Study Protocol and Statistical Analysis Plan

Nitrous Oxide for Identifying the Intersegmental Plane in Segmentectomy: A Randomized Controlled Trial

Registration number: NCT04302350

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Study Protocol

This study was registered at www.ClinicalTrials.gov (registration number: NCT04302350). The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu province, China) and written consent was obtained from all participants. The study was conducted at The First Affiliated Hospital of Nanjing Medical University, Nanjing, China between January 15, 2020 and May 15, 2020.

We contacted patients aged 20-70 y, with an American Society of Anesthesiologists (ASA) physical grade I or II, a body mass index (BMI) between 18 and 30 kg/m^2, with early stage lung cancer (diameter of tumor consolidation ≤ 2cm, none evidence of lymph node or distant metastasis, c-stage IA1 or IA2) (active limited resection) and patients at high risk due to poor general condition who cannot undergo lobectomy (c-stage IA1 to IA3) (passive limited resection). Exclusion criteria included a history of severe asthma or pneumothorax, pulmonary bullae on chest CT and patient refusal. High-resolution lung nodule CTA (Iopromide) and three-dimensional computed tomography bronchography and angiography (3D-CTBA) were applied to confirm nodules location and associated vessels and bronchi, and the simulated surgical path and resection range were confirmed before surgery.

Eligible subjects were randomly assigned to Group75, Group50 or Group0 at a 1:1:1 ratio. The order of allocation was generated by computer personnel that were not involved in trial through a computer program. Concealment was carried out using opaque envelopes, which were opened after the patients' arrival in operating room. Patients, surgeons, anesthesiologists, assessors, and statisticians were blinded to treatment allocation.

After admission, patients were routinely monitored for electrocardiogram, pulse oximetry, and invasive arterial blood pressure. When anesthesia induction was completed, intubation was carried out using an appropriate-size double-lumen endobronchial tube (DLT) under visual laryngoscope and the position of

the DLT was confirmed with fiberoptic bronchoscopy and adjusted as needed. OLV of the dependent lung with FiO_2=1.0 was begun in the lateral position, by inflation of the bronchial cuff of the DLT, clamping the DLT to the nonventilated lung proximally and opening the distal port of the DLT lumen to the atmosphere. Tidal volumes were 5 mL/kg ideal bodyweight (male: height -100, and female: height - 105) without positive end expiratory pressure (PEEP). In order to avoid possible confounding effects of inhalation of volatile anesthetics on oxygenation, all subjects received total intravenous anesthesia.

According to preoperative 3D-CTBA evaluation of bronchial and vascular structure of pulmonary nodules and pulmonary segments, the target segmental bronchus, arteries and intra-segment veins were accurately identified and dissected by ligation or stapler cutting. After that, the anesthesiologist began to make preparations for the lung inflation. The portable nitrous oxide concentration detector (TD600-SH-B-N_2O, tiandi shouhe, Beijing, China) was installed to detect N_2O concentration (vol%), and then adjusted the anesthesia machine to the manual control mode. The flow of the selected gas mixture was set to 8L/min (Group75 set to N_2O:O_2=6:2, Group50 set to N_2O:O_2=4:4, Group0 set to O_2=8), avoiding the interference of the total gas flow. When the N_2O concentration detector reached the predetermined gas concentration, and then the collapsed lung was re-expanded completely with controlled airway pressure under 20 cmH2O (1cm H2O=0.098 kPa) by the anesthesiologist. This procedure took approximately 1 min, and then FiO_2=1.0 was performed after the initiation of the OLV.

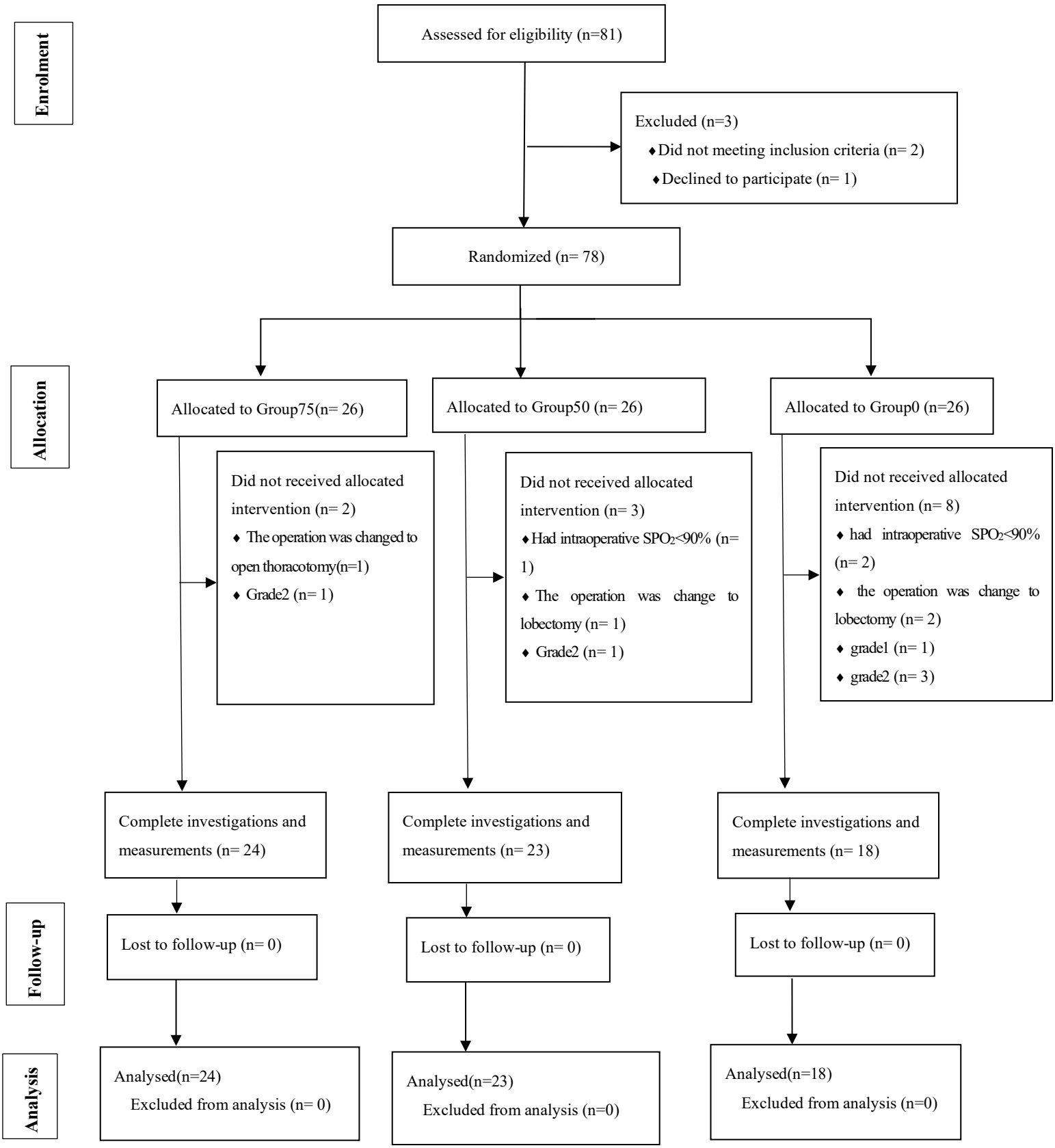

Fig. 1 Consort flow diagram

Statistical Analysis Plan

A power analysis indicated a sample size of 48 patients were needed based on the following assumptions: (i) $\alpha = 0.05$ (two-sided significance level); (ii) $1-\beta = 0.9$; (iii) the appearance time of visible ISP is 5-12 min in view of previous study [7]. Taking into consideration loss to follow-up and possible dropouts, 81 patients were ultimately enrolled.

The data collected were entered into a Microsoft Access database and then analyzed with SPSS software (version 24; IBM SPSS, Chicago, IL, USA). Primary outcome analysis was performed by one-way analysis of variance, and LSD-t test for pairwise comparison. Secondary outcome analyses included one-way analysis of variance for parametric variables (SPO_2, PaO_2 value, duration of surgery, total thoracic drainage, duration of drainage, postoperative hospital stay, lung function) and χ-square tests for nonparametric variables (incidence of postoperative complications, ASA grades). P value <0.05 (both sides) was considered statistically significant. Univariate and multivariate linear regression analysis were used to determine the predictors for the intersegmental plane. The β value and 95% confidence interval (95% CI) of each of the significant variables were calculated.