Can Opioid-Sparing based Anesthesia improve patient' quality of postoperative recovery in video-assisted thoracoscopic lung surgery? "Optimal" study: a randomized trial

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Brief background

Enhanced Recovery After Thoracic Surgery (ERATS) is a still developing area of research. Video-assisted thoracoscopic surgery (VATS), which is a minimally invasive technique, lays the basis of faster recovery for patients after lung surgery. To improve patient's postoperative recovery attracts great attention among thoracic surgeons and anesthesiologists.

Perioperative anesthesia and analgesia management plays a crucial role in ERATS and needs to be optimized accordingly. Uncontrolled acute pain may delay patients to leave from bed and take oral diet early after thoracic surgery. Additionally, opioid-associated side effects, including nausea and vomiting, dizziness, constipation, may impact on a patient's rapid recovery targets such as PONV control, early mobilization and quick returns to oral diet.

Nowadays, opioid-sparing analgesia has gained a wide range of popularity in thoracic surgery. Paravertebral blockade, along with tailored doses of short-acting opioids, might limit opioids use, reduce opioids related adverse effects and enhance safety without compromising analgesia. Even though the benefits have been described, there is a paucity of randomized trials about the benefit of opioid-sparing anesthesia in lung surgeries under VATS.

Scientific question

Can intraoperative opioid-sparing anesthesia improve patient-reported outcome of recovery in adults having lung surgeries under VATS?

Specific Aims

Objective: We tested the primary hypothesis that opioid-sparing anaesthesia provide better quality of patient' recovery compared to routine anaesthesia in VATS. Specifically, we incorporated a series of patient-centered outcome questionnaires including QOR15,OBAS, NRS to evaluate the effects of opioid-sparing anaesthesia on patient' postoperative early recovery.

Setting: A tertiary institution, Shanghai Chest Hospital.

Study execute period: From 2021.4.06 to 2021.12.31

Patient's inclusion and Exclusion criteria

Eligible patients were between 18 years and 70 years, scheduled for elective video-assisted thoracoscopic lung surgery, had an American Society of Anaesthesiologists physical status of I-III.

Patients were excluded if they had clinically important cardiovascular disease, were illiterate to conduct questionnaires, or converted to open thoracotomy. Patients were also excluded when they had contraindications to receive nerve blocks, or received the second surgery because of postoperative haemorrhage or infection immediately in postoperative period.

Randomization and masking

Patients were randomly allocated 1:1 without stratification into opioid-sparing anesthesia group and routine anesthesia group, using a consecutive list of computer-generated random numbers kept in sealed envelopes. An independent investigator was in charge of randomization. The envelopes were opened by the investigator not involved in clinical care shortly before anaesthetic induction.

Blocks were performed after induction of general anesthesia in the operating , so the anesthesiologists in the operating room were not masked to treatment. Patients, outcome assessors and clinicians in surgical ward were masked to treatment allocation.

Anesthesia Protocol

None of the patients received premedication. Patients were monitored with electrocardiography (ECG), invasive blood pressure, pulse oximetry, oesophageal temperature, Bispectral index (BIS) and Surgical Pleth Index (SPI, S/5 Collect

software, GE healthcare, Helsinki, Finland). Invasive blood pressure monitoring was achieved by radial artery cannulation and right internal jugular venous catheterization. Prophylactic antibiotics will be given per surgical routine.

In both groups, patients were given dexamethasone 5 mg before anesthesia and dolasetron 12.5 mg before the end of surgery as prophylactic treatment for PONV. Dexmedetomidine 1μg/kg was infused at least 10 minutes before anesthesia induction. After anesthesia induction, a double-lumen bronchial tube (DLT) was inserted and positioned using flexible bronchoscopy. Mechanical ventilation was initiated with a 100% oxygen and adjusted to maintain end-tidal CO2 pressure of 35-40 mmHg. Ventilator settings were maintained with tidal volume of 6 mL/kg of ideal body weight with or without PEEP. Propofol administration was adjusted to target BIS between 40 and 50. Remifentanil was infused at 0.5-3 ng/ml, adjusted to keep SPI between 20-50. After surgery, patients were transferred to the post-anesthesia care unit to extubate.

In routine anesthesia group, general anesthesia was achieved by routine opioid-based anesthesia. In the routine anesthesia group, patients were not given any blocks, neither paravertebral block or intercostal block, or serratus anterior blocks. General anesthesia was induced with **0.6-0.8 μg/kg sufentanil** and a target-controlled infusion of propofol set to a plasma concentration of 3-4 μg/ml. Cisatracurium 0.2 mg/kg was given to facilitate double-lumen bronchial tube intubation and 0.12-0.15 mg/kg/hour infused as clinical necessary. **Propofol and remifentanil target-controlled infusion was tailored to BIS and SPI**. **Before the end of surgery, sufentanil 5-10μg** and flurbiprofen axetil 50 mg was added intravenously to prevent pain.

In opioid-sparing anesthesia group, the anesthesia strategy is consisting with **paravertebral block with no long acting opioids.** Herein, we incorporated thoracic

paravertebral block with remifentanil throughout the intraoperative period. General anesthesia was induced with target-controlled infusion of propofol set to a plasma concentration of 3-4 μg/ml and remifentanil set to a plasma concentration of 3-4 ng/ml. Cisatracurium 0.2 mg/kg was given to facilitate double-lumen bronchial tube intubation and 0.12-0.15 mg/kg/hour infused as clinical necessary. After anesthesia induction, patients were positioned in the lateral decubitus position to receive **paravertebral blocks**. A 1.6-6.0 MHz curved array transducer was used to identify the paravertebral space at the T4 and T6 vertebral levels. Using in-plane approach, a 10-cm, 21-gauge needle (Pajunk, NanoLine, Germany) was inserted into the paravertebral spaces, and the total amount of 0.5% ropivacaine 0.6 ml/kg conjunct with 5 mg dexamethasone were injected at T4 and T6 vertebral levels. **Sufentanil was not given throughout the intraoperative period**. Propofol and remifentanil target-controlled infusion was tailored to BIS and SPI. Oesophageal temperature was maintained actively 36.0℃using forced-air warmers.

A patient-controlled intravenous analgesics pump (PCA) was started immediately after surgery in each patient: sufentanil 1-1.5 μg/kg, was diluted into 100 ml saline. The intravenous analgesics pump was infused at a 2 ml/hour rate, with a loading dose of 0.5 ml per request and lock time of 15 minutes. After completion of the surgery, patients were transferred to PACU to extubate. Muscle relaxants were routinely reversed with atropine/neostigmine. When patients had an Aldrete score > 9 and felt warm-alert-comfortable, then were allowed to discharge to the ward.

In the surgical ward, postoperative pain treatment was managed pragmatically by ward clinicians unaware of group assignment, including routine parecoxib intravenously given twice daily. The PCA was stopped after the second postoperative day or when patients discharged. Patients were discharged home when they: were able to mobilize; achieve adequate pain control with oral medication; able to eat and drink; had vital signs within normal limits and without severe pulmonary complications or air leak.

Outcomes

Primary outcome

The primary outcome was the global score QoR-15 at 6 hours after surgery. The QoR-15, a 15-item post-operative QoR scale (range 0–150, and in which 150 is the best possible outcome) derived from the QoR-40, was used to assess patient's postoperative recovery.

Furthermore, we used the Chinese translated version to help patients comprehend well. Similar to the original English version, the QoR-15 Chinese reveals satisfactory psychometric properties. The difference in QoR-15 that patients consider important has been estimated as 8 and QoR-15, and the patient acceptable symptom state for the QoR-15 is 118 according recent publication.

Secondary outcome

The Secondary outcome was QoR-15 at 24 hours and 48 hours postoperatively, Overall Benefit of Analgesia Score Satisfaction with pain treatment (OBAS) and acute pain at 6 hours, 24 hours and 48 hours after surgery. Total OBAS scores are calculated with 7-item OBAS scales, by summing responses from Q1 through Q6 and adding (4 – score from Q7); Lower total OBAS scores mean more benefit. The total OBAS score and analgesia-related side effects from Q2-Q6 were recorded. A 11-point Verbal Rating Scale (VRS) ranging from zero (no pain) to 10 (pain as bad as you can imagine) was used to assess acute pain. VRS at worst was obtained at postoperative 6 hours, during the first 24 hours and the second 24 hours. The secondary outcomes also included time to mobilize, time to first full diet and first bowel.

Tertiary outcomes

Tertiary outcomes were intraoperative consumption of sufentanil, remifentanil, propofol and cisatracurium recorded. Intraoperative hypertension, hypotension, severe bradycardia and supraventricular arrhythmia were collected and recorded. Emergence

time and DLTs extubation time after surgery were also recorded. Variables about PCA were also included.

Quality of life on postoperative 30-days was obtained by phone calls with Short Form-12 Health Survey (SF-12). Results were expressed in two meta-scores: a physical component summary and a mental component summary

Statistical analysis plan

The primary outcome is the global score of the QoR-15 measured at 6 hours after surgery. For normally distributed continuous outcomes, we use the student t-test to compare outcomes between the fast-track anesthesia and the routine group. If outcomes were discrete continuous, Mann-Whitney U test was used and outcomes was reported as the Hodges–Lehmann estimate.

The secondary outcome is the global score of QoR-15 at 24 hours and 48 hours after surgery, OBAS and acute pain at 6 hours, 24 hours and 48 hours after surgery. For discrete continuous outcome, Mann-Whitney U is used and outcomes is reported as the Hodges–Lehmann estimate.

The sample size of this study is based on a mean difference of QoR-15 between groups. We calculated sample size according to a previous article in patients undergoing robot-assisted radical prostatectomy. We assume an estimated decrease of 35% in QoR-15 at 6h after surgery in the routine anesthesia group and 25% in fast-track anesthesia group, with a standard deviation of 16%. A total of 134 patients were needed for a two-sided power of 0.95 and a P value of 0.05. To allow for some individuals not completing the trial, we planned to enrol 80 patients in each treatment group, with 160 patients in total.

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