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Effects of salbutamol on the kinetics of sevoflurane and the occurrence of early PPC in patients with mild to moderate COPD: a randomized controlled study

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ABSTRACT

Previous studies have demonstrated that bronchodilators can attenuate bronchoconstriction and improve lung volumes, further improve gas movement and distribution in COPD patients. Whether the improvement of gas movement and distribution can affect the kinetic of sevoflurane remains unknown.
The study was todetermine whether inhaled salbutamol aerosol affects the wash-in and wash-out kinetics of sevoflurane, or the occurrence of early postoperative pulmonary complications in COPD patients undergoing elective surgery.

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Purposes

1 We speculated that salbutamol aerosol used preoperatively ameliorates the bronchoconstriction, improves lung volume and gas distribution, eventually affects the alveolar-capillary interface.
To investigate the effects of salbutamol used preoperatively on the kinetics of volatile sevoflurane(wash-in) and the wash out curves after closing vaporizer, and the recovery profile when stay in the PACU, and whether this would reduce the occurrence of early postoperative pulmonary complications (the first 7days) in patients with mild to moderate chronic obstructive pulmonary disease.

Backgroud

2 Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airflow limitation, which is not completely reversible and develops progressively. A survey of 102230 adults in rural areas of northern and central China showed that COPD accounted for about 3% the population aged 15 and over, and the prevalence rate COPD people aged 40 and over was 8.2 %.COPD results mainly in excessive pulmonary inflation, limited airflow and abnormal gas exchange. Lung function examination showed total lung volume (TLC), functional residual volume (FRC), increased residual volume (RV) and vital capacity (VC), forced vital capacity (FVC), forced expiratory volume (FEV) in the first second. Because of the above pathophysiological changes in the respiratory system in COPD patients, COPD patients undergo a slow increase in intra-alveolar anesthetic concentrations during inhalation anesthesia, decreased uptake through alveolar capillary membrane transmembrane, causing a low concentration of "effector sites "(e.g. brain) drugs. The anesthetic depth is not easy to deepen or to reach the predetermined level within a certain period of time. Moreover, during the anaesthesia recovery phase, the concentration gradient between capillaries and alveoli decreases due to airflow obstruction. The patient had a delayed recovery, poor recovery quality (e.g., irritability after waking) or delayed respiratory depression, even life-threatening events occur. Salbutamol selectively stimulates the β2 of bronchial smooth muscle receptor, mainly used to prevent and treat bronchial asthma or asthmatic bronchitis. Salbutamol in the treatment of COPD patients, can improve lung function, improve exercise tolerance, improve the quality of life has been verified. Recent studies suggest β2 receptor agonists increase FEV1To FVC, reduce RV FRC and improve airflow patterns in COPD patients. This study was to explore whether salbutamol pretreatment can change COPD respiratory mechanics and lung volume, and affect the wash-in, uptake and elimination of sevoflurane. Whether it is beneficial to improve postoperative pulmonary function.

Research protocols

3 **Research protocol**

3.1 Research Methodlogy

3.2.1 Research site

Shaoxing People's Hospital

3.2.2 Research participants

3.2 Types of research

Prospective, randomized, controlled, clinical studies

Primary outcome

Ratio of inhaled sevoflurane concentration (In_{sevo}) to end-expiratory sevoflurane concentration (Et_{sevo}) namely the F_A/F_I fraction.

Secondary endpoints

(1) The time of opening eyes, extubation and oral birthday of patients in anesthesia recovery room.
(2) Number and incidence of pulmonary complications within 7 days after operation.

3.3 Research participants

80 patients with mild to moderate COPD with recruited in the study.

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3.4 Inclusion criteria

ASA I~ II grade ;65~75 years old;
long-term smoking history or previous confirmed chronic bronchitis, emphysema ;
Pulmonary function test was performed before surgery and the severity of classification was obtained (mild to moderate COPD);
Body mass index18~30 kg/m^2;
No upper respiratory infection within 2 weeks before surgery;
Stable COPD patients

3.5 Exclusion criteria

Allergic to β_2 receptor agonists, alcohol and freon;
pulmonary arterial hypertension (PAP ≥50 mmHg at rest);
cardiac insufficiency or heart failure;
patients refused to cooperate;
renal insufficiency (BUN≥10 mmol/L,Cr≥1.5mg/dl).

3.6 Elimination criteira

patient withdrawal;
incomplete data;
loss of follow-up ;
adverse events

4 Main research methods

Salbutamol (40 vial) and its similar in appearance placebo (40 vial, normal saline) were used in this study. The computer-generated random sequence numbers were stored in an opaque envelope. The investigators who were responsible for assessing the primary endpoints, as well as the anesthesiologists, postoperative care unit nursing staff, and variable assessors, were blinded to study group assignment.
Before operation, signed informed consent was obtained, no preoperative medication was administered , no food for 10 h and 4 h for drinking before operation.

Pre-anesthesia preparation:

Routine monitoring was initiated, the peripheral vein was cannulated, and sodium lactate Ringer's solution 500 mL for volume expansion;
Radial artery catheterization was performed to monitor invasive blood pressure;
Give salbutamol reagent oral spray 200 μg (2 spray) and record reagent number;
No drugs (antibiotics, hormones, etc.) were given before induction, and no test dose was injected if epidural catheter was retained.

BIS monitoring:

Clean the skin repeatedly with alcohol cotton balls and use BIS after drying^{XP}Dedicated four-conductor electrode (BIS-sensor) chip^{XP}), Electrode 1 is facing the eyebrow (about 5 cm from the nose root), Electrode 2 is located between 1 and 4 above the brow, The lower edge of electrode 4 is aligned with the right eyebrow arch, Electrode 3 is aligned with the center of the eye.

Anesthesia induction:

Salbutamol aerosol spray or placebo was administered through inhalation 30 min before anesthesia induction. Oxygen flow rate was set to 8 L/min before oxygenation. Fentanyl 3.0 μg/kgwas injected intravenously slowly, Propofol 1.5~2.0 mg/kg rocurium 0.9 mg/kg≥Tracheal tube was fixed after successful tracheal intubation (female ID 7.0, male ID 8.0), then mechanical control ventilation was initiated, adjusting tidal volume 8~10 ml/kgrespiratory rate 10 bpm, I/E ratio 1:2, to keep $EtCO_2$ within30 to 45 mmHg .When the hemodynamics is stable for 4~5 min, the sevoflurane volatile vaporizer was opened (2% sevoflurane was used to prime the respiration circuit to ensure the uniform filling of the circuit), the inhalation concentration was 2% and the oxygen flow rate was 2 $L{\cdot}min^{-1}$. The concentration of sevoflurane was collected at one end of the Y interface of the endotracheal tube through sidestremline method. During the wash - out period, the oxygen flow rate was 4 L/min .

Anaesthesia maintenance:

No exogenous stimulation (including changing the position) and no anesthetic drugs were added during observation. Ephedrine 5~10 were injected intravenously (MAP ≥50 mmHg) during observation. Atropine 0.25~0.5 mg was givenwhen the heart rate (≥45 times/min) .Salbutamol 200 or placebo was given through the respiratory circuit 30 min before the completion of surgery, The vaporizer was closed 30 minutes before the last skin suture was placed, with

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fresh gas flow set at 4L/min. Following this, end-tidal samples were collected from first breaths at 1, 2, 3, 4, 5, 7, 10 and 15 min after discontinuation of its administration.

Observation variables:

End-tidal samples were collected from first breaths at 1, 2, 3, 4, 5, 7, 10 and 15 min, and then the surgery began. The hemodynamic parameters and airway pressure data in the corresponding time points.

End-tidal samples were collected from first breaths at 1, 2, 3, 4, 5, 7, 10 and 15 min after discontinuation of its administration. The hemodynamic parameters and airway pressure data in the corresponding time points.

Arterial blood samples were extracted from the patients before induction (0 min), then at 30 min and 60 min after initiation of the operation.

Observe the occurrence of pulmonary complications in all patients within 7 days after operation.

Statistical analysis:

After all the tests, according to the random number, the subjects were divided into salbutamol group and control group for statistical analysis. Stata7.0 software package for statistical analysis, The mean ± standard deviation (mean±SD) are used for all measurements, A complete randomized t test was used to test the differences between groups, Analysis of variance (ANOVA,) within groups S-N-K methods), Comparison of counting data using chi-square test or Fisher exact probability calculation. P 0.05, the difference was statistically significant.

5 The flow chart

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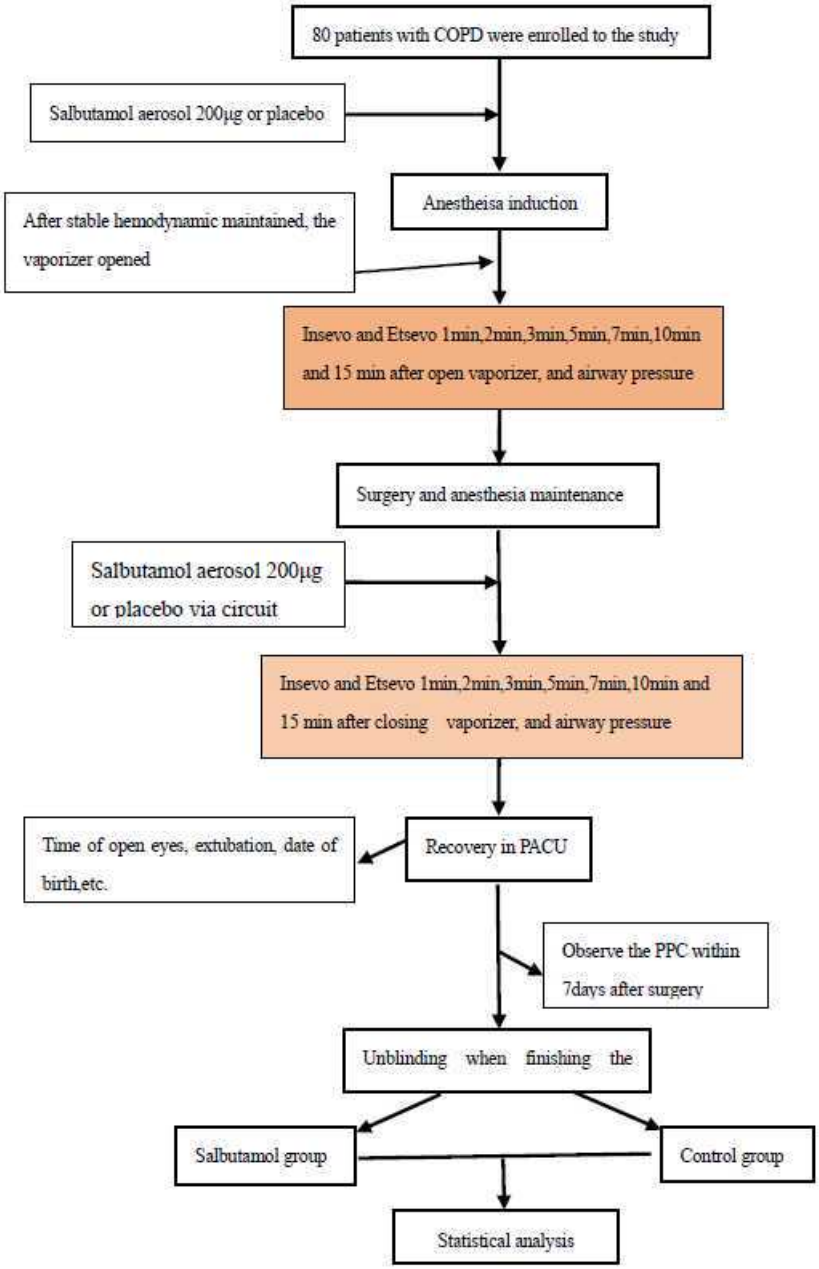

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6 Appendix

The diagnosis criteria of COPD patients: COPD diagnosis is mainly based on the comprehensive analysis of high risk history, clinical symptoms, signs and lung function of smoking. Long history of cough and expectoration; barrel chest, chest percussion, prolonged expiratory time; chest radiographs showing signs of emphysema; incomplete reversible airflow limitation as a necessary condition for COPD diagnosis ;70% FVC < and FEV after inhalation of bronchiectasis|<80% of the predicted value, it can be determined as incomplete reversible airflow limitation.

Bronchiectasis test positive: $\triangle FEV_1/FEV_1 \geq 12$ % and $\triangle FEV_1 \geq 200$ml.

Criteria for determining PPC: Components include pulmonary inflammation, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, aspiration pneumonia.

Definitions of postoperative pulmonary complications

Respiratory infection

Treatment with antibiotics for a respiratory infection,plus at least one of the following criteria□new or changed sputum,new or

changed lung opacities,fever,and leukocyte count >12,000/ mm 3 per cent

Respiratory failure

Postoperative PaO 2<60 mmHg on room air,a ratio of PaO 2to inspired oxygen fraction Postoperative PaO 2<300, or SaO 2Postoperative PaO 2<90 per cent

therapy

Pleural effusion

Chest radiograph demonstrating blunting of the costophrenic angle,evidence of displacement of adjacent anatomical structures,or

(in supine position) a hazy opacity in one hemithorax with preserved variable shadows

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Atelectasis
Collapse of the alveoli,lung opacification with shift of the mediastinum,hilum,or hemidiaphragm toward the affected area,and
compensatory overinflation in the adjacent nonatelectatic lung
Pneumothorax
(A collection of air in the pleural space)
Bronchospasm
Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis
Acute lung injury after the inhalation of regurgitated gastric contents
PaO2：partial pressure of oxygen in arterial blood;SaO 2：arterial oxyhemoglobin saturation.

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