Study Protocol and Statistical Analysis Plan

Official Title: Application of Pre-Emptive Analgesia with Parecoxib Sodium in CT-Guided Hook Wire Localization of Lung Nodules Before Video-Assisted Thoracoscopic Surgery and Exploration of the Optimal Clinical Dosing Window: A Single-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

NCT Number: Not Yet Assigned

Document Date: May 5, 2026

Document Type: Study Protocol and Statistical Analysis Plan

Clinical Study Protocol

1. Study Title

Application of Pre-Emptive Analgesia with Parecoxib Sodium in CT-Guided Hook Wire Localization of Lung Nodules Before Video-Assisted Thoracoscopic Surgery and Exploration of the Optimal Clinical Dosing Window: A Single-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

2. Background and Objectives

Background: Preoperative CT-guided hook wire localization is a critical step for the precise resection of small, indeterminate lung nodules in Video-Assisted Thoracoscopic Surgery (VATS). However, the severe pain induced by the puncture not only reduces the patient's experience but also may lead to poor patient compliance (such as the inability to hold breath), increasing the risk of complications such as wire dislodgement, pneumothorax, and hemorrhage. Preliminary experimental data show that preoperative administration of parecoxib sodium can significantly reduce the Visual Analog Scale (VAS) pain score immediately after puncture. Due to the unpredictability of sequential surgical scheduling in clinical practice, executing a Standard Operating Procedure (SOP) with fixed dosing times is difficult. Furthermore, the "golden time window" for parecoxib sodium to reach its peak analgesic effect in the real world remains to be precisely defined.

Primary Objective: To evaluate the efficacy of pre-emptive analgesia with parecoxib sodium during CT-guided hook wire localization.

Secondary Objectives:

To explore the optimal dosing time window for parecoxib sodium.

To assess the overall patient satisfaction with the pain management during the localization process.

3. Study Design Overview

Study Type: Prospective, randomized, double-blind, placebo-controlled clinical trial (RCT).

Randomization Ratio: The intervention group (parecoxib sodium) and the control group (normal saline) will be randomized in a 2:1 ratio.

Stratification Factors: Stratified block randomization will be conducted based on the "expected number of localized nodules" (single nodule vs. multiple nodules).

4. Subject Selection Criteria

Inclusion Criteria:

Informed Consent: Subjects voluntarily participate and sign the informed consent form approved by the Ethics Committee.

Age and Gender: Male or female adult patients aged 18 years or older.

Target Disease: Histologically or cytologically confirmed non-small cell lung cancer (NSCLC) scheduled for VATS treatment.

Operational Need: Preoperative CT-guided hook wire lung nodule localization is required.

Performance Status: Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

ASA Risk Classification: I-II.

Fully conscious, with no psychiatric or neurological disorders, and able to fully understand and correctly use the VAS pain scale.

Exclusion Criteria:

Known hypersensitivity to parecoxib sodium or other COX-2 inhibitors, sulfonamides, aspirin, or other non-steroidal anti-inflammatory drugs (NSAIDs).

History of active peptic ulcer, bleeding, or gastrointestinal perforation.

Severe cardiovascular disease, including unstable angina, history of myocardial infarction (within 6 months), severe arrhythmia, or poorly controlled hypertension.

Coagulation disorders with a bleeding tendency (e.g., hemophilia) or currently receiving full-dose anticoagulation therapy, where the investigator believes the risk of bleeding from localization is significantly increased.

Impaired respiratory function (e.g., severe COPD, interstitial pneumonia) that poses an unacceptable risk.

Currently using other analgesic medications that cannot be discontinued during the study period; or the investigator believes there are other conditions that may interfere with outcome assessment or increase risk.

Withdrawal Criteria:

Intervention Discontinuation: Includes withdrawal of consent, protocol deviation affecting safety/data integrity, emergence of contraindications before dosing, unacceptable toxicity (Grade 3 or higher AE related to the drug), or investigator decision based on clinical judgment.

Study Withdrawal: Participant requests complete withdrawal with no further follow-up, or a major violation of inclusion criteria discovered post-randomization.

5. Sample Size Calculation

Based on preliminary data: Control group VAS score: 3.73 ± 1.49, Trial group VAS score: 2.27 ± 1.71. Expected mean difference: 2 (Minimal Clinically Important Difference threshold ≥ 2 points). Significance level (α): Two-sided 0.05. Statistical power (1- β): 90%. Allocation ratio: 2:1. Attrition rate adjustment: 10%.

The pooled standard deviation is approximately 1.62. To achieve 90% power, a sample size of roughly 32 is needed. However, the core secondary objective requires utilizing the natural surgical scheduling time gradient to explore the optimal dosing window. To ensure robust statistical power for Restricted Cubic Spline (RCS) modeling across three time subgroups (<1h, 1-3h, >3h), a minimum of 30 valid samples per subgroup in the intervention arm is required. Factoring in a 10% attrition rate and heterogeneous time distributions, the final total sample size is set to 150 subjects (100 in the intervention group, 50 in the control group).

6. Interventions and Clinical Execution Flow (SOP)

Study Group (Parecoxib Sodium):

Drug: Parecoxib sodium for injection.

Dose: 40 mg via slow intravenous injection (≥ 30 seconds).

Time Window Subgroups: A (<1 hour prior), B (1-3 hours prior), C (>3 hours prior). Administered as a single dose.

Control Group (Placebo):

Drug: Normal saline (visually identical volume).

Route/Frequency: Slow intravenous injection (≥ 30 seconds) in matching time windows.

Blinding: Double-blind design; drug prepared by an independent nurse.

Precise Timestamp Recording (CRF Core Variable):

T1: Exact time of intravenous injection completion in the ward.

T2: Exact time of CT localization procedure initiation (instant of local anesthesia needle or hook wire insertion).

Calculated Interval: $\Delta T = T2 - T1$.

Concomitant Medication Restrictions:

Prohibited: Other NSAIDs (24 hours prior until primary endpoint completion), opioids (unless needed for rescue analgesia for VAS $\geqslant$ 7), and acetaminophen. Strong CYP2C9 inhibitors/inducers should be avoided.

Permitted: Routine preoperative antibiotics and maintenance medications for baseline diseases (stable for $\geqslant$ 2 weeks). Rescue short-acting opioids are permitted if VAS $\geqslant$ 7 and will be recorded as an intercurrent event.

7. Outcome Measures

Primary Endpoint: Patient VAS pain score (0-10) immediately after completion of CT-guided hook wire localization (within 5 minutes after guide needle withdrawal).

Secondary Endpoints:

Differences in VAS scores across different dosing interval windows (<1h, 1-3h, >3h).

Overall patient satisfaction regarding the pain-free experience (5-point Likert scale).

Incidence of localization-related complications: pneumothorax, local hematoma, hemoptysis, pleural reaction, and wire dislodgement.

Incidence of adverse reactions (e.g., PONV, dizziness) within 24 hours post-administration.

Exploratory Analysis: Best dosing window via non-linear regression; pain-related biomarkers (IL-6, IL-1β, TNF-α); Patient-Reported Outcomes (BPI); Health economics evaluation (ICER).

8. Data Management and Statistical Analysis Plan (SAP)

Analysis Sets: Intention-to-Treat (ITT), Per-Protocol (PP), and Safety Set (SS).

Primary Endpoint Analysis: Independent samples t-test or Mann-Whitney U test will evaluate VAS differences between arms. Analysis of Covariance (ANCOVA) will be used to adjust for the "actual number of localized nodules" as a covariate.

Secondary Endpoint Analysis (Optimal Time Window Exploration):

Categorical Variable Analysis: The intervention group will be split into three ΔT subgroups (<1h, 1-3h, >3h). One-way ANOVA will assess differences to determine a rough advantageous window.

Continuous Variable Non-Linear Analysis (RCS): Using ΔT (minutes) as a continuous independent variable and VAS score as the dependent variable, Restricted Cubic Splines (RCS) modeling will be fitted. A dose-time-effect smooth curve will be plotted to pinpoint the lowest point (maximum analgesia) corresponding to the optimal clinical dosing time window.

Qualitative Data: Analyzed using Chi-square or Fisher's exact test. A two-sided $P < 0.05$ indicates statistical significance.

9. Ethics and Safety

The study strictly adheres to the Declaration of Helsinki and GCP guidelines. The protocol and informed consent form require approval by the independent Ethics Committee prior to enrollment. Parecoxib sodium is a mature, widely used analgesic; this study optimizes pre-emptive strategies with very low safety risks. Serious Adverse Events (SAE) will be reported within 24 hours, triggering unblinding procedures if necessary.