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Celecoxib in combination with foot and ankle orthoses for the treatment of acute ankle injuries: A study on the correlation between anti-inflammatory and analgesic mechanisms and functional recovery

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Abstract: **Background**: Celecoxib combined with an ankle orthosis is widely used in the treatment of acute ankle injuries. However, details of local adverse reactions such as skin lesions and tenderness related to the orthosis are unclear and the safety differences among different intervention groups are not well understood, affecting the choice of treatment regimen. **Objective**: This study aimed to explore the anti-inflammatory and analgesic mechanism of celecoxib combined with an ankle orthosis in the treatment of acute ankle injuries and its correlation with functional recovery. **Method**: 160 patients with moderate acute ankle injuries were randomly divided into four groups (n=40 each): the control group received routine treatment, the celecoxib group received celecoxib in addition, the orthosis group received an ankle orthosis in addition and the synergistic treatment group received both treatments. Inflammatory markers (C-reactive protein (CRP), interleukin-6(IL-6), etc.), pain markers (Visual Analogue Scale (VAS) score, etc.) and functional markers (American Academy of Foot and Ankle Surgery (AOFAS) score, etc.) were compared among the four groups. Correlation and influencing factors were analyzed and stratified analysis was performed based on the side of injury. **Results**: The synergistic treatment group showed better results than the other three groups in terms of inflammation, pain and functional indicators at all time points (p<0.05); the degree of inflammation and pain relief was significantly positively correlated with functional recovery (r=0.71~0.83, p<0.001); celecoxib dosage, orthotic wear and the degree of IL-6 reduction were independent influencing factors for functional recovery (p<0.05); patients with left-sided injuries benefited more significantly from synergistic treatment (p<0.05). There was no difference in the incidence of adverse reactions among the four groups (p>0.05). **Conclusion**: The synergistic treatment enhances efficacy through anti-inflammatory and biomechanical stabilization effects, with good safety profile and patients with left-sided injuries benefit more.

Keywords: Anti-inflammatory and analgesic; Celecoxib; Correlation analysis; Foot and ankle orthosis; Functional recovery

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INTRODUCTION

Acute ankle injury (AAI) is the most common acute trauma in orthopedics and sports medicine, accounting for 40-50% of all sports injuries, with a global incidence of approximately 2.1%–3.8% and is showing a trend towards affecting younger people (Xiaofei and Fabao, 2023). Its injury mechanism mainly involves excessive ligament stretching and tearing during ankle inversion or eversion, accompanied by activation of local inflammatory response and release of pain mediators, leading to joint swelling, pain and limited range of motion. In severe cases, it can cause sequelae such as chronic pain, instability and traumatic arthritis, with an incidence rate as high as 20–40%, significantly affecting patients' motor function and quality of life (Zhiwei, 2022).

Currently, the core goal of clinical treatment for AAI is to rapidly control inflammation, relieve pain and restore joint stability and function, but single treatment methods have significant limitations. Existing studies on AAI treatment have explored the application of combined interventions to a certain extent. For example, some studies have tried combining nonsteroidal anti-inflammatory drugs (NSAIDs) with basic rehabilitation training, or orthoses with physical therapy; however, there is a notable lack of systematic research focusing on the combination of pharmacological interventions (specifically targeted anti-inflammatory and analgesic drugs) and orthopedic interventions (foot and ankle orthoses) for acute ankle injuries. Most relevant reports either focus on the efficacy of single pharmacological agents or single orthopedic devices, or involve non-specific combinations that do not deeply explore the synergistic mechanism between targeted pharmacology and biomechanical stabilization.

Celecoxib, as a highly selective cyclooxygenase-2 (COX-2) inhibitor, can specifically block COX-2-mediated prostaglandin(PG) (especially prostaglandin E2 (PGE2)) synthesis, inhibit the activation of the inflammatory cascade and reduce the release of pro-inflammatory factors (CRP, IL-6, tumor necrosis factor-α(TNF-α)), thus achieving anti-inflammatory and analgesic effects

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(Ebubekir *et al*., 2025). However, studies have shown that celecoxib alone can only relieve symptoms and cannot solve the problem of joint biomechanical instability. Some patients experience delayed functional recovery due to poor ligament repair, with a recurrence rate of approximately 15 to 25% (Xiuqing *et al*., 2025). Foot and ankle orthoses, through biomechanical adjustment, can limit abnormal ankle joint movement, reduce traction on damaged ligaments, improve local blood circulation and provide a stable environment for tissue repair. However, they lack direct anti-inflammatory effects and have limited pain relief effects during the acute inflammatory phase (Mason *et al*., 2024). The novelty of this study lies in addressing the aforementioned research gap by systematically combining celecoxib (a targeted COX-2 inhibitor with superior safety and anti-inflammatory/analgesic efficacy) with foot and ankle orthoses (a biomechanically optimized device for ankle stabilization). This combination is not a simple superposition of two treatments but a targeted synergy: celecoxib rapidly controls the acute inflammatory response and relieves pain (creating favorable conditions for early tissue repair and rehabilitation), while the ankle orthosis provides continuous biomechanical stabilization to prevent secondary injury to damaged ligaments and promote orderly collagen fiber regeneration. This synergy fills the gap where single pharmacological treatment fails to address biomechanical instability and single orthopedic treatment lacks direct anti-inflammatory effects.

Existing research largely focuses on the efficacy observation of single treatment methods, with limited systematic studies on the synergistic treatment of celecoxib and foot-ankle orthoses. Three major research gaps exist: First, the molecular mechanisms of their synergistic effect are unclear, particularly the interaction between the COX-2/PGE2 pathway and biomechanical stability; second, quantitative comparisons of multidimensional indicators are lacking, with existing studies mostly limited to pain scores and basic function scores and insufficient dynamic monitoring of indicators such as inflammatory mediators, joint range of motion and balance function; third, the correlation between anti-inflammatory analgesia and functional recovery has not been fully validated and the impact of individual differences such as injury side on efficacy has not been considered, affecting the optimization and adjustment of clinical treatment plans (Comez *et al*., 2023; Dongling *et al*., 2025). Based on this, this study, through a randomized controlled trial, introduced multidimensional inflammatory markers (CRP, IL-6, TNF-α, PGE2), pain-related markers (VAS score, tenderness threshold) and functional markers (AOFAS score, range of motion, balance function) to systematically explore the synergistic therapeutic effect of celecoxib and foot-ankle orthoses, reveal its anti-inflammatory and analgesic mechanism, quantitatively analyze the correlation between inflammation reduction, pain relief and functional recovery and conduct stratified analysis based on the side of injury to identify key factors affecting functional recovery, providing new theoretical basis and clinical strategies for the precision treatment of AAI.

MATERIALS AND METHODS

General information

This was a prospective randomized controlled parallel study conducted at the Orthopedics Department of Shanghai Yangzhi Rehabilitation Hospital (Jan 2023–Jan 2024), following the Helsinki Declaration.

160 patients were divided into 4 parallel groups (n=40 each) to compare the effects of routine treatment, celecoxib, ankle orthosis and their combination.

Sample size was calculated via PASS 15.0 (α=0.05, power=80%, 10% dropout rate).

Single-blind design: Patients and outcome assessors were unaware of group assignments; only pharmacists and orthosis fitters knew.

Study subjects

160 patients with acute ankle injuries who visited the Department of Orthopedics at Shanghai Yangzhi Rehabilitation Hospital from January 2023 to January 2024 were selected as the study subjects. *Inclusion criteria*: 1) Meeting the diagnostic criteria of AAI in the "Expert Consensus on the Diagnosis and Treatment of Acute Ankle Ligament Injury" (Çömez M et al.,2023) and being a fresh closed injury with a time ≤48 hours from injury to consultation; 2) Age 18-60 years; 3) Exclusion of fracture or dislocation by ankle X-ray or computed tomography(CT) examination; 4) Informed consent from the patient and their family. *Exclusion criteria*: 1) Comorbid severe liver and kidney dysfunction or cardiovascular disease; 2) Allergy to NSAIDs; 3) History of ankle surgery or chronic ankle disease; 4) Pregnant or lactating women; 5) Those unable to cooperate in completing treatment and follow-up. A total of 160 eligible patients were randomly allocated into four equal groups, with 40 cases in each group: the control group, celecoxib group, orthosis group and combined treatment group. Comparative analysis of baseline data revealed that the four groups were homogeneous in terms of gender distribution, age, injury type (inversion or valgus), injured side (left or right) and other general characteristics. No statistically significant differences were observed between groups (all $p > 0.05$), which confirmed the comparability of the four groups for subsequent therapeutic effect evaluations. See table 1 for details.

Randomization process

Stratified block randomization was used:
Stratification factors: Injury type (inversion/eversion) and injured side (left/right).

Table 1: Comparison of general characteristics of the four groups of patients ($\bar{x}$±s)

Group	N	Gender (male/female, N)	Age (years, $\bar{x}$±s)	Injury type (inversion/ valgus, N)	Side of injury (left/right, N)	Time from injury to medical treatment (h, $\bar{x}$±s)
Control group	40	22/18	32.5±8.6	30/10	21/19	28.6±10.3
Celecoxib group	40	23/17	33.2±9.1	29/11	20/20	29.3±11.2
Orthopedic group	40	21/19	31.8±8.9	31/9	19/21	27.9±10.8
Collaborative treatment group	40	24/16	32.9±9.3	32/8	22/18	28.8±11.0
Statistical value	-	χ^2=0.286	F=0.152	χ^2=0.357	χ^2=0.214	F=0.183
p	-	0.965	0.927	0.949	0.976	0.907

Block size=8; random sequences were generated by an independent statistician using SPSS 26.0, stored in sealed numbered envelopes (001–160). Envelopes were opened only after patients met inclusion criteria to confirm group assignment. Baseline data (Table 1) showed no significant differences between groups (all p>0.05), confirming valid randomization.

Treatment methods

All four groups of patients received basic treatment, including rest, elevation of the affected limb, cold compresses during the acute phase (within 48 hours), hot compresses during the chronic phase (after 48 hours) and routine rehabilitation guidance (such as active ankle joint movement training and balance training).The routine rehabilitation guidance was implemented in 3 phases based on the recovery process of acute ankle injuries, with simple and operable requirements as follows:

1) Acute inflammation control phase (0-7 days after injury). Core goals: control inflammation, maintain basic activity and prevent muscle atrophy. Specific training: Active ankle joint movement: In a supine position, slowly dorsiflex and depress the toes (plantar flexion), holding each position for 3 seconds. Do 10 sets each time, 3 times a day (once in the morning, once at noon and once in the evening). The initial angle should be painless and you can try to increase it by 1-2° each day. Inversion and eversion movements are prohibited. Calf muscle contraction: In a supine position, force the toes towards the knee (tibialis anterior) and away from the knee (gastrocnemius), tightening for 5 seconds and relaxing for 2 seconds each time. Do 15 sets each time, twice a day (once in the morning and once before bed). The intensity should be such that you can feel the muscles working but without pain. Elevation of the affected limb: Lie supine with the affected limb elevated using a soft pillow, so that the ankle joint is 10-15cm above the heart. Maintain this position for 20 minutes each time, 3 times a day. Slight toe flexion and extension can be used to promote circulation. Stage assessment: Measure ankle circumference (1cm below the lateral malleolus) and VAS score daily; check IL-6 on day 7. If it decreases by more than 30% from baseline, proceed to the next stage. 2) Subacute repair period (8-21 days after injury). Core goals: Restore all-directional mobility, strengthen muscle strength and prepare for weight-bearing. Specific training: All-directional mobility: Wearing an ankle orthosis (KD-AO-02 model), slowly perform dorsiflexion, plantar flexion, inversion and eversion movements while seated. Hold each movement for 3 seconds, 12 sets each time, 3 times a day. Gradually increase the inversion and eversion angles to more than 70% of the healthy side. Resistance band exercises: Using a 10-pound resistance band, perform seated dorsiflexion (band fixed in front) and plantarflexion (band fixed in back) exercises against resistance, 15 repetitions per movement, twice a day (dorsiflexion in the morning, plantarflexion in the afternoon). The resistance band should be adjusted to a level that causes slight muscle soreness after training. Static balance exercises: With hands on a wall, stand on the affected leg and bend the knee of the unaffected leg, raising it. Initially, stand with eyes open for 10 seconds, gradually increasing to 30 seconds; after adaptation, stand with eyes closed for 5 seconds, gradually increasing to 15 seconds, 5 repetitions each time, twice a day. A spotter should be present on the side during training. Phase assessment: Check AOFAS score (target ≥60 points), ankle range of motion (dorsiflexion ≥12°, plantarflexion ≥35°) and IL-6 (target decrease of more than 60% from baseline) every 7 days. 3) Functional recovery period (22-28 days after injury). Core goals: Restore daily activity ability and prevent recurrence. Specific training: Dynamic balance: Slowly squat down on one leg with eyes closed (knee angle ≤30°) and stand up, 8-10 times each time; practice going up and down stairs using a 10cm high step, 10 times each time, twice a day. Keep your knee from buckling inwards when squatting. Assistance is required for stair training. Calf strength: Slowly rise onto your toes while standing (using the affected side), lifting 5cm-8cm off the ground, hold for 3 seconds and then lower. Start with 15 repetitions per set, gradually increasing to 20 repetitions, 2 sets per day. Stretch your calves for 5 minutes after training. Daily simulation: Walk 20 meters in a straight line (maintaining a normal gait), then walk around 5 cones spaced 1 meter apart, twice and once a day, respectively. Wear non-slip shoes and maintain the same stride length as the healthy side. Phase assessment: On day 28, a comprehensive assessment of AOFAS score (target ≥90 points), single-leg standing time with eyes closed (≥20 seconds) and ankle range of motion (consistent with the

healthy side) will be conducted, along with simultaneous liver and kidney function tests.

In addition: 1) *Control group*: received only basic treatment; 2) *Celecoxib group*: basic treatment + celecoxib capsules (Pfizer Pharmaceuticals Co., Ltd., National Drug Approval Number J20140072) orally, 200mg once daily for 7 days, then discontinued (Dongling *et al*., 2025); 3) *Orthosis group*: basic treatment + ankle orthosis (Beijing Kangda Wuzhou Medical Device Center, Beijing Medical Device Registration Certificate 20172150398; Model: KD-AO-02, a semi-rigid lace-up ankle brace with adjustable Velcro straps, classified as medium stiffness (Shore A hardness 65±5, tested via durometer), featuring a lateral malleolus support pad (thickness 3mm, EVA material) and a medial longitudinal arch support to limit excessive inversion/eversion (range of motion restriction: inversion ≤10°, eversion ≤8°) worn for ≥8 hours/day (specifically: 4–6 hours during daytime activities such as walking and standing and 2–4 hours during evening rehabilitation training such as balance exercises; overnight wear was avoided to prevent local pressure injury) for 28 days, with adjustments made to the orthosis tightness based on the reduction of joint swelling (assessed via circumferential measurement of the ankle: 1cm below the lateral malleolus, target tightness allowing insertion of 1 finger between the brace and skin); 4) Synergistic treatment group: basic treatment + oral celecoxib (dosage and administration same as the celecoxib group) + ankle orthosis (dosage and administration same as the orthosis group).

Observation indicators and detection methods

Inflammatory factor level detection

Fasting venous blood (5 mL) was collected from patients before treatment and on treatment days 7, 14 and 28. Serum was isolated by centrifugation (3000 r/min, 10 min), and serum levels of CRP, IL-6,TNF-α and PGE2 were detected via enzyme-linked immunosorbent assay (ELISA).

Pain index assessment

1) Ankle pain was evaluated using the Visual Analogue Scale (VAS) (Dongling *et al*., 2025) at five time points: pre-treatment and 3-, 7-, 14- and 28-days post-treatment. The VAS score ranges from 0 to 10, with 0 representing no pain and 10 indicating severe pain. 2) Tenderness Threshold: The tenderness threshold of the ankle joint tender points was detected using a tenderness meter (Shanghai Taimei Medical Instrument Co., Ltd., TM-Y-100) before treatment, 14 days after treatment and 28 days after treatment. The unit is N. The higher the threshold, the stronger the pain tolerance.

Ankle function assessment

Ankle function was evaluated via the Ankle-Hindfoot Rating System developed by the AOFAS (Guangxin *et al*., 2025) at three time points: pre-treatment, 14 days into treatment and 28 days into treatment. This system assesses three aspects—pain (40 points), function (50 points) and alignment (10 points)—with a total score of 100; higher scores correspond to better ankle function. Additionally, a goniometer was used to measure ankle range of motion (including dorsiflexion and plantar flexion angles), while balance function was evaluated via the single-leg standing test (recorded as single-leg standing time in seconds).

Stratified analysis and correlation analysis

Stratified analysis was performed according to the side of injury (left, right) and injury type (inversion, eversion) to compare the differences in the efficacy of synergistic treatment among different subgroups. Pearson correlation analysis was used to explore the correlation between inflammatory markers, pain markers and ankle function recovery. Multiple linear regression analysis was used to screen for independent influencing factors on ankle function recovery.

Safety assessment

The occurrence of adverse reactions in the four groups of patients during treatment was recorded (such as gastrointestinal discomfort, dizziness, skin itching, discomfort when wearing orthotics, etc.) and liver and kidney function indicators (alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (Scr)) were measured on day 28 of treatment.

Statistical analysis

Statistical analysis was conducted with SPSS 26.0: quantitative data (mean ± SD) were analyzed via repeated measures analysis of variance(ANOVA), one-way ANOVA and least significant difference (LSD)-t test; categorical data (rates) via χ^2 test; correlations and influencing factors via Pearson correlation and multiple linear regression, with $p < 0.05$ as statistically significant.

RESULTS

Comparison of changes in inflammatory factor levels in the four groups

Before treatment, serum CRP, IL-6, TNF-α and PGE2 levels were comparable among the four groups ($p>0.05$). After treatment, the combined group had the lowest levels of these factors at 7, 14 and 28 days ($p<0.05$, vs. other three groups) and appronched normal by day 28; the celecoxib group was lower than the control and orthosis groups but higher than the combined group ($p<0.05$), with a slight post-withdrawal increase at day 14 ($p>0.05$ vs. orthosis group). Detailed data are shown in table 2.

Pre-treatment inflammatory factor levels were comparable among four groups ($p>0.05$). Post-treatment, the combined group had the lowest levels at all time points ($p<0.05$) and approached normal by day 28; the celecoxib group was superior to control/orthosis groups but inferior to combined group ($p<0.05$), with slight post-withdrawal increase on day 14.

Table 2: Comparison of changes in inflammatory factor levels before and after treatment in the four groups ($\bar{x}$±s)

Index	Group	Before treatment	Treatment for 7 days	Treatment for 14 days	Treatment for 28 days
CRP (mg/L)	Control group	18.6±4.2	15.3±3.8	11.2±3.1	6.8±2.0
	Celecoxib group	18.3±4.0	9.5±2.6*	8.7±2.4*	5.2±1.8*
	Orthopedic group	18.8±4.3	14.8±3.6	10.9±3.0	6.5±1.9
	Collaborative treatment group	18.5±4.1	6.2±2.1*#≥	4.3±1.5*#≥	2.1±0.9*#≥
IL-6 (pg/mL)	Control group	58.3±12.5	49.6±10.8	38.7±9.2	25.4±7.1
	Celecoxib group	57.9±12.3	32.5±8.6*	29.8±8.1*	18.6±6.3*
	Orthopedic group	58.5±12.6	48.2±10.5	37.5±9.0	24.8±7.0
	Collaborative treatment group	58.1±12.4	20.3±6.5*#≥	12.5±4.3*#≥	7.8±3.2*#≥
TNF-α (pg/mL)	Control group	32.5±7.3	28.6±6.8	22.4±5.9	15.8±4.6
	Celecoxib group	32.1±7.1	19.8±5.4*	17.6±5.1*	12.3±4.0*
	Orthopedic group	32.7±7.4	27.9±6.6	21.8±5.7	15.2±4.5
	Collaborative treatment group	32.3±7.2	13.5±4.2*#≥	9.8±3.5*#≥	5.6±2.3*#≥
PGE2 (pg/mL)	Control group	125.6±28.3	108.5±25.6	89.7±22.4	65.4±18.7
	Celecoxib group	124.8±28.1	75.3±20.5*	68.9±19.8*	52.6±17.3*
	Orthopedic group	126.1±28.4	105.8±25.3	87.5±22.1	63.8±18.5
	Collaborative treatment group	125.2±28.2	48.6±15.3*#≥	32.5±12.4*#≥	20.8±9.6*#≥

Note: * indicates $p<0.05$ compared with the control group at the same time point; # indicates $p<0.05$ compared with the celecoxib group at the same time point; ≥ indicates $p<0.05$ compared with the orthotic group at the same time point.

Table 3: Comparison of changes in pain indicators before and after treatment in the four groups ($\bar{x}$±s)

Index	Group	Before treatment	Treatment for 3 days	Treatment for 7 days	Treatment for 14 days	Treatment for 28 days
VAS score (points)	Control group	7.8±1.2	6.5±1.0	5.2±0.9	3.8±0.8	2.5±0.6
	Celecoxib group	7.7±1.1	4.8±0.9*	3.5±0.8*	2.6±0.7*	1.8±0.5*
	Orthopedic group	7.9±1.2	6.3±1.0	5.0±0.9	3.6±0.8	2.3±0.6
	Collaborative treatment group	7.8±1.1	4.1±0.9*#	2.3±0.7*#≥	1.5±0.5*#≥	1.0±0.4*#≥
Tenderness threshold （N）	Control group	2.1±0.6	-	-	3.2±0.8	4.1±1.0
	Celecoxib group	2.0±0.6	-	-	4.0±0.9*	4.9±1.1*
	Orthopedic group	2.2±0.6	-	-	3.1±0.8	4.0±1.0
	Collaborative treatment group	2.1±0.6	-	-	5.1±1.0*#≥	5.8±1.2*#≥

Note: Compared with the control group at the same time point, *$p<0.05$; compared with the celecoxib group at the same time point, #$p<0.05$; compared with the orthotic group at the same time point, ≥$p<0.05$.

Comparison of changes in pain indicators among four groups

Before treatment, the four groups had comparable pain indicators ($p>0.05$). After treatment, the combined group had the most significant pain relief at each time point ($p<0.05$ vs. the other three groups); the celecoxib group was better than the control and orthosis groups ($p<0.05$), with mild pain rebound after drug withdrawal. See Table 3 for detailed data.

Comparison of changes in ankle function indicators among four groups

Pre-treatment, the four groups showed no significant differences in AOFAS score, ankle range of motion and single-leg standing time ($p>0.05$), with good comparability.Pre-treatment inflammatory factor levels were comparable among four groups ($p>0.05$). Post-treatment, the combined group had the lowest levels at all time points ($p<0.05$) and approached normal by day 28; the celecoxib group was superior to control/orthosis groups but inferior to combined group ($p<0.05$), with slight post-withdrawal increase on day 14.After 14 days of treatment, all functional indicators in all four groups improved compared to before treatment, but the improvement in the synergistic treatment group was significantly greater than that in the other three groups ($p<0.05$): the AOFAS score in the synergistic treatment group reached 78.6±6.2 points, an increase of 34.4% compared to the control group (58.5±6.0 points); the ankle dorsiflexion angle reached 14.5±3.1°, an increase of 42.2% compared to the orthosis group (10.2±2.4°); and the single-leg standing time reached 32.7±7.1s, an increase of 46.6% compared to the celecoxib group (22.3±5.8s). At day 28 of treatment, the functional indicators in the synergistic treatment group reached their peak, with the AOFAS score (94.5±3.7 points) approaching the full score. Ankle dorsiflexion (18.6±3.2°), plantar flexion (42.2±4.4°) and single-leg standing time (45.6±8.5s) all returned to normal levels for

Table 4: Comparison of changes in ankle joint functional indicators before and after treatment in the four groups ($\bar{x}$±s)

Index	Group	Before treatment	Treatment for 14 days	Treatment for 28 days
AOFAS score (points)	control group	43.2±5.6	58.5±6.0	76.2±5.8
	Celecoxib group	42.8±5.9	65.2±6.4	85.6±6.1
	Orthopedic group	43.5±5.7	63.7±6.3	83.1±5.9
	Collaborative treatment group	42.9±5.8	78.6±6.2*#≥	94.5±3.7*#≥
Back extension angle (°)	control group	6.2±2.1	9.4±2.5	13.1±2.6
	Celecoxib group	6.0±2.0	10.7±2.6	15.5±2.8
	Orthopedic group	6.3±2.2	10.2±2.4	14.4±2.9
	Collaborative treatment group	6.1±2.1	14.5±3.1*#≥	18.6±3.2*#≥
Plantar flexion angle (°)	control group	25.3±3.6	29.7±3.8	35.5±4.0
	Celecoxib group	25.1±3.5	31.2±3.6	38.6±4.2*
	Orthopedic group	25.5±3.7	30.5±3.7	37.2±4.1
	Collaborative treatment group	25.2±3.6	36.8±4.0*#≥	42.2±4.4*#≥
Standing time on one leg (s)	control group	12.5±3.2	18.6±4.1	25.3±5.2
	Celecoxib group	12.3±3.1	22.3±5.8	32.6±6.3*
	Orthopedic group	12.6±3.3	21.5±5.6	30.8±6.1
	Collaborative treatment group	12.4±3.2	32.7±7.1*#≥	45.6±8.5*#≥

Note: Compared with the control group at the same time point, *p<0.05; compared with the celecoxib group at the same time point, #p<0.05; compared with the orthotic group at the same time point, ≥p<0.05.

Table 5: Comparison of liver and kidney function indicators in the four groups after 28 days of treatment ($\bar{x}$±s)

Index	control group (n=40)	Celecoxib group (n=40)	Orthopedic group (n=40)	Collaborative treatment group (n=40)	F value	p
ALT (U/L)	28.6±6.3	30.2±6.8	27.9±6.1	29.5±6.5	0.872	0.457
AST (U/L)	26.3±5.9	27.8±6.2	25.7±5.7	26.9±6.0	0.654	0.582
BUN (mmol/L)	5.2±1.1	5.4±1.2	5.1±1.0	5.3±1.1	0.521	0.668
Scr (μmol/L)	78.5±10.3	80.2±10.8	77.9±10.1	79.3±10.5	0.436	0.728

healthy individuals. Although the celecoxib group and the orthosis group showed continued improvement, all indicators remained significantly lower than those in the synergistic treatment group (p<0.05). The control group showed the smallest improvement and the worst functional recovery. Detailed data are shown in table 4.

Stratified and correlation analysis results

Stratified analysis by injury side showed that in the left-sided injury subgroup, the AOFAS score of the synergistic treatment group at 28 days of treatment (94.2±3.8 points) was significantly higher than the other three groups (p<0.05). In the right-sided injury subgroup, the AOFAS score of the synergistic treatment group (94.7±3.6 points) was also significantly better than the other three groups (p<0.05), but the improvement in AOFAS score of the synergistic treatment group in the left-sided injury subgroup was greater than that in the right-sided subgroup and the difference was statistically significant (p<0.05). Stratified analysis by injury type showed that the AOFAS scores of the varus injury subgroup (94.3±3.7 points) and the valgus injury subgroup (94.6±3.8 points) were significantly higher than those of other treatment methods in their respective subgroups (p<0.05), while the injury type had no significant effect on the efficacy of synergistic treatment (p>0.05). Pearson correlation analysis showed that at 28 days of treatment, the AOFAS score was significantly negatively correlated with CRP (r=-0.782, p<0.001), IL-6 (r=-0.815, p<0.001), TNF-α (r=-0.763, p<0.001), PGE2 (r=-0.796, p<0.001) and VAS score (r=-0.832, p<0.001) and significantly positively correlated with the tenderness threshold (r=0.805, p<0.001).

Results of multiple linear regression analysis

Multiple linear regression analysis was performed using the AOFAS score at 28 days of treatment as the dependent variable and celecoxib administration (yes=1, no=0), orthotic wearing (yes=1, no=0), IL-6 level at 7 days of treatment, VAS score at 7 days of treatment, age, side of injury (left=1, right=0) and injury type (inversion=1, eversion=0) as independent variables. The results showed that celecoxib administration (β=0.289, p<0.001), orthotic wearing (β=0.312, p<0.001) and IL-6 level at 7 days of treatment (β=-0.285, p<0.001) were independent influencing factors for ankle joint function recovery (R^2=0.768, F=89.362, p<0.001).

Safety assessment results

No serious adverse reactions occurred in any of the four groups during the treatment period. In the control group, 1

patient (2.5%) experienced gastrointestinal discomfort; in the celecoxib group, 3 patients (7.5%) experienced gastrointestinal discomfort and 1 patient (2.5%) experienced dizziness, with a total incidence of 10.0%; in the orthosis group, 2 patients (5.0%) experienced orthosis discomfort(One case of tenderness was found on the lateral side of the ankle joint, characterized by local skin tenderness, VAS score of 1-3 and mild pain; another case of skin lesion was found on the heel, which was a mild epidermal abrasion with an area of <1cm², with only epidermal detachment and no bleeding or exudation.); and in the combined treatment group, 2 patients (5.0%) experienced gastrointestinal discomfort and 1 patient (2.5%) experienced orthosis discomfort (One case of tenderness was found on the dorsum of the foot, without skin discoloration or swelling, VAS score of 1-3, with mild pain.), with a total incidence of 7.5%. There was no statistically significant difference in the total incidence of adverse reactions among the four groups (χ^2=2.136, p=0.545). At 28 days of treatment, liver and kidney function indicators (ALT, AST, BUN, Scr) in all four groups were within the normal range and there were no statistically significant differences between the groups (p>0.05). Detailed data are shown in table 5.

DISCUSSION

Core pharmacological mechanism of celecoxib

Celecoxib, as a highly selective COX-2 inhibitor, exhibits clear molecular target specificity in its pharmacological effects (Youtian *et al*., 2025). Human cyclooxygenase has two subtypes: cyclooxygenase-1(COX-1)(constitutively expressed, mainly regulating gastric mucosal protection, platelet aggregation and other physiological functions) and COX-2 (inducible enzyme, low expression in normal tissues).When the body experiences trauma or inflammation, it is activated by upstream inflammatory signals such as interleukin-1(IL-1) and TNF-α, resulting in high expression and catalysis of arachidonic acid conversion to prostaglandins (PGs). Among these, PGE2 is a key mediator of inflammatory responses and pain perception (Anning *et al*., 2025; Ping *et al*., 2022).

Celecoxib specifically blocks the catalytic activity of COX-2 by binding to amino acid residues in the active site of the enzyme, inhibiting PGE2 synthesis at its source, thereby blocking the initiation and amplification of the inflammatory cascade (Ghadeer AbouBakr A *et al*., 2025). Furthermore, celecoxib can reduce the transcription and release of pro-inflammatory factors such as IL-6 and TNF-α by inhibiting the activation of the nuclear factor-κB (NF-κB) pathway, while downregulating the infiltration of inflammatory cells (such as neutrophils and macrophages), further alleviating local inflammatory responses (Arash *et al*., 2024; Qijun and Yi, 2024). Its high selectivity results in a weak inhibitory effect on COX-1, which is the core reason why its incidence of gastrointestinal adverse reactions is lower than that of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) (JingLan L, 2025).

Complementary mechanisms and outcome correlation of synergistic therapy

The results of this study clearly correspond to the pharmacological mechanism of celecoxib and the biomechanical effects of foot and ankle orthoses. The advantage of synergistic therapy stems from the precise complementarity of their mechanisms of action.

From the perspective of inflammation control, after 7 days of treatment, the levels of CRP, IL-6, TNF-α and PGE2 in both the celecoxib group and the synergistic therapy group significantly decreased, with a greater decrease in the synergistic therapy group. This result directly confirms the targeted anti-inflammatory effect of celecoxib. After 14 days of treatment, inflammatory factors slightly increased in the celecoxib group due to drug discontinuation, while they continued to decrease in the synergistic treatment group. This indicates that the ankle orthosis, by limiting abnormal ankle joint movement, reduced secondary traction injury to the damaged ligaments, avoiding the re-release of inflammatory factors induced by mechanical stimulation, thus forming a sustained synergistic effect with the pharmacological anti-inflammatory effect of celecoxib. The interaction between the two not only inhibited the COX-2/PGE2 pathway-mediated inflammatory response but also reduced the physical triggers for inflammation through biomechanical stability, achieving a dual effect of "chemical anti-inflammatory + mechanical anti-inflammatory."

The pain relief results were highly consistent with the trend of inflammatory factor changes, further confirming the correlation between the pharmacological mechanism and clinical efficacy. Celecoxib, by inhibiting PGE2 synthesis, reduced the stimulation of nerve endings by pain mediators and simultaneously decreased the pain sensitivity of dorsal horn neurons in the spinal cord, exerting a dual analgesic effect on both the central and peripheral systems (Zhongwen *et al*., 2025). The ankle orthosis, by dispersing pressure on the injured site through external support, reduced the mechanical pain signal transmission caused by ligament traction. Synergistically, this, combined with the pharmacological analgesic effect of celecoxib, resulted in a significantly lower VAS score in the synergistic treatment group compared to other groups after 3 days of treatment and this advantage persisted. By day 28 of treatment, the VAS score had decreased to 1.0 ± 0.4 points, meeting the clinical pain relief criteria.

The excellent recovery of ankle joint function is the ultimate manifestation of the complementary mechanisms of the synergistic treatment. Celecoxib, through rapid anti-inflammatory and analgesic effects, created conditions for early rehabilitation training, avoiding joint mobility limitations and muscle disuse atrophy caused by pain; the

ankle orthosis, by maintaining ankle joint biomechanical stability, provided a suitable biomechanical environment for the repair of injured ligaments, promoting the orderly regeneration and remodeling of ligament collagen fibers (Shan *et al*., 2025; Mingli and Xiaodong, 2024). Multiple linear regression analysis showed that IL-6 levels at 7 days of celecoxib administration, orthotic wear and treatment were independent influencing factors for functional recovery. As a key pro-inflammatory factor, the early decrease in IL-6 directly reflected the intensity of celecoxib's pharmacological effects, further confirming the direct link between pharmacological mechanisms and functional recovery. Stratified analysis showed that patients with left-sided injuries benefited more significantly from synergistic therapy, possibly related to differences in nerve innervation and movement habits between the two sides of the body. The left limb may rely on more complex neuromuscular coordination in balance control and fine motor regulation. Synergistic therapy, through the dual protection of anti-inflammatory analgesia and biomechanical stability, more effectively restored the neuromuscular regulatory function of the left ankle joint. This result provides a reference for precision clinical treatment.

Pharmacological interpretation of safety results

The incidence of adverse reactions did not differ significantly among the four groups and liver and kidney function indicators were all within the normal range, demonstrating the good safety of the combined therapy. The incidence of gastrointestinal discomfort was slightly higher in the celecoxib group, but no serious reactions occurred. This is closely related to its highly selective COX-2 inhibitory properties-the weak inhibition of COX-1 reduces the impact on prostaglandin synthesis in the gastric mucosa, thus lowering the risk of mucosal damage (Junhong W *et al*., 2024). The incidence of discomfort with the orthosis was low and tolerable after adjustment, indicating good biocompatibility and fit. It did not induce additional tissue damage or inflammatory reactions, synergistically with the pharmacological safety of celecoxib, ensuring the clinical applicability of the combined therapy.

Limitations and future directions

This study has certain limitations: the sample size was only 160 cases and it was a single-center study, which may have selection bias; the follow-up period was only 28 days and the long-term efficacy and preventive effect on chronic ankle instability need further observation; the molecular mechanism of the combined treatment on ligament repair was not explored in depth. Future studies can further verify the effects of celecoxib on ligament fibroblast proliferation and collagen synthesis, as well as the molecular interaction mechanism with the biomechanical action of foot and ankle orthoses, through animal experiments or histological studies.

CONCLUSION

Celecoxib combined with foot and ankle orthoses for the treatment of acute ankle injuries, through the COX-2/PGE2 pathway-targeted anti-inflammatory and analgesic effects of celecoxib, complements the biomechanical stabilizing effect of foot and ankle orthoses, significantly inhibiting the release of inflammatory factors(CRP, IL-6, TNF-α, PGE2), rapidly relieving pain, accelerating ankle joint function recovery and with good safety. Patients with left-sided injuries benefited more significantly from this combined treatment regimen and the type of injury had no significant impact on the efficacy. Celecoxib administration, orthoses and IL-6 levels at 7 days of treatment were independent influencing factors on ankle joint function recovery. This combined treatment regimen has high clinical application value and can be considered a preferred treatment strategy for acute ankle injuries, especially suitable for patients with left-sided injuries.

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Author's contributions

Qilong Hu was responsible for planning and writing this paper; Dan Hu was responsible for data collection and analysis; Fengxi Qiu was responsible for data processing; and Shaodan Cheng was responsible for the conceptualization of this study.

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Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by the Ethics Committee of Shanghai Yangzhi Rehabilitation Hospital (approval number: LL20240316).

Conflict of interest

The authors declare no conflicts of interest.

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