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STUDY PROTOCOL

TEDOFA Trial Study Protocol: A Prospective Double-Blind, Randomized, Controlled Clinical Trial Comparing Opioid-Free versus Opioid Anesthesia on the Quality of Postoperative Recovery and Chronic Pain in Patients Receiving Thoracoscopic Surgery

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Introduction: Seeking effective multimodal analgesia and anesthetic regimen is the basis for the success of ERAS. Opioid-free anesthesia (OFA) is a multimodal anesthesia associating hypnotics, N-methyl-D-aspartate (NMDA) antagonists, local anesthetics, anti-inflammatory drugs and α-2 agonists. Although previous studies have confirmed that OFA is safe and feasible for VATS surgery, there is great heterogeneity in how to select and combine anti-harm drugs to replace opioids. We hypothesized that the reduced opioid use during and after surgery allowed by OFA compared with standard of care will be associated with a reduction of postoperative opioid-related adverse events and an improvement in the quality of rehabilitation of patients after partial VATS lung resection.

Methods/Analysis: The TEDOFA Study is a prospective double-blind, randomized, controlled clinical trial with a concealed allocation of patients scheduled to undergo elective partial VATS pneumonectomy 1:1 to receive either a standard anesthesia protocol or an OFA. A total of 146 patients were recruited in the study. Primary endpoint was the 15-item recovery quality scale (QoR-15) at 24 hours after surgery.

Ethics and Dissemination: This trial has been approved by the Institutional Review Board of Beijing Friendship Hospital of China Capital University. The TEDOFA trial study protocol was approved on 27 February 2023. The trial started recruiting patients after registered on the Chinese Clinical Trial Registry.

Trial Registration Number: ChiCTR2300069210; Pre-results.

Keywords: opioid-free anesthesia, thoracoscopic surgery, postoperative recovery, chronic pain

Introduction

Lung cancer is the leading cause of cancer-related mortality for both men and women all over the world.[1] Annually, approximately 631000 deaths were reported because of lung cancer according to Chinese national statistics.[2] In contrast to the decline in lung cancer incidence in Western countries, it is still rising in China, which is a major public health problem and places a huge burden on society. Despite tremendous advances in targeted therapies, immunotherapy, and radiotherapy, complete surgical resection still remains the gold standard for curative treatment of early-stage non-small-cell lung cancer in patients who are physiologically fit. Traditionally, resection is done via a thoracotomy, but during the past two decades, video-assisted thoracoscopic surgery (VATS) has emerged as a minimally invasive alternative for advanced resections, including lobectomy. According to many authors, VATS lobectomy decreases postoperative pain, induces less impairment in pulmonary function, and has a shorter chest tube duration and, consequently, a shorter hospital stay.[3,4] Results from many non-randomized studies have suggested that VATS is less traumatic than thoracotomy, resulting in less postoperative pain, less perioperative bleeding, shorter hospital stays, and earlier return to normal activities.[3,4] However, due to intercostal nerve compression, muscle and fascia injury, soft tissue edema around the

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incision, and thoracic drainage tube placement, the proportion of patients with acute pain at 24 hours after VATS [numerical rating scale, (NRS) ≥3] was 38%,[5] up to 3.4% of patients with severe pain (NRS ≥7).[6] Improper postoperative acute pain management not only increases the incidence of postoperative pulmonary complications such as postoperative pneumonia, atelectasis or respiratory failure, affecting rapid recovery and prolonged hospital stay, but also are risk factors for postoperative analgesic use and development of chronic postoperative pain (CPSP), depression, and delirium.[7,8]

Since the 1960s, intraoperative administration of opioids is considered a keystone of anesthesia as well as hypnotics and muscle relaxants. For most common surgeries, opioids are irreplaceable drugs for analgesia regimens. Thoracic surgery is a much more challenging field associated with a higher rate of pain and pulmonary complications compared to other surgeries. Adequate analgesia after thoracic surgery is essential for a successful outcome.[9] However, opioid administration consequences are neither scarce nor benign for the patient. Perioperative opioids are associated with nausea and vomiting,[10] sedation,[11] ileus,[12] confusion/delirium,[13] respiratory depression,[14] increased postoperative pain and morphine consumption,[15] immunodepression,[16] hyperalgesia and chronic postoperative pain.[17] Among these complications, hypoxemia, ileus and confusion/delirium are the most frequent. In patients with partial lung resection, it is particularly important to avoid postoperative hypoxemia and respiratory depression, considering the influence of their lesions and surgical factors. Moreover, recent reports have suggested that opioids should be used prudently in patients with malignancy due to their hypothesized role in promoting tumor recurrence and metastasis.[18] Therefore, seeking effective multimodal analgesia and anesthetic regimen is the basis for the success of ERAS. These multimodal combination regimens are designed to reduce postoperative pain, intraoperative and postoperative opioid requirements, and opioid-related adverse effects to accelerate postoperative recovery. Multimodal analgesic regimens for reducing opioid medication have become the gold standard for postoperative analgesia, and the effectiveness of non-opioid multimodal analgesia has been validated in patients undergoing abdominal and pelvic surgery.[19,20] Opioid-free postoperative analgesia has therefore been recommended for more than 10 years.[21] Based on the same principle of opioid sparing, opioid-free anesthesia (OFA) is a multimodal anesthesia associating hypnotics, N-methyl-D-aspartate (NMDA) antagonists, local anesthetics, anti-inflammatory drugs and α-2 agonists. The first studies on OFA focused on bariatric surgery where respiratory complications are frequent. OFA with dexmedetomidine (Dex) significantly attenuated postoperative pain and reduced opioid requirements without causing respiratory depression in obese patients.[22,23] Although previous studies have confirmed that OFA is safe and feasible for VATS surgery, there is great heterogeneity in how to select and combine anti-harm drugs to replace opioids.[24–26] We hypothesized that the reduced opioid use during and after surgery allowed by OFA compared with standard of care will be associated with a reduction of postoperative opioid-related adverse events and an improvement in the quality of rehabilitation of patients after partial VATS lung resection. Reducing CPSP could improve quality of life and reduce the economic burden of patients.[27] Symptoms including pain-related interference with mood (28%), sleep (30%), enjoyment of life (30%) and psychological factors are also decreased as the CPSP is controlled.[28]

Methods and Analysis

Trial Design

The TEDOFA Study is a prospective double-blind, randomized, controlled clinical trial with a concealed allocation of patients scheduled to undergo elective partial VATS pneumonectomy 1:1 to receive either a standard anesthesia protocol or an OFA. The study started in April 2023 and the recruiting period will be 12 months. The trial started recruiting patients after registered on the Chinese Clinical Trial Registry.

Eligibility Criteria

Patients are eligible for enrolment if they fulfill the inclusion criteria at screening and are not allowed to have any of the exclusion criteria. Additionally, patients are allowed to withdraw from the trial at any time if they withdraw informed consent, loss to follow-up, do not report the efficacy and safety data or are required by investigators.

Inclusion criteria: Patients aged >18 years, ASA grade I–III, planned to undergo elective VATS partial lung resection.

Exclusion criteria: allergy or contraindication to study medication; chronic pain (pain persisting for at least 3 months after surgery, which was either not present before or differs from pre-operative pain, and which is localized to the surgical

site, and without other obvious cause); severe liver dysfunction (total bilirubin 2 mg dl-1); severe renal dysfunction (glomerular filtration rate 60mL min-1 1.73m-2); pregnancy or lactation; preoperative heart rate <50 beats/min, sick sinus syndrome, severe heart block; body mass index >30 kg/m-2; dementia or obvious neurological disorders (such as stroke, epilepsy, intracranial tumor, history of Parkinson's disease, etc.); history of alcohol or drug abuse.

Participant Eligibility and Consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients will receive written and oral information and will be included after investigators have obtained informed written consent.

Randomization and Blinding

Before the start of the trial, study subject serial number was generated according to the sample size, the random code was generated by Excel software through computer and placed in an opaque envelope and kept by the anesthesia nurse who did not participate in the other matters of the study. Before the entry on the day of the operation, the nurse gave an envelope responsible for intraoperative anesthesia management and data collection (not postoperative data collection), eligible patients with odd random numbers were randomly assigned to no opioid anesthesia and analgesia group (TEDOFA, OFA group) and patients with even random numbers were randomly assigned to conventional opioid anesthesia and analgesia group (OBA group), and those responsible for postoperative follow-up anesthesiologist B, surgeon, and the patient himself were not aware of the grouping.

Interventions

All included patients will be allocated to one of the following two study groups:

- ► OBA group: patients will receive standardized conventional opioid anesthesia and analgesia.
- ► OFA group: patients will receive a standard anesthesia protocol with no opioid anesthesia and analgesia.

All patients receive routine monitoring, including electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP), pulse oxygen saturation (SpO2), and depth of anesthesia monitoring (BIS). After placing peripheral intravenous cannula, both groups then receive radial artery puncture under local anesthesia.

Intravenous Induction of General Anesthesia and Intubation Will Include

In both groups, intravenous dexamethasone 10mg for prophylaxis of postoperative nausea and vomiting before general anesthesia induction and intravenous flurbiprofen ester 50mg for advanced analgesia.

* OFA group: A loading dose of dexmedetomidine 1ug/kg was infused within 10min immediately after the opening of the peripheral vein. After that, midazolam 2mg, propofol 2mg/kg, esketamine 0.5mg/kg and rocuronium 0.6–1mg/kg were intravenously infused to patients, and endotracheal intubation was given 3min after.

* OBA group: midazolam 2mg, propofol 2mg/kg, sufentanil 0.3–0.5ug/kg, rocuronium 0.6–1mg/kg, endotracheal intubation was given 3min after.

Endotracheal intubation: after exposing the glottis, insert a bronchial blocker and then intubate with a single-lumen endotracheal tube (male 8#, female 7.5#). After successful endotracheal intubation, fiberoptic bronchoscopy was used to examine if the endobronchial blocker was correctly positioned. Fill the bronchial blocker plug sac with 5–7mL air, and check whether the seal is good, the bronchial occluder is fully fixed. Then extract the air in the bronchial occluder to continue to double lung ventilation. The setting of mechanical ventilation parameters: tidal volume 8mL kg-1, respiratory rate 12 breaths/min, breath–breath ratio (I: E) 1:2, inhaled oxygen concentration (FiO2) 100%, positive end-expiratory pressure (PEEP) 5 cmH_2O.

Intraoperative Analgesia: Ultrasound-Guided Thoracic Paravertebral Block

After turning the patient to the lateral position, before the surgeon disinfected, ultrasound-guided thoracic nerve block (TPVB) was performed in about 2.5cm near the spinous process in the parasagittal plane on the transverse process of the 5th thoracic spine, and no air and blood were withdrawn after successful puncture, 0.25% ropivacaine was configured to be 30mL and then slowly injected. During injection, pleural was seen gradually down along with local anesthetic

injection. After the injection of the local anesthetic solution, the catheter was inserted through the nerve blocking needle only in the OFA group and then properly fixed for postoperative continuous analgesia.

Standardized Maintenance of General Anesthesia and Single Lung Ventilation Will Include

The OFA group: after successful endotracheal intubation, start intravenous continuous infusion of propofol, esketamine and dexmedetomidine hydrochloride mixture (esketamine 50mg + dexmedetomidine hydrochloride 150 ug + 0.9% saline into 50mL) 0.1mL/kg/h-0.2mL/kg/h to maintains a BIS value between 40 and 60, 10–20mg rocuronium was added intraoperative as appropriate. After the start of the operation, esketamine 0.1 mg/kg was added according to the patient's blood pressure and heart rate, and the pump infusion of esketamine and dexmedetomidine hydrochloride was stopped 40min before the end of the operation. Tropisetron 5mg and flurbiprofen axetil 50mg were injected before the end of the procedure, and propofol was stopped at the end of the operation.

The OBA group: after successful endotracheal intubation, continuous intravenous pump injection of propofol and remifentanil was started to maintain BIS values between 40 and 60, and additional rocuronium 10–20mg as appropriate. After the start of the surgery, adjust continuous intravenous pump injection of propofol and remifentanil according to blood pressure and heart rate. At the end of the operation, Tropisetron 5mg and flurbiprofen axetil 50mg were injected before the end of the procedure, and propofol and remifentanil were stopped at the end of the operation.

After the patient changed from supine to lateral position, the bronchial blocker was confirmed (or adjusted) by using fiberoptic bronchoscopy, and 5–7mL air was injected into the cuff and single lung ventilation was started. Mechanical ventilation parameters during single lung ventilation: tidal volume 5mL/kg, respiratory rate 14–16 times/min, inhalation ratio (I:E) 1:1.5–1:2, positive end-expiratory pressure (PEEP) 5cmH_2O. After the start of single lung ventilation for 30 min, if SpO_2 ≥95%, reduce FiO_2 gradually to maintain SpO_2 ≥92%. After the patient was fully awake, muscle relaxation was completely reversed (intravenous atropine 0.5mg, neostigmine 1mg), and both the bronchial blocker and single lumen tracheal tube were removed.

Postoperative Analgesia Treatment

The OFA group: PCA analgesia was performed via the TPVB catheter. The PCA protocol was a mixture of 0.2% ropivacaine and 200 μg DEX of 250mL, no background dose infusion, setting a single push infusion of 15mL, locking time of 240min.

The OBA group: PCA analgesia was performed intravenously, PCA regimen used 2.5 μ g/kg sufentanil which was diluted to 100mL normal saline without background dose infusion, a single push infusion of 1.5mL, locking time of 10min, and a maximum limit of 9mL.

Both groups were returned to the postoperative recovery room (PACU) by an anesthesiologist and nurse who did not know the standard condition, titrated at 2.5–5 μ g if numerical rating scale (NRS) score was >3, and returned to the thoracic care unit when the patient's Aldrete score was >9.

Relevant Complications of Management During Anesthesia

During anesthesia, continuous intravenous pump injection of noradrenaline 0.01~0.2 ug/kg·min to maintain blood pressure at ± 20% of the basal value. If heart rate decreased to less than 45 times/min, intravenous atropine 0.5mg.

Pain Management in the Thoracic Surgery Ward

For analgesia management in the thoracic surgery unit, in addition to continuous TPVB and PCIA analgesia, respectively, intravenous flurbiprofen axetil was administered twice per day (50 mg/time). When the patient's resting NRS score was ≥4, additional injection of flurbiprofen axetil 50mg and meperidine hydrochloride 50mg or morphine hydrochloride 10mg if necessary.

Outcome Measures

Primary Outcome Measure

The 15-item recovery quality scale at 24 hours after surgery (global score Quality of Recovery-15 scale, QoR-15).[29]

Secondary Outcomes Measures

1. Preoperative: age, gender, BMI, laboratory tests, comorbidities, QoR-15 score, Mini-Cog score.
2. Intraoperation: blood pressure, heart rate, BIS value, dose of anesthetic drugs required, duration of operation, duration of anesthesia, duration of awakening time, complications during anesthesia, dose of vasoactive drugs, infusion amount, amount of bleeding, etc.
3. Postoperative period: duration of until postoperative PACU Aldrete score >9 points; QoR-15 score at 48 hours after surgery; anesthesia-related complication; the 3-minute diagnostic interview for CAM (3D-CAM) of postoperative day 1 to day 7 (if the postoperative hospital stay is <7 days then follow-up to discharge day); Overall benefit of satisfaction with pain treatment (OBAS)[30] at 6.24 and 48 hours and pain NRS score. Time to first postoperative discharge; time of first postoperative mobilization; dose of postoperative analgesic; intensity of chronic pain at rest and incidence of chronic pain at rest at 1 and 3 months after surgery.

Statistical Analysis and Sample Size Calculation

SPSS 23.0 was used for statistical analysis of the data and GraphPad Prism 6.0 software was for mapping. Data will be expressed as means (SD), frequency (percentage) and median (IQR) as appropriate. For baseline data, the Student's *t*-test or Mann-Whitney *U*-test (continuous variables) and Pearson $\chi 2$ or Fisher's exact test (categorical variables) will be used when appropriate. The analysis of the primary outcome QoR-15 score will be performed using the Student's *t*-test or Mann-Whitney *U*-test (after the normality test). Mini-Cog score, intraoperative data, duration of until postoperative PACU Aldrete score >9 points, 3D-CAM score of postoperative day 1 to day 7, pain NRS score at 6.24 and 48 hours, time to first postoperative discharge, time of first postoperative mobilization, dose of postoperative analgesic, OBAS score at 6.24 and 48 hours, intensity of chronic pain at rest at 1 and 3 months after surgery will be compared between the two groups using Student's *T*-test or Mann–Whitney *U*-test (after the normality test). Anesthesia-related complication, incidence of chronic pain at rest at 1 and 3 months after surgery will be compared between the two groups using Chi-square test or Fisher's exact test. We will use intention to treat analysis, all recruited patients will analyze as randomized regardless of the actual treatment received or whether they withdrew before the end of follow-up.

According to our pre-experimental results, the standard deviation (SD) of the overall QoR-15 score was 11.2 and 9.8 after 24 hours in the OFA and OBA groups, respectively, and the difference in the QoR-15 score was 6 that indicates a clinical significant difference.[31] Assuming $\alpha = 0.05$, $\beta = 0.1$, 66 patients in each group, considering the 10% follow-up rate, require a total of 146 patients, 73 in each group.

Ethical Considerations, Amendments and Dissemination

This trial is conducted in accordance with the Declaration of Helsinki. The informed consent and assent process are in line with the Good Clinical Practice guideline. This trial has been approved by the Institutional Review Board of Beijing Friendship Hospital of China Capital University. Any significant modifications to the study protocol or significant modifications in other study documents which may affect the study, potential benefit or safety of patients, including the changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects, will be submitted for approval to the local medical ethical committee, and meanwhile require a formal amendment to the protocol. Regarding patient confidentiality and data protection measures, in our study anonymized data were used in reports and publications to avoid specific subjects being identified, we desensitized sensitive information, such as replacing sensitive words and deleting personal identification information. If sharing data is required, we will ensure that the shared data is properly desensitized to protect subject privacy. When sharing data, numbers will be used instead of personal identification information. It will only allow authorized personnel to access and process the data to prevent unauthorized access.

All study participants will be notified, and informed consent will be requested again when necessary. The amendment will be updated on the Trial Register website to ensure transparency. Results of this trial will be publicly disclosed, published in scientific journals or presented at scientific conferences, regardless of the outcome.

Trial Status

This trial has been approved by the Institutional Review Board of Beijing Friendship Hospital of China Capital University. The TEDOFA trial study protocol was approved on 27 February 2023. The trial started recruiting patients after registered on the Chinese Clinical Trial Registry.

Discussion

Malignant tumor has become a major medical and health problem in the world, greatly increasing the pressure of the national economy and social burden. According to the determination report of the global cancer survival trend published by the WTO organization in 2018, the 5-year survival rate of lung cancer patients with clear diagnosis is only 10%~20%. One of the main reasons for the high mortality of lung cancer lies in its insidious onset. Once the symptoms appear, it has reached the middle and late stage, and the prognosis is very poor.[32] Different from the extremely low survival rate of patients with intermediate and advanced lung cancer, surgery is currently the standard treatment for patients with stage I non–small cell lung cancer (NSCLC), whose 5-year survival rate of patients with early lung cancer can reach 80% to 95% after aggressive treatment such as surgical resection after detection.[33] Compared to open thoracotomy, video-assisted thoracoscopic surgery (VATS) is used increasingly as an alternative to thoracotomy for lobectomy in the treatment of early-stage NSCLC, which is expected to experience less postoperative pain due to less traumatic than thoracotomy and is characterized by less perioperative bleeding, shorter hospital stays, and earlier return to normal activities.[3,4] Meanwhile, previous studies also found that patients who received VATS also reported experiencing similar pain intensity and 20%–47% chronic post-surgical pain as patients having thoracotomy.[34,35] Evidence also suggests that long-term postoperative pain and post-surgical neuroinflammation are widespread and commonly associated with sleep disturbances and negative moods, which may result in delirium and cognitive dysfunction, as well as long-term, irreversible disorders such as dementia perse.[36,37] Opioid analgesics as one cornerstone option for the treatment of postoperative pain remain the most effective.[38] However, opioid analgesics may cause well-recognised side effects, such as respiratory depression, vomiting, nausea, ileus, hyperalgesia and deterioration of consciousness, which limit their use in clinical application.[39] Multimodal analgesia is advocated for pain management to reduce opioid consumption, therein achieving adequate postoperative pain relief, fewer side effects and reduced surgical stress response. TPVB, esketamine, and DEX alone in VATS can reduce the amount of sedative drugs, block nociceptive afferents, and analgesia during general anesthesia. The continuous maintenance dosage chosen in our study was that esketamine 50mg + dexmedetomidine hydrochloride 150 ug + 0.9% saline into 50mL, maintenance speed was 0.1mL/kg/h-0.2mL/kg/h, which means that esketamine 0.1mg/kg/h-0.2mg/kg/h, dexmedetomidine 0.3ug/kg/h-0.6ug/kg/h. The selected drug doses of our study were all within the safe range of the previous studies,[40–42] and our pre-experiments also confirmed the effectiveness of the drug dose in our study. The TEDOFA Study is a prospective double-blind, randomized, controlled clinical trial evaluating the effect of OFA on severe postoperative opioid-related adverse events. TEDOFA OFA protocol for VATS partial lung resection may have the following advantages in accelerating postoperative rehabilitation: ① the incidence of opioid related adverse reactions such as hypoxemia and PONV is significantly reduced, and patient safety and comfort are guaranteed; ② TPVB has satisfied perioperative analgesic effect, and esketamine and DEX can effectively avoid the occurrence of perioperative neurocognitive disorder. The TEDOFA regimen using continuous TPVB combined with esketamine and DEX could theoretically have the potential to promote rapid postoperative recovery and reduce CPSP on the basis of avoiding opioid side effects, but no relevant studies have been reported.

Despite the careful design of this trial, there are still some limitations. First, these questionnaires are mostly subjective in nature, influenced by the patient impression of pain; thereby, they may not directly measure the analgesic effect and lead to subjective bias. Thus, before the initiation of this trial, the investigator and site staff received systemic training for the use of these questionnaires and were certificated to avoid subjective bias as much as possible. Meanwhile, in this trial, objective assessment, including the duration of postoperative analgesia, the incidence of rescue analgesia and time to

fully alert, will also be performed to fully assess the analgesic effect. Second, due to different methods of postoperative analgesia in two groups, the lack of blinding is another limitation of the trial. However, our study has been designed to separate the surgeons and anesthesiologists from the follow-up doctors (outcome assessors), and the outcome assessors will not be informed about treatment assignment, which will eliminate the limitation to a large extent. Third, though OFA is an acceptable and safe alternative compared with OBA patients undergoing VATS for lung resection, the impact of OFA on long-term outcomes like chronic postsurgical pain or cancer recurrence may be really difficult to assess. Many confounding factors have to be taken into account in the perioperative period, and very large populations of patients are required to allow consistent statistical analysis. Until now, the majority of OFA studies have only concerned a small number of patients. Moreover, conclusive evidence is lacking that OFA can improve cancer outcomes, despite the impact of OBA on immunity is documented.[43]

Overall, this study is a significant attempt to evaluate the efficacy and safety of OFA in perioperative pain management, If TEDOFA yields positive results, it would bring strong data to promote OFA, showing the benefits of OFA in terms of reduction of opioid-related adverse events, reduction of global morbidity, reduction of the economic burden associated with opioid-related adverse events, and reduction in length of stay would result in a collective benefit for future patients and could lead to significant changes in the standard of care in anesthesia. However, OFA is not without challenges. Whether OFA is beneficial and can improve short-term and long-term patient outcomes remains unknown and still needs further study.

Data Sharing Statement

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

Disclosure

The authors report no conflicts of interest in this work.

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