SPSS22.0 software. All measurement data were expressed as mean ± SD. Only these data from the 12 cases at 6 crossing points of a positive (negative) versus negative (positive) response in each group were analyzed. The delta HR, delta MAP, delta E, and delta NE value was calculated as the difference between its change value and baseline value, respectively. One-way analysis of variance (ANOVA) for the complete random design was used to compare the differences of age, weight, MAC<sub>BAR</sub>, delta HR, delta MAP, delta E, and delta NE among the three groups, respectively. The sex constituent ratio was tested by Fisher's exact probability among the three groups. *P* value < 0.05 was considered as a statistical significance.

## Results

A total of 52 children were recruited in this study. Two cases in the group R<sub>2</sub> with hypotension were excluded from the study. Ultimately, to obtain six crossing points (Fig. 2), 18, 13, and 19 cases were used in groups R<sub>0</sub>, R<sub>1</sub>, and R<sub>2</sub>. The general information and the MAC<sub>BAR</sub> of sevoflurane in the three groups were shown in Table 1. Target-controlled infusion of 1ng/ml and 2ng/ml remifentanyl can reduce the MAC<sub>BAR</sub> of sevoflurane in children by 36% and 61%, respectively (*P* < 0.05). The baseline values of HR and MAP in groups R<sub>1</sub> and R<sub>2</sub> were lower than those in group R<sub>0</sub> (*P* < 0.05), but no significant differences were found between group R<sub>1</sub> and group R<sub>2</sub> (*P* > 0.05). No significant differences were found in the delta HR, delta MAP, delta E, and delta NE among the three groups, respectively (*P* > 0.05).

Table 1

The comparison of patients' characteristics, delta HR, delta MAP, delta E, and delta NE among the three groups. Values are presented as mean  $\pm$  SD or n. The baseline value of each parameter was the average value measured 3 and 1 min before CO<sub>2</sub> pneumoperitoneum. The value of delta represents the difference between before and after pneumoperitoneum stimulation. HR, heart rate; MAP, mean arterial pressure; E, epinephrine concentration; NE, norepinephrine concentration. #*P* < 0.05, compared with group R<sub>0</sub>; \* *P* < 0.05, compared with group R<sub>1</sub>.

Parameter	Group R <sub>0</sub>	Group R <sub>1</sub>	Group R <sub>2</sub>
Age (years)	4.6 $\pm$ 1.0	5.5 $\pm$ 1.1	4.9 $\pm$ 1.0
Body weight (kg)	17.1 $\pm$ 2.5	18.3 $\pm$ 2.2	17.5 $\pm$ 2.1
Male/Female (n)	16/2	12/1	16/3
MAC <sub>BAR</sub> (%)	3.29 $\pm$ 0.17	2.12 $\pm$ 0.10 <sup>#</sup>	1.29 $\pm$ 0.11 <sup>#*</sup>
Baseline HR (bpm)	135 $\pm$ 13	106 $\pm$ 15 <sup>#</sup>	94 $\pm$ 11 <sup>#</sup>
Delta HR	9 $\pm$ 12	7 $\pm$ 13	8 $\pm$ 5
Baseline MAP (mmHg)	68 $\pm$ 5	59 $\pm$ 2 <sup>#</sup>	54 $\pm$ 6 <sup>#</sup>
Delta MAP	8 $\pm$ 6	11 $\pm$ 10	13 $\pm$ 9
Baseline E (ng/ml)	2.20 $\pm$ 0.63	2.10 $\pm$ 0.80	2.05 $\pm$ 0.91
Delta E	0.20 $\pm$ 1.23	0.33 $\pm$ 0.95	-0.06 $\pm$ 1.21
Baseline NE (pg/ml)	540.30 $\pm$ 65.64	498.40 $\pm$ 61.66	464.09 $\pm$ 76.91
Delta NE	65.31 $\pm$ 20.75	56.24 $\pm$ 21.01	52.85 $\pm$ 24.37

## Discussion

Previous studies have found that opioid analgesics can reduce the MAC<sub>BAR</sub> of sevoflurane under skin-cutting stimulus both in children and adults<sup>[4, 8-10]</sup> and also can reduce the MAC<sub>BAR</sub> of sevoflurane when using pneumoperitoneum stimulation in adults<sup>[3]</sup>. However, whether opioid analgesics have the same effect on sevoflurane's MAC<sub>BAR</sub> in children under pneumoperitoneum stimulus has not been reported. This study found that remifentanyl plasma target concentrations 1ng/ml and 2ng/ml could make the MAC<sub>BAR</sub> of sevoflurane (3.29%) in children decreased 36% and 61% under pneumoperitoneum stimulus, respectively. The decreased degree is very similar to our previous result using the same target concentrations of remifentanyl in adult laparoscopic surgery (decreased 48% and 63%)<sup>[3]</sup>. It is also similar to another study's result (base value 2.98%) in pediatric patients with the same plasma target concentrations of remifentanyl by skin-cutting stimulus (decreased 44% and 69%)<sup>[11]</sup>. It means that the

same plasma target concentration of remifentanyl can induce a similar decreased degree of sevoflurane's  $MAC_{BAR}$  no matter using pneumoperitoneum stimulus or incision stimulus either in adults or in children.

However, at the same target concentration of remifentanyl, the  $MAC_{BAR}$  of sevoflurane in children using pneumoperitoneum stimulus is higher than that using skin incision stimulus, which may be mainly related to that pneumoperitoneum stimulus is more intensive than skin incision stimulus<sup>[3]</sup> because the laparoscope pneumoperitoneum stimulus not only includes a direct stimulus of the needle to the skin but also include the stimulus of  $CO_2$  pneumoperitoneum pressure. A stronger pneumoperitoneum stimulus must have a greater impact on a patient's heart rate and blood pressure<sup>[12]</sup>. Deeper anesthesia is required to inhibit an intense cardiovascular response. As all know, the setup of  $CO_2$  pneumoperitoneum will increase the patient's intra-abdominal pressure and thoracic pressure, which will induce a decrease of venous return and cardiac output and excite the sympathetic nervous system. In addition, the absorption of  $CO_2$  through the peritoneum can also indirectly stimulate the central nervous system and activate the sympathetic adrenal system<sup>[13]</sup>. As a result, it will lead to a significant increase in the secretion of cortisol, epinephrine, norepinephrine, renin,

and vasopressin, and eventually manifest as a increase of patients' blood pressure and heart rate<sup>[14]</sup>. However, when we analyzed the changes of plasma epinephrine and norepinephrine concentrations, heart rate, and blood pressure before and after pneumoperitoneum stimulus in pediatric patients with crossover points to cardio vascular response, no significant differences were found among the three groups, respectively (Table 1). It indicates that at a similar depth of anesthesia, the changes of plasma epinephrine and norepinephrine levels and hemodynamic parameters are consistent and not affected by different target concentrations of remifentanyl, which is consistent with the results of Zou's study in adult patients with laparoscopic surgery<sup>[3]</sup>.

In this study, the HR and MAP in groups  $R_1$  and  $R_2$  were significantly lower than those in group  $R_0$  before the creation of pneumoperitoneum, which may be related to multiple mechanisms of remifentanyl causing slow heart rate and low blood pressure, such as exciting vagus nerve, inhibiting sinus node's self-regulation, and relaxing the peripheral vascular smooth muscle and so on<sup>[15, 16]</sup>. However, no severe hypotension and bradycardia occurred when the remifentanyl's plasma target concentration was 1ng/ml. Only 2 cases experienced transient hypotension when the target concentration of remifentanyl was 2ng/ml. It can be quickly corrected by intravenous bolus injection of ephedrine 3-5mg. Our preliminary experiment found that severe hypotension or bradycardia would happen when the remifentanyl's plasma target concentration was more than 3ng/ml, and the end-tidal sevoflurane concentration was close to  $MAC_{awake}$ <sup>[17]</sup>, which may appear intraoperative awareness. Therefore, we had not attempted to measure the  $MAC_{BAR}$  of sevoflurane using a higher target concentration of remifentanyl over 2ng/ml.

One limitation of the study is that the children included in this study are mostly concentrated in preschool. The effects of age subgroups on the  $MAC_{BAR}$  of sevoflurane are concentrated in preschool children. The effects of age subgroups on the  $MAC_{BAR}$  of sevoflurane with pneumoperitoneum stimulus

needs further study. Another limitation is that we have not measured the actual plasma remifentanyl concentration, although the Minto pharmacokinetic model for target-controlled infusion is safe in adults [18–20]. The accuracy of the Minto pharmacokinetic model of remifentanyl in the pediatric population needs further study.

## Conclusions

remifentanyl by target-controlled infusion can significantly reduce the  $MAC_{BAR}$  of sevoflurane responding to laparoscopic pneumoperitoneum stimulus in children. In addition, at a similar effect of sevoflurane's  $MAC_{BAR}$ , adrenergic response changes are similar.

## Abbreviations

### MAC

minimum alveolar concentration;

### $MAC_{BAR}$

minimum alveolar concentration for blocking adrenergic response;

### CO<sub>2</sub>

Carbon dioxide;

### ASA

American Society of Anesthesiologists;

### HR

Heart rate heart rate;

### MAP

Mean arterial pressure;

### SBP

systolic blood pressure;

### BIS

Bispectral index;

### E

epinephrine;

### NE

norepinephrine;

### ANOVA

One-way analysis of variance;

## Declarations

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Approved No. 2018ERR009). Written informed consents were obtained from all participants. All experiment procedures (consisted of invasive manipulation) and data collection were conducted with prior informed consent.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

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

### **Competing interests**

All authors declare that they have no conflicts of interest.

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### **Authors' contributions**

D W and J X were the co-first authors of this article, conducted the study, collected and analyzed the data and wrote the paper. XL Y was the corresponding authors of this article, helped with the study design and revision of the paper. YX Gand PP J helped with the clinical anaesthesia management. GY Z helped with the determination of blood samples. All authors read and approved the final manuscript.

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Not applicable.

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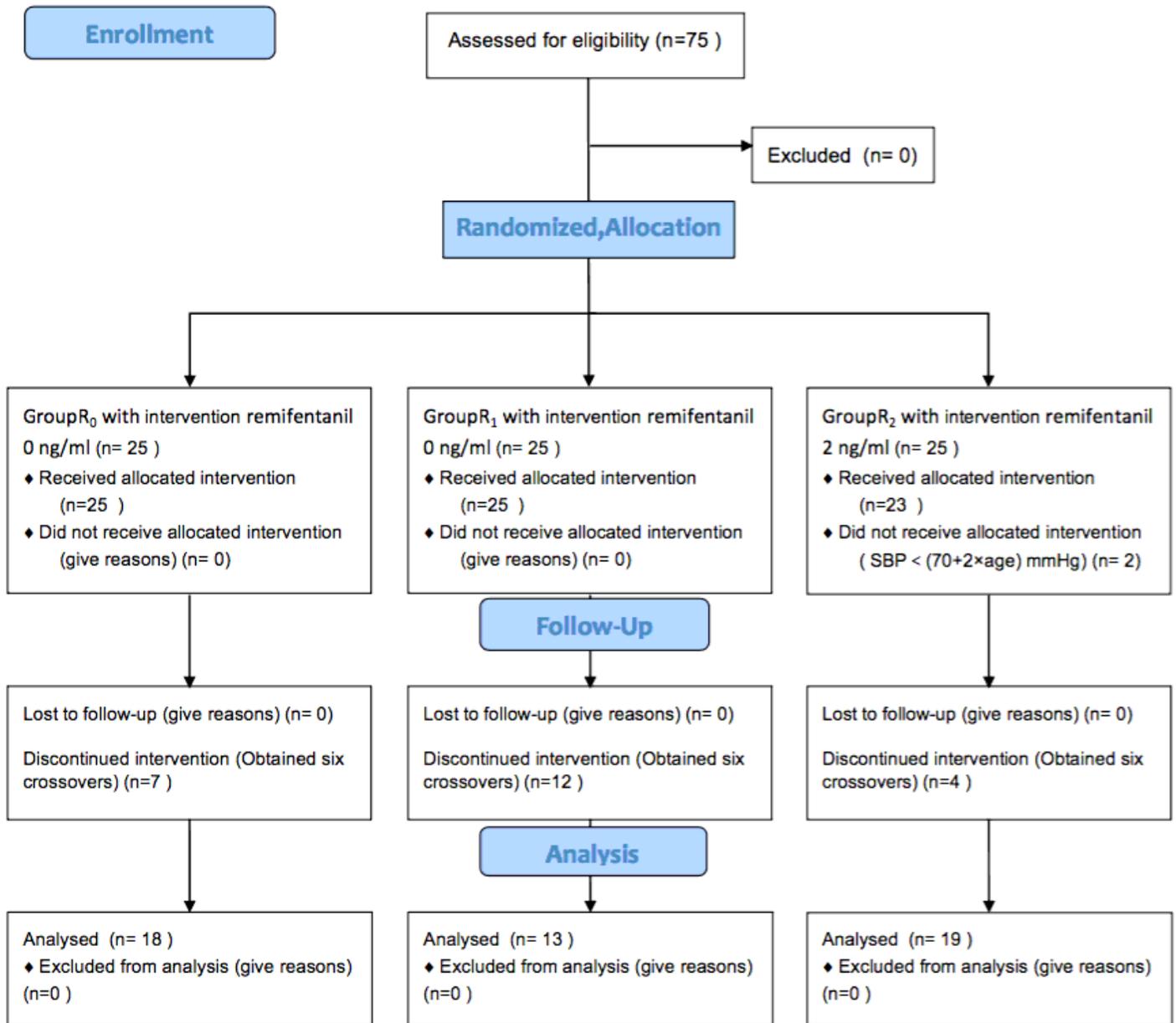
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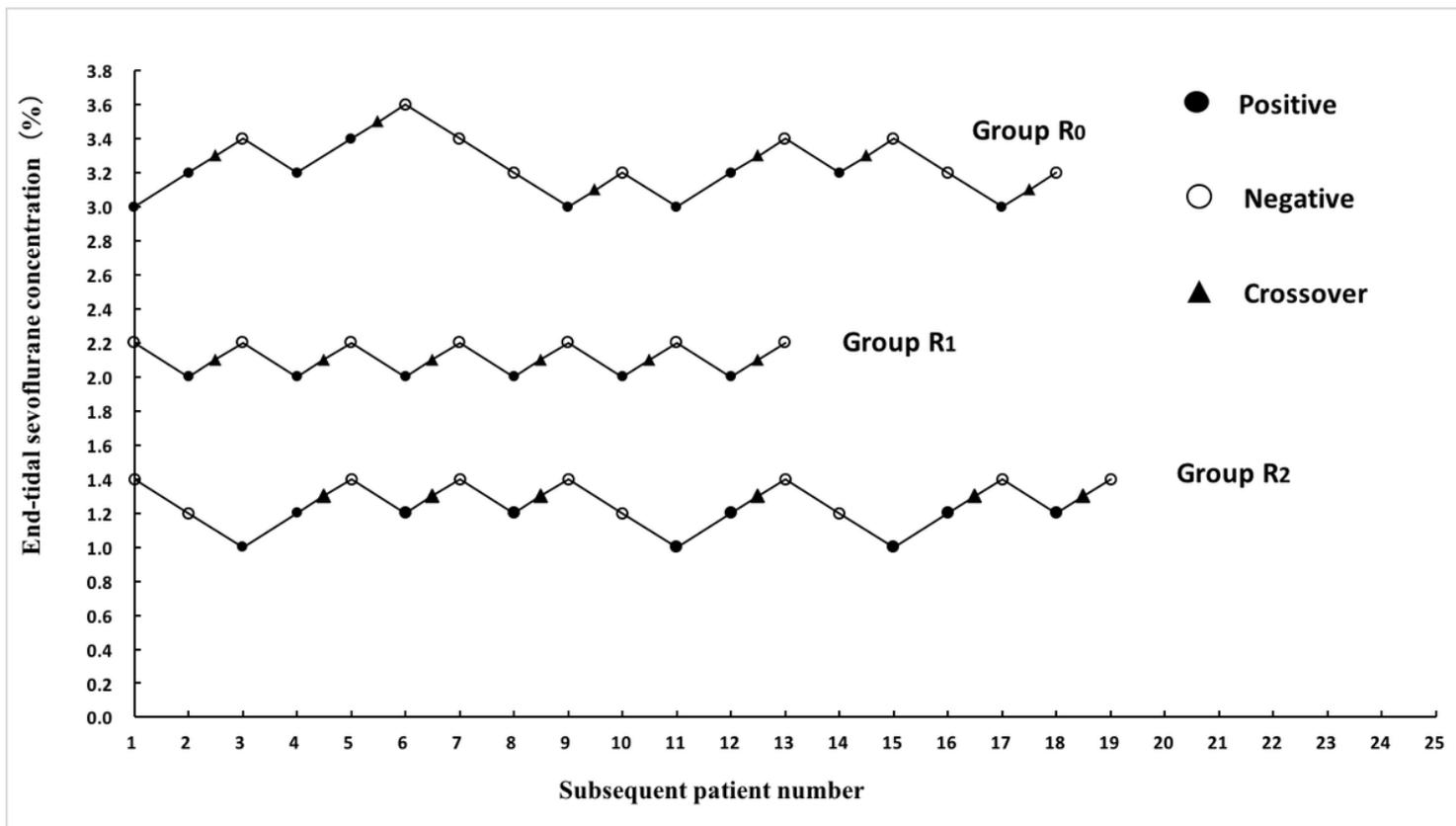
## Figures

## CONSORT Diagram



**Figure 1**

CONSORT flowchart. In this study, 75 patients were randomly allocated into 3 groups, 25 patients in each group. Two patients were stopped the intervention due to hypotension and withdrew from the experiment. To obtain six crossover points of positive vs negative response in each group, 18, 13 and 19 patients in groups R<sub>0</sub>, R<sub>1</sub> and R<sub>2</sub> were needed respectively. Finally, remaining 23 patients did not undergo the experimental intervention.



**Figure 2**

The measurement of MACBAR of sevoflurane in 3 groups. The plasma target concentration of remifentanyl in groups R0, R1 and R2 was 0, 1 and 2 ng ml<sup>-1</sup>, respectively. An empty (solid) circle represents a negative (positive) reaction to hemodynamics parameters, and a triangle indicates an intersection of a negative reaction with a positive reaction. To get six crossovers, 18, 13 and 19 patients were needed in groups R0, R1 and R2, respectively.