Effects of different sufentanil target concentrations on the MAC_{BAR} of sevoflurane in patients with carbon dioxide pneumoperitoneum stimulus

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Abstract

Background: The objective of this study is to observe the effects of different target controlled plasma sufentanil concentrations on the minimum alveolar concentration (MAC) of sevoflurane for blocking adrenergic response (BAR) in patients undergoing laparoscopic cholecystectomy with carbon dioxide pneumoperitoneum stimulation.

Methods: Eighty-five patients undergoing laparoscopic cholecystectomy, aged 18-65 years, with American Society of Anaesthesiologists physical status Ⅰ-Ⅱ, were enrolled in this study. All the patients were randomly divided into 5 groups (S_0, S_1, S_2, S_3, S_4) with different sufentanil plasma target concentration (0.0, 0.1, 0.3, 0.5, 0.7 ng ml^{-1}). Anaesthesia was induced by inhalation of 8% sevoflurane in 100% oxygen, and 0.6 mg kg^{-1} of rocuronium was intravenously injected to facilitate the insertion of laryngeal mask airway. The end-tidal sevoflurane concentration and sufentanil plasma target concentration were adjusted according to respective preset value in each group. The hemodynamic response to pneumoperitoneum stimulus was observed after the end-tidal sevoflurane concentration had been maintained stable at least for 15 min. The MAC_{BAR} of sevoflurane was measured by a sequential method. Meanwhile, epinephrine and norepinephrine concentrations in the blood were also determined before and after pneumoperitoneum stimulus in each group.

Results: The basic MAC_{BAR} of sevoflurane in group S_0 was 5.33% (confidence interval[CI] 95%: 5.19-5.47%), which was decreased 15%, 46%, 58% and 60% by the infusion of sufentanil with 0.1, 0.3, 0.5 and 0.7 ng ml^{-1} plasma target concentration, respectively. But the decreased degree had no significant difference between 0.5 and 0.7 ng ml^{-1} of sufentanil plasma target concentrations. No significant difference was found in the change of epinephrine or norepinephrine concentration between before and after pneumoperitoneum stimulation in each group.

Conclusions: The MAC_{BAR} of sevoflurane can be decreased with increasing sufentanil plasma target concentrations. A capping effect of the decrease occurred at a sufentanil plasma target concentration of 0.5 ng ml^{-1}. When the sympathetic adrenergic response was inhibited in half patients to pneumoperitoneum stimulation in each group, the changes of epinephrine and norepinephrine concentrations showed no significant differences.

Trial registration: The study was registered at http://www.chictr.org.cn (ChiCTR1800015819, 23, April, 2018) .

Background

With the development of minimally invasive technique, laparoscopic surgery under inhalation anaesthesia has become increasing popular in general surgery[1,]. However, inhalation anaesthetic used alone to provide all the necessary components of general anesthesia under laparoscopic surgery may increase the risk of cardiovascular inhibition and inhaled anaesthetic toxicity[1,]. Many other agents have

been used to decreased the minimal alveolar concentration (MAC) of inhalation anaesthetic [9,]. Sufentanil, as an adjuvant, offers numerous advantages, including reduced the incidence of nausea and vomiting compared with the fentanyl[], reduced pioid-induced hyperalgesia compared with the remifentanil[], maintenance of stable hemodynamics, excellent analgesic effect. The MAC of sevoflurane for blocking the adrenergic response combined with different sufentanil plasma target concentrations under laparoscopic pneumoperitoneum stimulus has not been reported. Therefore, our primary aim of this study is to observe the MAC_{BAR} of sevoflurane combined with different sufentanil plasma target concentrations in patients under carbon dioxide pneumoperitoneum stimulation. A secondary aim is to explore the concentrations of epinephrine and norepinephrine in the blood when the adrenergic response was inhibited in half of the patients

Methods

Study design

The study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Approved No. 2017/043). Written informed consent were obtained from all participants. This study adhered to the applicable CONSORT guidelines. The study was registered with the Chinese Clinical Trials Registry at http://www.chictr.org.cn (ChiCTR1800015819, principal investigator:Yanxia Guo, date of registration: April 23, 2018) .

The research was conducted between May 2018 and March 2019. 85 patients were American Society of Anesthesiologists (ASA) physical status □-□, aged between 30 and 65 years, and randomly assigned to five groups (S_0, S_1, S_2, S_3, S_4) according to computer generated randomization. Patients in the five groups were anaesthetized by inhalation of sevoflurane and intravenous infusion of sufentanil with different plasma target concentrations (0.0, 0.1, 0.3, 0.5, 0.7 ng ml^{-1}), respectively. Exclusion criteria included patients with a history of cardiovascular, lung, kidney or brain disease; long-term drug and alcohol abuse; recent taking drugs known to affect the sympathetic adrenergic and cardiovascular systems; body mass index (BMI) ≧ 30 kg m^{-2}. Withdrawal criteria included the patients with mean arterial pressure (MAP) < 50 mmHg or heart rate (HR) < 50 bpm at any time during experimental observation; failing to the creation of carbon dioxide pneumoperitoneum for the first time or asking for adjustment of the pneumoperitoneal pressure above or below the preset value.

Anaesthesia Administration

Induction

All patients were fasted at least for 8 h before surgery and without any preoperative medication. Before induction of anaesthesia, patient’s MAP, HR, electrocardiogram, pulse oxygen saturation were routinely monitored with a PM-9000 express monitor (Mindray Medical International Limited, Shenzhen, China).

Simultaneously, a peripheral intravenous catheter was inserted for infusion of Ringer's solution with a rate of 10 ml kg^{-1} h^{-1}. An arterial catheter was inserted into the left radial artery for monitoring patient's invasive arterial blood pressure and collecting blood samples. In each group, anaesthesia was induced by inhalation of 8% sevoflurane with 100% oxygen until patients lost their consciousness, and 0.6 mg kg^{-1} of rocuronium was intravenously injected to facilitate laryngeal mask airway(tuoren medical equipment group co. LTD, Henan, China) insertion. Then mechanical ventilation was begun using 100% oxygen with a tidal volume of 6 to 8 ml kg^{-1}. A normal end tidal carbon dioxide (CO_2) tension (35 to 45 mmHg) was obtained by adjusting the respiratory frequency at 12 to 16 breaths min^{-1}. The end-tidal sevoflurane concentration and CO_2 partial pressure were monitored continuously using the above mentioned monitor. Depth of anaesthesia was monitored by the bispectral index (BIS) (Canwell Medical International Limited, Zejiang, China) installed before induction.

Measurement of MAC_{BAR}

After laryngeal mask airway insertion, sufentanil was administered by target-controlled infusion with Bovil pharmacokinetic model using a micro pump (TCI-I, ver 4.0, Guangxi VERYARK Technology Co., Ltd), and the plasma target concentration of sufentanil was 0.0, 0.1, 0.3, 0.5, 0.7 ng ml^{-1} in groups S_0, S_1, S_2, S_3, S_4, respectively. Simultaneously, the inhaled sevoflurane concentration was adjusted to obtain a stable preset end-tidal value according to our pilot study. In order to avoid a potential risk of intraoperative awareness, a higher initial end-tidal sevoflurane concentration was tested in the pilot study. Eventually, the first patient in S_0, S_1, S_2, S_3 and S_4 group receiving a start end-tidal sevoflurane preset concentration of 5.0%, 4.6%, 3.0%, 2.3% and 2.0% which was measured to be close to the MAC_{BAR}, respectively. An up-and-down sequential-allocation method was applied to determine the MAC_{BAR} of sevoflurane in each group as described in our previous studies[].

The CO_2 pneumoperitoneum was created when the preset end-tidal sevoflurane concentration had been maintained stable at least 15 min. The pressure of pneumoperitoneum was set at 13 mm Hg. A veress insufflaion was used to estabilish CO2 pneumoperitoneum. A positive or negative sympathetic adrenergic response to haemodynamic parameters (HR or MAP) was observed when the pneumoperitoneum pressure had been maintained stable for 1 min. Where a positive response to adrenergic response was defined as the increase of patient's HR or MAP over 20% of its baseline value, and a negative response means the increase of HR or MAP was less than 20% of its baseline value. The mean value of the MAP or HR measured 3 and 1 min before pneumoperitoneum stimulation was defined as its baseline value, and the mean value of HR or MAP measured 1 and 3 min after the pneumoperitoneum pressure maintained stable was defined as the changed value. If the response was positive, the subsequent tested patient's end-tidal sevoflurane concentration would be increased by 0.2%, in contrast, If the response was negative, the subsequent tested patient's end-tidal sevoflurane concentration would be decreased by 0.2%. The study was continued until six crossing points of a negative versus positive response in the pre-and the next patient had occurred. The investigator responsible for recording the the response of the patients to CO2 pneumoperitoneum was blinded to the plasma target controlled sufentanil concentrations and end-

tidal sevoflurane concentration used in all the 5 groups. The MAC_{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 was completed, the target controlled infusion of sufentanil was stopped in each group. All patients were received a routine intravenous and inhaled combined anaesthesia according to our departmental standard for laparoscopic operation. After removed laryngeal mask airway, patients were transported to post- anaesthesia care unit(PACU). In the PACU all patients were asked about whether there was an intraoperative awareness or not.

Analysis of blood samples

Arterial blood samples were collected 3 min before and after CO_2 pneumoperitoneum with sodium-heparin-containing tubes. Soon after, the plasma was separated and kept frozen at -70 °C in a refrigerator until analysis. The method used to measure the concentrations of epinephrine and norepinephrine in the current investigation had been described previously[8].

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software. MAC_{BAR} values were calculated as the mean of six independent crossing points of responses in which negative response and positive response were paired up for each group (Fig. 1). The data are presented as mean (SDs or 95% confidence intervals). The preoperative data, including gender and ASA class were compared with X^2 test. The preoperative data (age, BMI), the intraoperative data, the postoperative data, the MAC_{BARS}, the concentrations of epinephrine and norepinephrine, delta epinephrine, delta norepinephrine, MAP, delta MAP, HR, delta HR were compared among the 5 groups using one-way analysis of variance (ANOVA). P value < 0.05 was considered as statistical significance.

Results

A total of 85 patients are recruited in this study. One case in group S_0 and one case in group S_3 both with MAP < 50 mmHg were excluded from the study. One case with HR < 50 bpm in group S_4 was excluded from the study. Eventually, to obtain six crossing points, 14, 14, 18, 20 and 15 patients were used in groups S_0-S_4, respectively (Fig. 1), 81 patients completed the study. No significant differences were found in the patients' preoperative data, operation time and rocuronium consumed dose among the 5 groups (table 1). No intraoperative awareness was reported in the postoperative follow up.

The MAC_{BAR} of sevoflurane and its deceased degree by different plasma target concentration of sufentanil in groups S_0-S_4 were showed in table 2. The data of HR and delta HR were similar among groups S_2, S_3, and S_4, but significantly lower than the group S_0 and S_1 (P < 0.05, Table 3). No significant differences were found in the MAP, delta MAP, epinephrine and norepinephrine concentration, delta epinephrine and norepinephrine concentration among the 5 groups (table 3). The total administered dose

of sufentanil in both group S_3 and group S_4 was higher than that in the group S_0, S_1, S_2 ($P < 0.05$, Table 1). The spontaneous breathing recovery time, eye opening time and extubation time in the group S_4 were longer than those in the other 4 groups, respectively ($P < 0.05$, Table 1).

Discussion

The results of this study indicate that the reduction of the MAC_{BAR} of sevoflurane is dose-dependent. A ceiling effect of the decrease of MAC_{BAR} of sevoflurane was found when sufentanil plasma target concentration increased to > 0.5 ng ml^{-1} (Table 2). The ceiling effect of sufentanil was similar to the result measured by Brunner and colleagues[] at the same plasma target concentration when they evaluated the reduction of isoflurane's MAC by sufentanil responding to skin incision. As all know, sufentanil is a μ receptor agonist, which can be saturated when its plasma target concentration beyond a certain level[]. Therefore, we speculate that a similar ceiling effect will occur under a similar plasma target concentration of sunfentanil no matter what kinds of surgery and stimulus are selected. However, the plasma target concentration of sunfentanil (0.18 ng ml^{-1}) for occurring ceiling effect in Shun-Huang and colleague's study[] is significantly lower than that of our experiment result. It may be reasonably explained by the concomitant administration of 60% nitrous oxide[–]. Studies shows nitrous oxide can combine with the μ receptor and decrease the binding sites of sufentanil in humans[,,,].

In this study, the MAC_{BAR} of sevoflurane (5.33%) under laparoscopic pneumoperitoneum stimulation is higher than that measured by Katoh and his colleagues (4.15%) under skin incision[]. It indicates that the laparoscopic pneumoperitoneum stimulus is stronger than the skin incision stimulus, so that a higher concentration of sevoflurane is needed to inhibit the stress reaction in laparoscopic surgery, which is consistent with the results of our previous study[]. However, the MAC_{BAR} of sevoflurane measured in this study is also significantly higher than the value (4.6%) reported in our previous study in gynecologic patients[9]Although the same CO_2 pneumoperitoneum stimulus was used, the MAC_{BAR} of sevoflurane could be affected by many factors, such as the location of perforation for establishing pneumoperitoneum, the patient's age and sex[,]the methods of measurement[25–26] and the criterion of judgment for a positive or negative response, et al[27–28]. Dixon thought that the MAC_{BAR} values could be estimated as the mean of four independent crossovers of responses[]. Paul and his colleagues thought that the reliability of the Dixon method increased with the number of pairs and six pairs was enough[]. An increase of 15% or more from the baseline value of MAP or HR was taken as the criterion of a positive response in many studies[,]. However, in clinic, the fluctuation of MAP or HR within the range of 20% is also acceptable and reasonable. Therefore, in our current study, an increase of 20% or more from pre-pneumoperitoneum stimulation values of MAP or HR was taken as the standard to judge a positive response.

Our results indicated the delta epinephrine or norepinephrine concentration did not differ among all the 5 groups (Table 3). It implied that when the sympathetic adrenergic response was inhibited in half patients

to pneumoperitoneum stimulation in each group, the change of epinephrine or norepinephrine concentration would be similar, no matter the target controlled sufentanil concentration and the end tidal sevoflurane concentration. Our results also showed patients' HR could be depressed to some degree with the increase of sufentanil plasma target concentration (Table 3). However, the decrease in HR did not result in the decrease of patients' MAP, especially when high concentration of sufentanil was administrated. It implies the safety range of sufentanil is large, which is consistent with the results of Fechner and his colleagues[]. Nevertheless, our study showed the use of sufentanil at a large dose results in the delay of anaesthesia recovery (table1). Therefore, the administration of sufentanil in large dose for short surgeries such as laparoscopic cholecystectomy is not recommended.

One limitation of the study is that we did not measure arterial blood gas during the pneumoperitoneum period. Although the end-expiratory CO_2 partial pressure was maintained in normal range by adjusting the tidal volume and respiratory rate, it was still necessary to measure the actual CO_2 partial pressure to exclude the influence of hypercarbia on sympathetic adrenergic response. Another limitation is that we did not measure the actual plasma sufentanil concentration. Although the Bovill pharmacokinetic model for target-controlled infusion has been shown to be safe in Asian people, it is still necessary to measure the actual plasma sufentanil concentration to exclude individual error.

In conclusion, target-controlled infusion of sufentanil can significantly reduce the MAC_{BAR} of sevoflurane responding to laparoscopic pneumoperitoneum stimulation. Moreover, when the plasma target concentration of sufentanil is higher than 0.5 ng ml^{-1}, a capping effect of decrease will occur. In addition, when the sympathetic adrenergic response is inhibited at a same extent, the changes of epinephrine and norepinephrine concentrations are not affected by the sufentanil target concentration.

Conclusions

The MAC_{BAR} of sevoflurane can be decreased with increasing sufentanil plasma target concentrations. A capping effect of the decrease occurred at a sufentanil plasma target concentration of 0.5 ng ml^{-1}. When the sympathetic adrenergic response was inhibited in half patients to pneumoperitoneum stimulation in each group, the changes of epinephrine and norepinephrine concentrations showed no significant differences.

Abbreviations

MAC_{BAR}: minimum alveolar concentration of sevoflurane for blocking adrenergic response; **BMI**: body mass index; **ASA**: American Society of Anesthesiologists; **CO_2**: Carbon dioxide; **BIS**: Bispectral index;**MAP**: Mean arterial pressure; **HR**: Heart rate; **PACU:**post- anaesthesia care unit

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Approved No. 2017/043). Written informed consent were obtained from all participants.

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

YXG and DW were the co-first authors of this article, helped conduct study, collect and analyze the data and write the paper. XLY were the corresponding authors of this article, helped with the study design and revision of the paper. PPJ and JX helped with the clinical anaesthesia management. GYZ helped with the determination of blood samples. All authors read and approved the final manuscript.

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Tables

Table 1 Patients characteristics and Intraoperative and Postoperative data.

Parameter	Group S_0	Group S_1	Group S_2	Group S_3	Group S_4
Preoperative data					
Gender (n, M/F)	6/8	6/8	6/12	10/10	7/8
ASA class (Ⅰ/Ⅱ)	7/7	6/8	10/8	10/10	8/7
Age (yr)	41 (8)	38 (9)	37 (10)	41 (11)	39 (9)
Body weight (kg)	68.3 (9.8)	65.7 (8.4)	67.2 (7.9)	66.2(8.5)	67.3 (9.2)
BMI (kg m^{-2})	23.1 (2.2)	23.4 (2.3)	23.1 (2.7)	23.6 (1.9)	24.0 (2.3)
Intraoperative data					
Operation time (min)	62.3 (7.9)	59.6 (8.1)	60.7 (8.9)	56.5 (9.2)	58.9 (5.0)
Total sufentanil consumed dose (μg)	31.4 (5.6)	29.8 (3.9)	30.3 (4.5)	44.6 (5.8)*	61.4 (4.8)*#
Rocuronium consumed dose (mg)	35.0 (5.0)	37.5 (6.3)	36.7 (4.9)	38.3 (4.6)	38.6 (6.2)
Postoperative data					
Spontaneous breathing recovery time (min)	5.2 (2.1)	4.8 (2.5)	5.0 (1.9)	4.5 (2.8)	10.0 (3.9)#
Eye opening time (min)	7.8 (3.1)	8.0 (1.9)	7.5 (1.8)	8.2 (3.3)	16.4 (5.2)#
Extubation time (min)	10.2 (1.7)	11.7 (2.3)	10.5(1.7)	11.0 (3.0)	20.2 (3.8)#

Data are presented as mean (SD).

*$P < 0.05$ vs. the value of group S_0, S_1, S_2, respectively. #$P < 0.05$ vs. the value of S_0, S_1, S_2, S_3, respectively.

Table 2 The MAC_{BAR} of sevoflurane and its decreasing degree by different plasma target concentration of sufentanil in 5 groups.

Group	MAC_{BAR} (95% CI)	Target concentration of sufentanil (ng ml^{-1})	decreasing degree(%)
S_0	5.33 (5.19-5.47)	0.0	/
S_1	4.53 (4.45-4.61)*	0.1	15
S_2	2.86 (2.75-2.98)*#	0.3	46
S_3	2.23 (2.14-2.32)*#※	0.5	58
S_4	2.13 (2.05-2.21)*#※	0.7	60

The data of MAC_{BAR} were presented as means (95% CI).

*P <0.05 *vs.* value of group S_0. #P <0.05 *vs.* value of group S_1.※P <0.05 *vs.* value of group S_2.

Table 3 The comparison of MAP, HR, epinephrine and norepinephrine concentrations before and after pneumoperitoneum stimulus among 5 groups.

	Group S_0	Group S_1	Group S_2	Group S_3	Group S_4
MAP (mmHg)					
Before pneumoperitoneum	63 (5)	62 (4)	64 (4)	63 (5)	62 (5)
After pneumoperitoneum	78 (8)	75 (8)	79 (8)	78 (7)	76 (6)
Delta	15 (7)	13 (8)	15 (6)	16 (2)	14 (8)
HR (bpm)					
Before pneumoperitoneum	89 (11)	82 (15)	67 (6)*▯	61 (5)*▯	62 (6)*▯
After pneumoperitoneum	100 (13)	92 (15)	69 (7)*▯	64 (8)*▯	66 (6)*▯
Delta	11 (5)	10 (4)	2 (1)*▯	3 (1)*▯	3 (2)*▯
Epinephrine (ng ml^{-1})					
Before pneumoperitoneum	2.85 (0.23)	2.97 (0.19)	2.92 (0.19)	2.82 (0.28)	2.67 (0.18)
After pneumoperitoneum	2.92 (0.25)	3.04 (0.40)	2.91 (0.17)	2.85 (0.29)	2.62 (0.11)
Delta	0.07 (0.04)	0.07 (0.02)	0.03 (0.02)	0.03 (0.01)	-0.04(0.03)
Norepinephrine (ng ml^{-1})					
Before pneumoperitoneum	3.23 (0.21)	3.63 (0.23)	2.89 (0.19)	3.18 (0.95)	3.12 (0.74)
After pneumoperitoneum	3.11 (0.33)	3.55 (0.13)	2.81 (0.25)	3.15 (0.65)	3.07 (0.45)
Delta	-0.12(0.07)	-0.08(0.04)	-0.08(0.05)	-0.03(0.02)	-0.05(0.03)

The value of each parameter before pneumoperitoneum was the average value measured 3 and 1 min before CO_2 pneumoperitoneum. The value of each parameter after pneumoperitoneum was the average value measured 3 and 1 min after CO_2 pneumoperitoneum and the delta value of each parameter was the difference between the average value measured 1 and 3 min after CO_2 pneumoperitoneum and before CO_2 pneumoperitoneum value.

*$P<0.05$ *vs*. values of group S_0. ▯$P<0.05$ *vs*. values of group S_1.

Figures

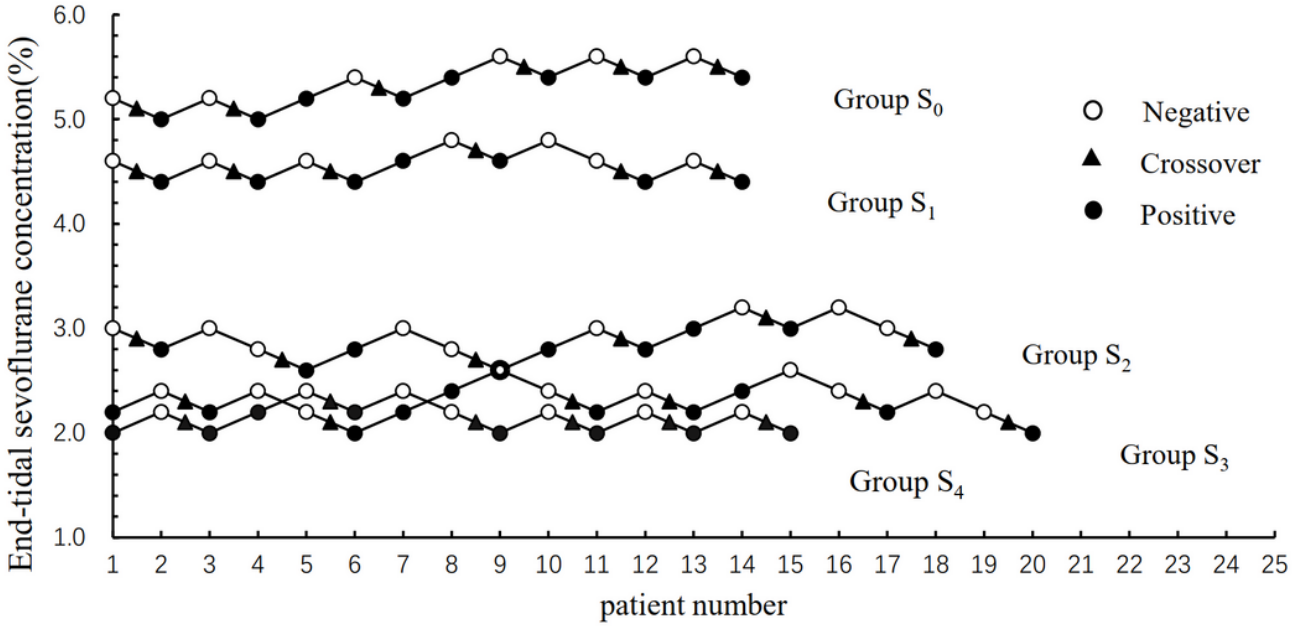

Figure 1

Dixon up-and-down plots for each group. The plasma target concentration of sulfentanil in groups S0, S1, S2, S3 and S4 was 0.0, 0.1, 0.3, 0.5 and 0.7ng ml-1, respectively. The empty (solid) circle represents the negative (positive) reaction to hemodynamics parameters, and the triangle indicates the intersection of negative and positive reactions. The ninth patient was given the same concentration of sevoflurane both in group S2 and group S3. To get six crossovers, 14, 14, 18, 20 and 15 patients were needed in grousps S0-S4, respectively.

Supplementary Files

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- CONSORTChecklist.pdf