Opioid-Sparing vs Opioid-Based Analgesia After Ankle Arthroscopy Procedures: A Single-Center, Randomized, Non-Inferiority Trial Protocol

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Trial registration: ClinicalTrials.gov

NCT number:NCT07154433

Trial Synopsis

Item	Description
Design	Prospective, parallel-group, 1:1 randomization; single-center, assessor-blinded, non-inferiority RCT.
Population	Eligible participants were adults aged 18 to 65 years undergoing unilateral ankle arthroscopy, with an American Society of Anesthesiologists (ASA) physical status of I or II and a body mass index (BMI) of 16 to 32 kg/m² and were able to understand the study procedures and provide written informed consent.
Sample size	110 participants, allowing ~10% attrition; non-inferiority margin 1.0 point on 0–10 NRS at 24 h.
Intervention	Opioid-sparing protocol (patient education, celecoxib 400 mg post-op then 200 mg BID; acetaminophen 500 mg Q6H; rescue oxycodone/acetaminophen 5/325 mg, ≤10 tablets).
Control	Usual care with opioid-centered prescribing (e.g., oxycodone/acetaminophen Q6H per surgeon discretion), without standardized NSAIDs/acetaminophen guidance.
Primary endpoint	NRS pain intensity at 24 hours post-operation (0–10).
Secondary endpoints	AUC of NRS within 24 h (2, 6, 12, 24 h); The total consumption of additional rescue opioids ; time-course of NRS (days 2–6); opioid-related adverse effects; satisfaction (4-level Likert); PROMIS-PI-SF-8a & Insomnia Severity Index on day 6 .
Randomization/Stratification	Centralized REDCap™ randomization; simple randomization; stratified by incision type (arthroscopy vs mini-open).
Blinding	Outcome assessors and statisticians blinded; patients and treating surgeons unblinded due to educational component.
Analysis	Details are specified in the Statistical Analysis Plan (SAP).

List of Abbreviations

Abbreviation	Definition
AE/SAE	Adverse event/Serious adverse event
ANCOVA	Analysis of covariance
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
DSMB	Data Safety Monitoring Board

GCP	Good Clinical Practice
ICH	International Council for Harmonisation
ITT / PP	Intention-to-treat / Per-protocol
MME / OME	Morphine milligram equivalents / Oral morphine equivalents
NRS	Numeric rating scale (0–10)
NSAIDs	Non-steroidal anti-inflammatory drugs
OSP	Opioid-sparing protocol
PNB	Peripheral nerve block
PROMIS-PI-SF-8a	Patient-Reported Outcomes Measurement Information System—Pain Interference Short Form 8a
PROMIS-SD-SF-4a	PROMIS—Sleep Disturbance Short Form 4a
RCT	Randomized controlled trial
REDCap™	Research Electronic Data Capture

1. Background and Rationale

Ankle arthroscopy has become a cornerstone in the management of diverse ankle disorders, including osteochondral lesions, chronic ankle instability, impingement syndromes, and synovial pathology[1-3]. Compared with traditional open procedures, arthroscopic techniques allow precise visualization and targeted intervention while minimizing soft-tissue disruption and surgical morbidity, thereby facilitating earlier mobilization and faster functional recovery[2,4]. Consequently, ankle arthroscopy has been increasingly adopted in contemporary foot and ankle practice, with an estimated annual global volume of 150,000 to 400,000 procedures[4,5]. Despite these advantages, postoperative pain remains a major clinical challenge. Intraoperative procedures such as synovectomy, cartilage or bone bed preparation, and suture anchor implantation may induce substantial inflammatory and nociceptive responses, potentially delaying rehabilitation and impairing early functional recovery[6-8].

Perioperative analgesic strategies after ankle arthroscopy remain poorly standardized, and opioid-based regimens continue to be widely used despite their association with adverse effects such as dizziness, postoperative nausea and vomiting, somnolence, and constipation[9-11]. Increasing evidence from knee and shoulder arthroscopy suggests that opioid-sparing multimodal analgesia can effectively reduce opioid consumption without compromising pain control or patient satisfaction[12-15]. However, high-quality evidence specific to ankle arthroscopy is limited. Therefore, the primary aim of this randomized clinical trial was to compare postoperative pain at 24 hours between an opioid-sparing multimodal analgesic regimen based on nonsteroidal anti-inflammatory drugs and acetaminophen and a standard opioid-based protocol.

2. Objectives

2.1 Primary Objective

To test non-inferiority of the opioid-sparing protocol vs standard opioid-based protocol on 24-hour postoperative NRS pain (0–10) among adults aged 18–65 years; non-inferiority margin: 1.0 point.

2.2 Secondary Objectives

To compare: (i) AUC of NRS over 24 h (2, 6, 12, 24 h); (ii) The total consumption of additional rescue opioids, expressed as oral morphine equivalent dose (OME); (iii) NRS trajectories over days 2–6; (iv) opioid-related adverse events (nausea, vomiting, dizziness, constipation, respiratory depression) ; (v) 4-level satisfaction; (vi) PROMIS-PI-SF-8a and Insomnia Severity Index (ISI) at day 6.

3. Trial Design

Single-center, prospective, randomized, assessor-blinded, parallel-group, non-inferiority trial with 1:1 allocation to an opioid-sparing group or a standard opioid group. Stratification by incision type (arthroscopy vs arthroscopy-assisted mini-open).

3.1 Study Setting

Zhejiang University School of Medicine, Second Hospital (Department of Orthopaedics), inpatient wards and outpatient follow-up.

3.2 Eligibility Criteria

Inclusion criteria:

Category	Criteria
Age/Sex	18–65 years, any sex; written informed consent.
Surgery	Unilateral ankle arthroscopy (incision ≤2 cm); expected duration ≤3 h.
General condition	ASA I–II; BMI 16–32 kg/m².

Exclusion criteria:

No.	Criteria
1	Known allergy/contraindication to study-related medications.
2	Surgery duration > 3 hours.
3	Preoperative chronic opioid use.
4	Pregnant or breastfeeding.
5	Screening labs: ALT or AST > 2×ULN; Cr > 1.5×ULN; Tbil > 1.5×ULN.

3.3 Recruitment, Consent, and Screening

Eligible patients presenting for ankle surgery will be pre-screened from operative schedules. Trained research staff will contact candidates in clinic or by phone/email before surgery, explain the study, and obtain written informed consent on or before the day of surgery. Screening logs will record included, excluded, and erroneously missed-randomized cases.

3.4 Allocation and Randomization

Centralized 24-hour REDCap™ system with concealed simple randomization, stratified by incision type. Randomization is targeted as close to the surgical day as feasible.

3.5 Interventions

3.5.1 Opioid-Sparing Protocol (Intervention)

• Immediately post-op: celecoxib 400 mg PO once, then 200 mg BID.
• Acetaminophen 500 mg PO Q6H.
• Rescue only if inadequate analgesia: oxycodone/acetaminophen 5/325 mg PO (maximum 10 tablets).
• Patient education infographic covering correct use, opioid risks, storage and disposal.

3.5.2 Standard opioid group

Opioid-centered prescribing per surgeon discretion (e.g., oxycodone/acetaminophen Q6H). No standardized guidance or routine prescription of NSAIDs/acetaminophen for mild-to-moderate pain.

3.6 Strategies to Improve Adherence

Printed medication schedules and structured nurse/CRC reminders were implemented during inpatient stay, followed by web-based electronic questionnaires alongside scheduled telephone reminders after discharge to maximize the follow-up rate.

3.7 Outcomes

Primary endpoint

NRS pain at 24 hours post-operation (0–10).

Secondary endpoints

(i) AUC of NRS over 24 h (2, 6, 12, 24 h); (ii) The total consumption of additional rescue opioids, expressed as oral morphine equivalent dose (OME); (iii) NRS trajectories over days 2–6; (iv) opioid-related adverse events (nausea, vomiting, dizziness, constipation, respiratory depression) ; (v) 4-level satisfaction; (vi) PROMIS-PI-SF-8a and ISI at day 6.

3.8 Participant Timeline

Schedule of enrolment, interventions, and assessments (SPIRIT-style):

Procedure/Assessment	**Pre-op**	**Intra-op**	**2 h**	**6 h**	**12 h**	**24 h**	**Days 2–5**	**Day 6**
Informed consent, demographics, comorbidities, CrCl	X							
Surgical details		X						
NRS (0–10)	X (baseline)		X	X	X	X	X	X
PROMIS-PI-SF-8a	X (baseline)							X
ISI score	X (baseline)							X
Opioid-related adverse events						X	X	X
OMEs consumed						X	X	X
Satisfaction (Likert)								X

3.9 Blinding

Due to the educational component, patients and treating clinicians cannot be blinded. Outcome assessors and statisticians will remain blinded to allocation.

4. Sample Size and Statistical Analysis

4.1 Sample Size

Based on arthroscopy ankle populations, the SD of 24-h NRS is ~1.3. With a one-sided $\alpha = 0.05$, 80% power, and a non-inferiority margin of 1.0, the required sample size is 50 per arm. Allowing ~10% attrition yields 55 per arm (total n = 110).

4.2 Statistical Methods

Details are specified in the Statistical Analysis Plan (SAP).

5. Data Management

Data will be captured via eCRF in REDCap™ hosted by the sponsor site. Site-level accounts will be provisioned for data entry of demographics, peri-operative medications, analgesia, NRS scores, opioid consumption, adverse events, and adherence. Data must be entered within 48 hours of occurrence; automatic range, consistency, and missingness checks will be enforced. Authorized study personnel will access data according to their assigned roles.

Data queries will be issued for missing/implausible entries; sites must respond and resolve within specified windows. Paper source documents and consent forms are stored in locked cabinets with access limited to authorized staff. REDCap™ enforces role-based access and password protection; routine server backups occur within China in compliance with the Personal Information Protection Law and Data Security Law.

6. Monitoring and Safety

6.1 Ethics Approval and Consent

The protocol, CRFs, informed consent documents, and recruitment materials will be submitted to the ethics committees of participating institutions prior to initiation. Any substantial amendments will undergo prior approval.

6.2 Confidentiality

Participants will be identified by unique study codes; direct identifiers (e.g., names, ID numbers) will not be recorded in REDCap™. De-identified data will be used for analysis and publications.

6.3 Adverse Events

All AEs and SAEs will be documented. Research staff will report study-related SAEs within 24 hours to the coordinating center, which will assess relatedness and, when required, notify the ethics committee.

6.4 DSMB

An independent DSMB (orthopaedics, anaesthesiology, clinical pharmacology) will periodically review safety, adherence, and study conduct, and may recommend pausing or terminating the trial.

7. Organisation and Responsibilities

Sponsor: Department of Orthopaedics, Second Affiliated Hospital of Zhejiang University School of Medicine. Principal Investigator: Zongyou Pan, MD (Associate Chief Physician). Coordinating Centre: Zhejiang University Clinical Research Centre (protocol coordination, data management, monitoring, ethics coordination, statistics). Each participating unit will designate an orthopaedic PI, an anaesthesia co-PI, and a study coordinator.

8. Dissemination

Results will be disseminated in peer-reviewed journals and conferences following CONSORT-NI and ICH-E9(R1) reporting standards. Authorship will follow ICMJE criteria. De-identified datasets may be shared upon reasonable request and approval by the PI and sponsor.

9. Declarations

Competing interests: None declared.

Funding: To be specified.

Protocol version/date: Version 2.0, 2025-11-06.

Trial registration: ClinicalTrials.gov, NCT07154433.

SPIRIT checklist and participant information/consent forms: available upon request.

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Informed Consent Form for Clinical Research

The Second Affiliated Hospital, Zhejiang University School of Medicine

Introduction

Dear Patient,
We invite you to participate in a clinical research study entitled:
“Multimodal Non-Opioid Analgesia vs. Opioid-Based Analgesia on Postoperative Pain Following Ankle Arthroscopy: A Non-Inferiority Randomized Clinical Trial.”

Before you decide whether to participate, please carefully read the following information. It explains the purpose of this study, its procedures and duration, potential benefits and risks, as well as your rights.

1. Background and Purpose

Opioid analgesics are commonly used in orthopedics, but their use carries risks such as nausea, vomiting, drowsiness, constipation, hypotension, and even serious issues such as addiction, misuse, and life-threatening respiratory depression.

Multimodal analgesia—using a combination of different pain control strategies—can reduce the postoperative opioid burden. Some studies suggest that non-opioid regimens can provide pain relief comparable to opioids, with fewer side effects.

This study aims to compare the efficacy and safety of a non-opioid regimen with a traditional opioid regimen after ankle arthroscopy, providing evidence for safer, more effective pain management and reducing opioid use.

2. Study Site and Duration

This study is conducted in the Department of Orthopedics, Second Affiliated Hospital, Zhejiang University School of Medicine.
- Duration: 2 years
- Start date: upon ethics approval
- End date: May 31, 2027

3. What You Will Need to Do

1. Before enrollment, your physician will review your medical history and perform preliminary examinations.

2. If you are eligible, you may voluntarily join this study and sign this informed consent form. If you choose not to participate, you will continue to receive routine medical care.
3. If you agree to participate:
- You will sign the consent form.
- After surgery, you will take analgesics according to group allocation:
• Opioid group: oxycodone/acetaminophen (325 mg/5 mg) every 6 hours as needed.
• Non-opioid group: immediately after surgery, acetaminophen 500 mg + celecoxib 400 mg. Thereafter, celecoxib 200 mg BID + acetaminophen 500 mg Q6H (not exceeding 3000 mg/day).
- Postoperative pain will be assessed at 2, 6, 12, and 24 hours using NRS (pain scores), and questionnaires will be completed on days 1–6, along with records of medication use and adverse effects.

4. Possible Benefits
- This study may identify an analgesic regimen that effectively controls pain, reduces side effects, and minimizes opioid use.
- You may benefit from improved pain management education and closer follow-up after surgery.
- However, there may be no direct personal benefit from participating.

5. Possible Risks and Safety Measures
- You may experience adverse effects related to medications (e.g., dizziness, nausea, constipation).
- If you develop any discomfort or changes in your condition, notify your physician immediately. Appropriate medical treatment will be provided.

6. Costs
All treatments and examinations will be charged according to standard hospital fees.

7. Compensation and Insurance
There is no financial compensation for participating in this study.

8. Alternatives
If you choose not to participate, you will continue your standard clinical treatment with no impact on your care.

9. Confidentiality
Your medical records and study data will be securely stored in the hospital. Only the investigators, the ethics committee, auditors, inspectors, or regulatory authorities may review them. Reports and publications from this study will not reveal your personal identity.

10. Withdrawal from the Study

Participation is voluntary. You may refuse or withdraw at any time without affecting your medical care or your relationship with your physician.

You may also be withdrawn from the study if:
1. You do not follow the physician's instructions.
2. You develop a condition requiring alternative treatment.
3. The investigator decides that withdrawal is in your best interest.

11. Ethics Committee

This study has been reviewed and approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine.

For any concerns regarding your rights as a participant, please contact:
- Daytime: 0571-87783759
- After hours: 13757118366
- Email: HREC2013@126.com

Consent

I confirm that I have read and understood the information above. I voluntarily agree to participate in this study, accept the treatment procedures described, and consent to the use of my medical data for research publication.

Participant Signature: _____ Contact: _____ Date: _____

Legal Representative (if applicable): _____ Relationship: _____
Contact: _____ Date: _____

Witness (if applicable): _____ Contact: _____ Date: _____

Investigator Statement:
I confirm that I have explained the details of this study to the participant, including rights, possible benefits, and risks. A signed copy of the informed consent form has been provided to the participant.

Investigator Signature: _____ Contact: _____ Date: _____