

A Comparison between Total Intravenous Anaesthesia Using Propofol plus Remifentanyl and Propofol plus Sevoflurane in Children undergoing Fiberoptic Bronchoscopy: A Randomized, Single-Blind Study

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Research Article

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Abstract

Background

Fibreoptic bronchoscopy is an important used to evaluate and manage paediatric patients with respiratory disease. This study aimed to compare the effect of two different anaesthesia methods, propofol combined with remifentanyl and propofol combined with sevoflurane, on children undergoing fibreoptic bronchoscopy (FOB).

Method:

Sixty children were enrolled and randomly divided into two groups. In the remifentanyl group (Group R), the patients were induced with $4 \text{ mg}\cdot\text{kg}^{-1}$ propofol + $4 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$ remifentanyl (slow intravenous injection) and maintained with $0.3\text{--}0.5 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ remifentanyl. In the sevoflurane group (Group S), the patients were induced with $2 \text{ mg}\cdot\text{kg}^{-1}$ propofol and 8% sevoflurane and maintained with 4–6 vol% sevoflurane. Heart rate (HR), mean blood pressure (MBP) and pulse oxygen saturation (SpO_2) were monitored and recorded at four time points: baseline (T_0), when the bronchoscope reached glottis (T_1), the time of lavage (T_2), and the time of brush biopsy (T_3). Waking time and the satisfaction score of physicians were recorded, and emergence agitation (EA) was evaluated in the postanesthesia care unit (PACU). Finally, any supplementary medicine or adverse events were also recorded.

Results

Compared with group S, the waking time was significantly shorter and the incidence of EA was significantly lower in Group R. During bronchoscopy, significant differences in MAP or HR were not observed between the two groups at T_0 . Compared with group S, the HR of group R was significantly decreased at T_1 , T_2 and T_3 , and MAP was significantly decreased at T_1 , but the fluctuation range was within 20% of the baseline. A significant difference in SpO_2 was not observed between the two groups at any time point. No significant differences in the operation time of FOB, the incidence of complications, such as moving, hypoxemia, bronchospasm, and bucking, or the level of satisfaction were observed between the two groups.

Conclusions

Total intravenous anaesthesia using propofol plus remifentanyl in children undergoing fibreoptic bronchoscopy potentially reduces the waking time and decreases the incidence of EA to improve the work efficiency and turnover rate of the outpatient operating room.

Trial registration

Registered at the China Clinical Trial Registry (<http://www.chictr.org.cn>) (ChiCTR1900026098).

Background

Flexible bronchoscopy has become widely used by paediatric pulmonologists as an important diagnostic and therapeutic tool for respiratory diseases in children(1). Nevertheless, due to non-cooperation, fear and pain during the examination, most children need a certain depth of sedation or general anaesthesia(2).

Children, particularly infants, have a higher oxygen consumption rate than older children and adults, tissue and organ development is imperfect, sick children's oxygen reserve is also poorer than relatively healthy children, and partial or whole airway block by bronchoscopy and depression of respiratory drive by sedation, all of which pose considerable challenges to paediatric fibre bronchoscope anaesthesia(3-5). At the same time, fiberoptic bronchoscopy is a short process, and the use of long-acting sedative drugs will increase the length and cost of hospitalization(6). Therefore, we must choose short-acting anaesthesia drugs to quickly induce and emerge from anaesthesia.

Propofol is the most commonly used intravenous anaesthetic due to its rapid onset of action, stable induction, and low level of agitation after surgery(7-8). However, the anaesthesia method of only intravenously injecting propofol to retain spontaneous breathing is uncontrollable. Remifentanyl, an ultrashort-acting opioid with no accumulation of metabolites, is widely used in surgical anaesthesia and procedural sedation in children. Remifentanyl causes children to quickly wake up under the premise of providing adequate analgesia, but significant respiratory depression will occur. Propofol combined with remifentanyl anaesthesia has the advantages of a rapid onset of recovery, easy maintenance of anaesthesia during the operation, and low incidence of postoperative nausea and vomiting. Multiple studies(9) have shown that the anaesthesia regimen of propofol combined with remifentanyl is safe and effective for paediatric bronchoscopy. However, the current composite methods for propofol and remifentanyl have vast differences.

Our research aimed to determine the effects of total intravenous anaesthesia using propofol plus remifentanyl on waking time and emergence agitation (EA) compared with propofol plus volatile induction/maintenance anaesthesia using sevoflurane in children undergoing fiberoptic bronchoscopy.

Methods

Design and Setting

This study is a prospective, randomized, comparative, single-blind study comparing the effects of two different anaesthesia methods on the waking time and EA in children undergoing bronchoscopy. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University and registered at the China Clinical Trial Registry on September 21, 2019(<http://www.chictr.org.cn>) (ChiCTR1900026098). The study began to recruit patients on October 10, 2019. This study adhered to the applicable CONSORT guidelines.

Patient selection

According to the previous preliminary test, the average recovery time of the experimental group was 15.58 min, $\alpha = 0.05$, and $\beta = 0.1$, and the difference between the two groups reached 5.78; namely, the difference between the two groups was considered statistically significant. Using PASS software for the calculation, the sample size was 25 cases per group, considering a 20% dropout rate of the clinical sample. The final sample size was 60 patients, with 30 patients per group.

After obtaining written informed consent from the parents of each child, 60 children with ASA (American Society of Anaesthesiologists physical fitness classification) grade I or II aged 1-3 yrs who were scheduled for an FOB examination were included. The exclusion criteria were a BMI <14 or >28, haemoptysis, treatment and removal of foreign bodies through an FOB examination, neurological and endocrine system diseases, a family history of malignant hyperthermia, a long-term medication history, children with allergies to soybeans, and any situation that the researchers believe may affect the evaluation of the scale.

Patients were randomly allocated to different groups using a computer-generated digit-number program (SAS PLAN; SAS Institute Inc.) before starting the study and identified in numbered sealed envelopes. On the day of the operation, we randomly selected one envelope and opened it approximately 30 min before anaesthesia. The patient was administered a different anaesthesia regimen according to the randomized group. The researcher was aware of the group chosen throughout the study, while data recorders and processors were blinded to the group assignment during the study.

Medication

According to ASA guidelines, the children complied with principles of fasting and drinking. A peripheral venous catheter was inserted prior to the operation. Heart rate (HR), noninvasive blood pressure (NIBP), pulse oxygen saturation (SpO_2), end-expiratory carbon dioxide pressure ($PEtCO_2$) and anaesthetic gas concentration were monitored. After preoxygenation via a face mask, the children in the remifentanyl group (group R) were induced with $4 \text{ mg}\cdot\text{kg}^{-1}$ propofol and $4 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$ remifentanyl (slow intravenous injection). After the eyelash reflex disappeared, the laryngeal mask airway (LMA) was inserted. Anaesthesia was maintained with $0.3\text{-}0.5 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ remifentanyl. The pressure-controlled ventilation parameters were adjusted to maintain $P_{ET}CO_2$ between 35 and 45 mmHg. The children in the sevoflurane group (group S) were induced with $2 \text{ mg}\cdot\text{kg}^{-1}$ propofol and 8% sevoflurane. After the eyelash reflex disappeared, the LMA was inserted. Anaesthesia was maintained with 4-6 vol% sevoflurane and retained spontaneous respiration. The bronchoscope was introduced through a bronchoscopy adaptor connected to the LMA after general anaesthesia had been established. Topical lidocaine was sprayed to the glottis vera and trachea before FOB.

During the FOB examination, if $SpO_2 < 90\%$ lasted for more than 30 s in group S, assisted ventilation by a balloon was provided until SpO_2 returned to normal. If the BP was less than 70% of the baseline, phenylephrine was administered, and if it was more than 130% of the baseline, urapidil was administered. If the HR was less than 70% of the baseline, 0.01 mg/kg atropine was administered, and if it was more

than 130% of the baseline, esmolol was administered. In cases of continuous choking, laryngeal spasm or bronchospasm during FOB, the patients in group R were administered a single dose of $2 \text{ mg}\cdot\text{kg}^{-1}$ propofol to increase the depth of anaesthesia, and the patients in group S were administered an increased inhaled sevoflurane concentration with topical lidocaine sprayed onto the airway again. The procedure was stopped and complications were treated if serious adverse events, such as severe hypoxia, bradycardia, and arrhythmia, occurred. Additionally, $1 \text{ mg}\cdot\text{kg}^{-1}$ propofol was administered via IV for EA if the patient was determined to be pain-free and when the parent or caregiver was unable to comfort the child.

After the completion of FOB, all drugs were stopped, and the LMA was removed from children with spontaneous breathing. Then, the patients were moved to the postanesthesia care unit (PACU), and the children naturally regained consciousness. EA was assessed by the study staff upon arrival in the PACU using the Paediatric Anaesthesia Emergence Delirium (PAED) scale (0–20 scale), with a score of > 10 considered a diagnosis of EA(10). Finally, patients with an Alderete score ≥ 9 were sent back to the ward.

Data collection

A CRF (case report form) was designed for the registration of clinical data and study results. Data were stored in a password-protected computer to ensure patients' confidentiality. The study closely followed the guidelines of GCP (good clinical practice). One investigator was explicitly responsible for data collection, filing, and transmission, while another investigator was explicitly responsible for verifying the data accuracy and safety.

Primary outcomes: The waking time was recorded, and EA was assessed with the PAED in the PACU every five minutes.

Secondary outcomes: MAP, HR, and SpO_2 were monitored and recorded at four time points: baseline (T_0), when the bronchoscope reached the glottis (T_1), the time of lavage (T_2), and the end of the brush biopsy (T_3). Any complementary medicine and adverse events were also recorded. Finally, the satisfaction scores of physicians were recorded (0 points = satisfied; 1 point = basically satisfied; 2 points = dissatisfied).

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normality of the measurement data, and Levene's test was used to test the homogeneity of the variance of the measurement data. If the measurement data displayed a normal distribution, they were presented as the means \pm standard deviations (Mean \pm SD), and the parametric test was used for comparisons between groups; otherwise, results are presented as the medians (interquartile ranges) (Median (QR)) and nonparametric tests were used for comparisons between groups. If the measurement data displayed a normal distribution and homogeneity of variance, the two groups were compared using Student's t-test. If the measurement data displayed a normal distribution with unsatisfactory homogeneity of variance, the nonparametric test of two independent samples was suitable for the experiment. Repeated measurement data were analysed using repeated-

measures ANOVA and $P < 0.05$ was considered statistically significant. Count data are reported in absolute numbers (percentages), and comparisons between groups were performed using the χ^2 test or Fisher's exact probability method. Moreover, we use SPSS 24.0 for data analysis.

Results

Sixty paediatric patients were enrolled and randomly divided into two groups. The research flow chart is shown in **Figure 1**. No significant differences in demographic or FOB characteristics were observed between the two groups ($P > 0.05$) (**Table 1**).

The incidence of EA was significantly lower in group R. The waking time was significantly shorter in group R than in group S (**Table 2**).

Significant differences in the incidence of other adverse actions, including body movement, hypoxemia, bronchospasm, and bucking, and the satisfaction of the operating doctor were not observed between the two groups (**Table 3**).

During bronchoscopy, no significant differences in MAP or HR were observed between the two groups at T_0 . The HR of group R was significantly lower than the HR of group S at T_1 , T_2 and T_3 , and the MAP of group R was significantly lower at T_1 , but the fluctuation range was within 20% of the baseline. A significant difference in SpO_2 was not observed between the two groups at any time point (**Figure 2**).

Discussion

Our research showed that propofol-remifentanil resulted in a shorter waking time and a lower incidence of emergence agitation and haemodynamic features with less complications than propofol-sevoflurane for fiberoptic bronchoscopy in children.

In our study, the waking time of Group R was shorter than Group S, suggesting that propofol-remifentanil induces a rapid waking time. In a previous study, comparisons of waking times between propofol-remifentanil and propofol-sevoflurane were limited and inconclusive. Liao et al(11) showed a more quicker waking time after the administration of sevoflurane than propofol-remifentanil, which is inconsistent with the results of our study. The discrepancy may be due to the combined use of propofol and remifentanil for anaesthesia maintenance in the previous study.

Emergence agitation frequently occurs, particularly among children. In our study, the incidence of emergence agitation was higher in Group S, although the reason is uncertain. This observation can be explained by at least five possible explanations. Firstly, agitation acts as a role of anaesthesia in the central nervous system, and thus patients induced with sevoflurane or propofol anaesthesia might suffer from seizure-like movements and electroencephalographic epileptiform activity, but its incidence after induction anaesthesia with sevoflurane was significantly higher than induction anaesthesia with propofol. Presuming that epileptiform discharges affect postoperative brain function, propofol rather

than sevoflurane and higher levels of remifentanyl is recommended for anaesthesia induction in children(12). Second, stage of excitation of inhalation anaesthesia is more obvious with volatile induction and maintenance anaesthesia (VIMA) than with total intravenous anaesthesia (TIVA). A patient may be more prone to haemodynamic instability and sensitive to environmental stimulation during this period. Third, Dismantling anaesthesia quickly in an emergency may cause acute pain and anxiety(13). Fourth, as children were induced without the companion of their parents, they will be nervous and contradict inhalation with a mask. At the end, the occurrence of agitation will be decreased by preoperative sedation with a benzodiazepine(14), but the administration of these drugs was not performed during this research in accordance with 'conventional practice' in our hospital.

Differences in HR and MAP were observed between patients administered propofol-remifentanyl and propofol-sevoflurane. Propofol-sevoflurane was related to a higher HR than propofol-remifentanyl TIVA. It has been shown that propofol-sevoflurane provides a satisfactory depth of anaesthesia for procedures in paediatric patients(15), and we wanted to compare the effect of the two different anaesthesia methods. Therefore, additional analgesic was not administered to patients in Group S, whereas remifentanyl was administered to patients in Group R. The lack of opioids administered to Group S may lead to higher HR, which was a limitation of the research. In addition, MAP was greatly higher in Group S than that in Group R after anaesthetic induction, which may be because that the quick induction of anaesthesia with 8% sevoflurane and tidal volume breathing caused minor haemodynamic variations but had no inhibitory role in sympathetic activities(16), whereas propofol-remifentanyl exerted a greater inhibitory effect of the neuroendocrine reaction to stress than sevoflurane(17).

Kati et al.(18) reported, a significantly higher incidence of respiratory depression in patients treated with propofol during outpatient day surgery than in patients treated with sevoflurane, and the incidences of apnoea were 40.00% and 0.00%, respectively. In the present study, all children in group R experienced respiratory depression and needed to control breathing to maintain blood oxygen saturation during the examination. In group S, sevoflurane was used for induction and maintenance anaesthesia, supplemented with a small dose of propofol, and most children were able to maintain spontaneous breathing, with only 3 patients developing hypoxemia, which was corrected by manual control of the balloon.

Limitations

This study also has certain limitations. First, most of the children undergoing fiberoptic bronchoscopy in our hospital were considered to have bronchitis or pneumonia, and the procedure was performed to establish a precise diagnosis and identify the pathogens. In this study, children who underwent fiberoptic bronchoscopy, alveolar lavage and brush biopsy were selected. The average microscopic examination time of the 60 patients was 9.78 ± 1.91 min. The anaesthesia method in group R may not be suitable for operations with long microscopic examination times, such as bronchial foreign body removal, lesion removal and other operations. Second, fiberoptic bronchoscopy is mostly performed in the outpatient operating room. Due to the short operation time, we did not monitor the sedation level of the two groups

of children during FOB. Therefore, we were unable to guarantee the same level of sedation in the two groups of patients before they were sent to the PACU. Third, this study was limited to children aged 1 to 3 years. We have not studied whether these two different anaesthesia methods have the same outcomes in children under 1 year old and aged 4 to 12 years old.

Conclusions

In summary, total intravenous anaesthesia using propofol plus remifentanyl in children undergoing fibreoptic bronchoscopy reduced the waking time and the incidence of EA to improve the work efficiency and turnover rate of the outpatient operating room.

Abbreviations

FOB Fibreoptic bronchoscopy

HR Heart rate

MBP Mean blood pressure

SpO₂ Pulse oxygen saturation

IV Intravenous injection

EA Emergence agitation

ASA American Society of Anaesthesiologists physical fitness classification

BMI Body Mass Index

CRF Case report form

GCP Good clinical practice

NIBP Noninvasive blood pressure

PEtCO₂ End-expiratory carbon dioxide pressure

ANOVA Analysis of Variance

VIMA Volatile induction and maintenance anaesthesia

TIVA Total intravenous anaesthesia

LMA Laryngeal mask airway

PACU Postanaesthesia care unit

Declarations

Ethics approval and consent to participate

Ethical approval for the clinical trial, was obtained from the Ethics Committee of the 2nd Affiliated Hospital of Wenzhou Medical University LCKY2019-286 , and written informed consent was obtained from parent of each child.

Competing interests: The authors declare that they have no competing interests.

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Availability of data and materials The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication None.

Authors' contributions

RFZ designed the study. FC, ZLW, BWH, JCL, and MMC performed the trial, FC analyzed the data and wrote the manuscript. RFZ revised the manuscript. All authors have read and approved the final manuscript.

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Tables

Table 1. Demographic and bronchoscopy characteristics of patients

Variable	Group R	Group S	<i>P</i>
	(n=30)	(n=30)	
Sex(Male/Female)	17/13	14/16	0.6054
Age(y)	2(1,3)	2(1,3)	0.8877
Weight(kg)	0.86±0.14	0.87±0.13	0.6094
Height(m)	13.42±2.58	12.88±2.88	0.4532
Bronchoscopy time(min)	9.67±1.86	9.90±1.99	0.6865

There were no statistically significant differences ($P > 0.05$) between the two groups.

Table 2. Comparison of the incidence of EA ,the time of awaking

Variable	Group R	Group S	<i>P</i>
	(n=30)	(n=30)	
awaking time (min)	16.33±6.42*	23.03±6.46	0.0002
Emergence agitation	5(16.67)*	12(40)	0.0451

Compared with group S * $P < 0.05$.

Table 3. Comparison of the incidence of adverse actions and satisfactions

Variable	Group R	Group S	<i>P</i>
	(n=30)	(n=30)	
Hypoxemia	1(3.33)	3(10)	0.3013
Movement	4(13.33)	2(6.66)	0.3893
Bronchospasm	1(3.33)	2(6.66)	0.5543
Bucking	1(3.33)	1(3.33)	
Surgeon satisfaction	27(90)	28(93.33)	0.1924

There were no statistically significant differences ($P > 0.05$) between the two groups.

Figures

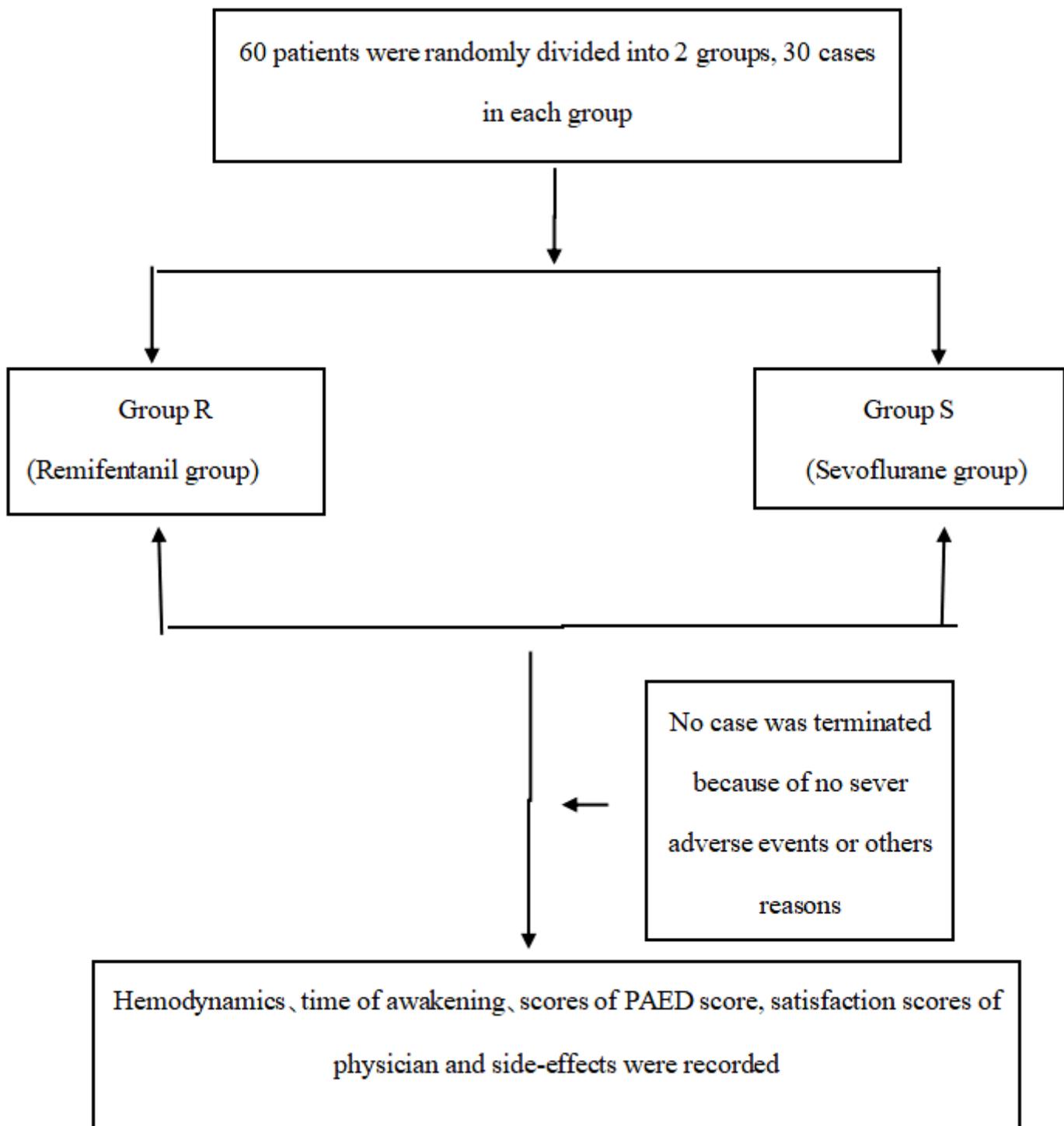
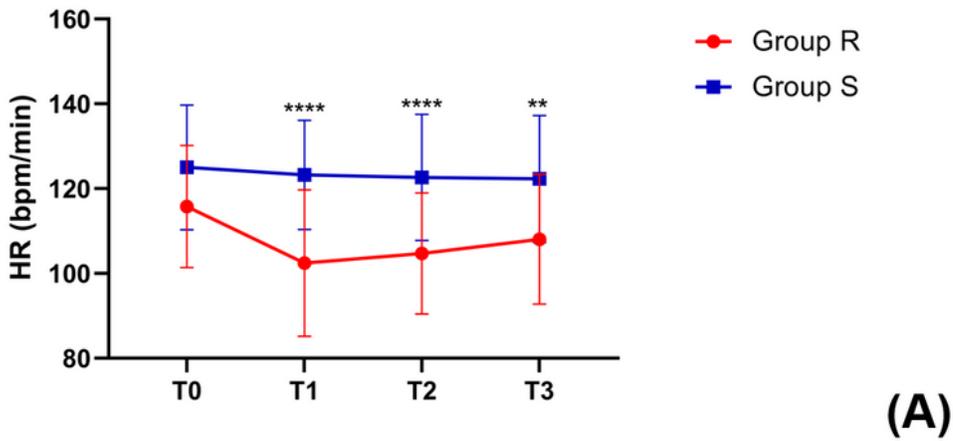
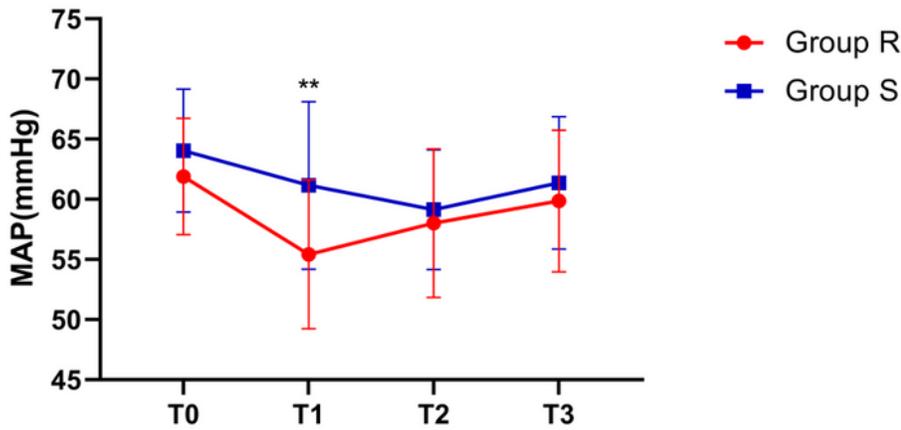


Figure 1

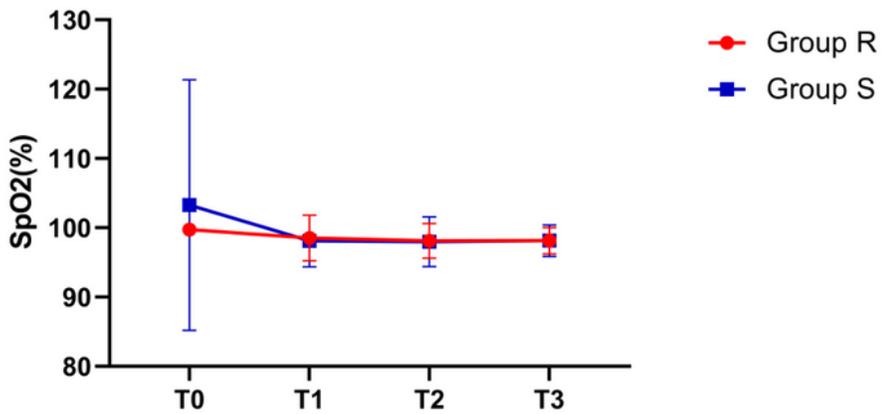
Flowchart of the study.



(A)



(B)



(C)

Figure 2

Changes of HR, MAP and SpO2 in two groups, *P 0.05, **P 0.01, ***P 0.001, ****P 0.0001.

Supplementary Files

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- [CONSORT2010Checklist1.2.doc](#)