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Original Article

Pregabalin plus celecoxib for knee osteoarthritis: impact on pain, knee function recovery, and inflammatory biomarkers

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Abstract: Objective: Focusing on knee osteoarthritis (KOA) patients, we explore the impact of pregabalin plus celecoxib on patients' pain, knee function recovery, and inflammatory biomarkers. This was a retrospective study. Methods: Firstly, 116 KOA patients were selected and grouped into a control group (n=55) receiving celecoxib and a research group (n=61) receiving pregabalin+celecoxib. Comparative inter-group analyses covered curative effects, Visual Analogue Scale (VAS), American Knee Society Knee Score (AKSS), serum inflammatory biomarkers, Pittsburgh Sleep Quality Index (PSQI), and adverse events. Subsequently, we explored therapeutic response-associated determinants. Results: The data indicated higher overall efficacy in the research group versus the control group. Pregabalin+celecoxib therapy also led to greater reductions in VAS scores, inflammatory biomarker levels, and each PSQI domain score than celecoxib alone, together with a more pronounced increase in AKSS scores across all dimensions. Similar total adverse events were found between the treatments. Finally, tumor necrosis factor (TNF)-α and treatment modality were factors independently influencing curative efficacy. Conclusion: Pregabalin+celecoxib therapy is definitely effective for KOA treatment. High TNF-α (≥110 μg/L) and sole celecoxib use increase the risk of ineffective treatment in KOA patients.

Keywords: Pregabalin, celecoxib, knee osteoarthritis, pain, knee function recovery, inflammatory biomarker

Introduction

As a chronic disabling disease affecting the whole knee joint, knee osteoarthritis (KOA) is influenced by age, weight, gender, and educational level [1]. Clinical presentations typically encompass pain, knee joint deformity, activity limitation, and even disability, which adversely influence patients' life quality [2]. According to statistics, KOA exhibited a higher prevalence in females than in males (1.81:1), with the incidence peaking in the >60 age group (19.4%) [3]. Pathogenetically, it involves abnormal variations in collagen and proteoglycan structures and meniscus structure degeneration, culminating in meniscus injury and articular cartilage erosion [4]. Moreover, inflammation is a vital mechanism underlying early joint injury in KOA. Inflammatory mediators trigger chondrocyte hypertrophy and matrix metabolism imbalance, leading to progressive degradation of the articular cartilage and its spread to the synovium and subchondral bone, thereby promoting KOA progression [5]. KOA can be treated either non-pharmaceutically or pharmaceutically, but the curative effect is limited and it can be accompanied by potential side effects [6]. It is thus essential to explore novel therapies for treatment optimization.

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has been widely used in KOA treatment due to its anti-inflammatory and analgesic actions [7]. Its application to KOA treatment has been indicated to help relieve pain and improve physical function compared to placebo and some traditional non-steroidal anti-inflammatory drugs, on the premise of ensuring certain clinical safety [8]. Though effective in short-term symptom control by inhibiting inflammation and pain signals, the safety and efficacy of its long-term application need optimization [9].

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Being a structural analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), pregabalin suppresses voltage-dependent calcium channels in the peripheral and central nervous system to exert a significant anti-pain sensitization role [10]. As indicated in a systematic review and meta-analysis, it shows utility in chronic neuropathic pain mitigation following total hip and knee replacement while also reducing opioid dependence and demonstrating acceptable tolerability and safety [11].

Studies examining the role of pregabalin plus celecoxib in pain, knee joint function recovery, and inflammatory biomarkers in KOA treatment is rare. This study takes this as the research direction, aiming at providing more viable treatment for KOA patients.

Information and methodology

Patient information

Inclusion criteria: Meeting the KOA diagnostic criteria [12] with single-knee onset; adhering to the Kellgren-Lawrence (K-L) imaging classification standard of osteoarthritis (Grade 0: no change (normal); Grade I: suspicious osteophyte and suspicious joint space narrowing; Grade II: obvious osteophyte and suspicious joint space narrowing; Grade III: moderate osteophyte, definite joint space narrowing and sclerosing changes; Grade IV: massive osteophytes, obvious joint space narrowing, severe sclerosing lesions, and obvious deformities) [13]; no recent glucocorticoid use; no knee joint tumor, tuberculosis, or suppurative infection; complete clinical data. Exclusion criteria: allergies to pregabalin or celecoxib; presence of systemic inflammation or autoimmune diseases; conditions (e.g., acute trauma, metabolic osteopathy) affecting the knee joint; concurrent vital organ dysfunction; mental disorders; rheumatoid arthritis or meniscus injury; previous bone/joint surgeries; pregnant or lactating women. This was a retrospective study. This research has been approved by the Ethics Committee of Puyang People's Hospital. This study enrolled 116 KOA patients admitted between April 2022 and April 2025 after strict screening based on the above selection criteria. Grouping was performed based on the actual treatment plan received: 55 patients comprised the control group, treated with celecoxib; 61 patients constituted the research group, who were managed via pregabalin+celecoxib therapy. The groups were clinically comparable without any statistical differences in general information ($P>0.05$). The diagnostic criteria for KOA are detailed below: (1) repeated knee pain in the past month; (2) X-rays (standing or weight-bearing position) indicating joint space narrowing, subchondral sclerosis and/or cystic degeneration, and osteophyte formation at the joint margin; (3) clear and viscous synovial fluid (at least two samplings) and leukocyte count <2,000/mL; (4) middle-aged and elderly people (≥40 years); (5) morning stiffness for 30 minutes; (6) bony crepitus (sensation) of the joint during movement. KOA is diagnosed if the patient meets the conditions of either 1+2 or 1+3+5+6 or 1+4+5+6.

Methods

The control group was treated with oral celecoxib. Celecoxib capsules (200 mg) were administered once a day. The research group was additionally given pregabalin per os. The drug was taken once daily at 75 mg. According to patient response and tolerability, the dose could be increased to 300 mg/d within one week. The maintenance dose was 75-150 mg/time, twice/day. An eight-week treatment cycle was implemented for all patients.

Endpoints

Efficacy [14]. Criteria for efficacy judgment: Marked effectiveness is characterized by no knee pain/swelling, occasional pain during activity, no pain during walking, and no influence on work. Improvement corresponds to occasional knee pain, mild pain when walking, and certain restriction of the knee joint. No improvement or worsening in the patient's condition is judged as ineffectiveness. Overall effective rate = (markedly effective cases+improved cases)/total case number.

Pain intensity [15]. We used the Visual Analogue Scale (VAS) to evaluate knee joint pain severity before and after (1, 4, and 8 weeks) treatment. With a maximum of 10 points, the score correlates positively with the knee joint pain intensity.

Knee function recovery [16]. Using the American Knee Society Knee Score (AKSS), patients' knee function recovery was assessed across

Table 1. Comparative analysis of baseline data

Indicators	Control group (n=55)	Research group (n=61)	χ^2/t	P
Sex			0.109	0.741
Male	20 (36.36)	24 (39.34)		
Female	35 (63.64)	37 (60.66)		
Age (years)	60.65±5.85	61.13±6.04	0.434	0.665
Disease duration (months)	29.27±8.09	27.33±10.07	1.136	0.258
Lesion site			0.422	0.516
Left knee	24 (43.64)	23 (37.70)		
Right knee	31 (56.36)	38 (62.30)		
K-L classification			1.481	0.224
I-II	35 (63.64)	32 (52.46)		
III-IV	20 (36.36)	29 (47.54)		
Educational level			0.131	0.717
< senior high school	27 (49.09)	32 (52.46)		
≥ senior high school	28 (50.91)	29 (47.54)		

pain (0-50 points), joint range of motion (0-25 points), stability (0-25 points), walking (0-50 points), and stair climbing (0-50 points) dimensions. The score (maximum: 200) is proportional to the functional recovery.

Serum inflammatory biomarkers. All patients provided peripheral venous blood draws (3 mL) on an empty stomach, both before and after treatment. Serum separated via centrifugation was measured by enzyme-linked immunosorbent assay (ELISA) for vascular endothelial growth factor (VEGF), interleukin (IL)-1β, and tumor necrosis factor (TNF)-α contents.

Sleep quality [17]. Patients underwent sleep quality evaluation pre- and post-therapy, utilizing the Pittsburgh Sleep Quality Index Scale (PSQI) from sleep duration, sleep latency, sleep disturbances, and sleep quality domains. Each dimension scores 0-3 and demonstrates a negative correlation with sleep quality.

Incidence rate of adverse events. This study documented the cases of vomiting, nausea, and dizziness in both patient groups.

Statistical analysis

Counting data were shown as case number/percentage (n/%), with between-group comparisons made by the χ^2 test. For measurement data, the normality test was conducted using the Shapiro-Wilk method. The mean ± Standard Deviation (SD) was used for the statistical description of normally distributed data, whose between-group and within-group comparisons employed the t-test and the paired t-test, respectively; if not normally distributed, the data were presented as the median (interquartile range) [M(Q1, Q3)] and analyzed by the Mann-Whitney U test for between-group differences. All statistical analyses were performed with SPSS 20.0. To pinpoint efficacy determinants in KOA patients, univariate and multivariate Logistic regression were carried out. $P<0.05$ indicated the presence of statistical significance.

Results

Comparative analysis of baseline data

The inter-group of baseline data (**Table 1**) showed no marked inter-group differences in sex, age, disease duration, lesion site, K-L classification, and educational level ($P>0.05$).

Comparative analysis of therapeutic effectiveness

Curative effect analysis (**Table 2**) revealed a total effective rate of 91.80% in the research group, higher compared to 72.73% in the control group ($P=0.007$).

Comparative pain assessment

VAS-pain severity analysis (**Table 3**) determined similar baseline VAS scores between the groups ($P>0.05$). At the 1st, 4th, and 8th week post-treatment, the VAS scores decreased

Table 2. Comparative analysis of therapeutic effectiveness

Indicators	Control group (n=55)	Research group (n=61)	χ^2	P
Marked effectiveness	20 (36.36)	30 (49.18)		
Improvement	20 (36.36)	26 (42.62)		
Ineffectiveness	15 (27.27)	5 (8.20)		
Overall effectiveness	40 (72.73)	56 (91.80)	7.376	0.007

Table 3. Comparative analysis of VAS

Indicators	Control group (n=55)	Research group (n=61)	Z	P
Pre-treatment	7.00 (6.00, 8.00)	7.00 (6.00, 8.50)	-0.446	0.656
1 week post-treatment	5.00 (4.00, 7.00)	5.00 (4.00, 5.00)	-2.434	0.015
4 weeks post-treatment	3.00 (2.00, 4.00)	3.00 (2.00, 3.00)	-3.592	<0.001
8 weeks post-treatment	2.00 (2.00, 3.00)	1.00 (1.00, 2.00)	-4.912	<0.001

Note: VAS, Visual Analogue Scale.

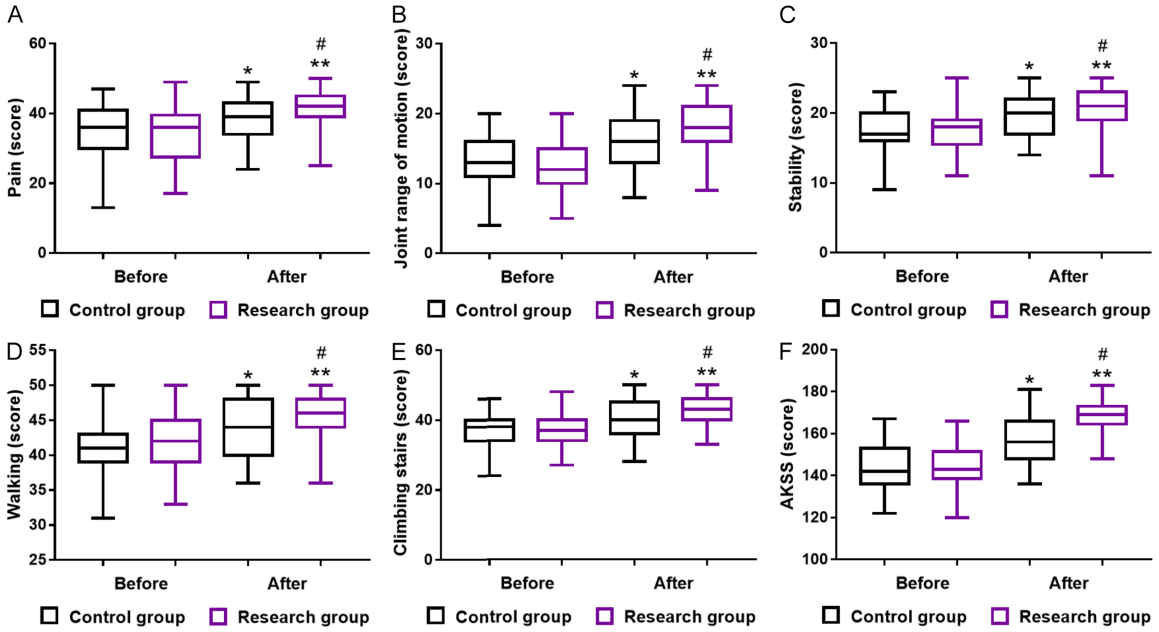

Figure 1. Comparative analysis of knee joint function recovery. A. Pre- and post-treatment pain scores. B. Joint range of motion scores pre- and post-treatment. C. Stability scores before and after treatment. D. Pre- and post-treatment walking scores. E. Pre- and post-treatment stair climbing scores. F. Pre- and post-treatment AKSS scores. Note: *P<0.05, **P<0.01 (within-group comparison vs. pre-treatment); #P<0.05 (between-group comparison vs. control group). AKSS, American Knee Society Knee Score.

notably in both cohorts, with even lower scores in the research group versus the control across all assessed time points (P<0.01).

Comparative analysis of knee function recovery

According to AKSS measurement (**Figure 1**), the two groups differed little in pre-treatment AKSS scores in various dimensions (P>0.05). A post-treatment elevation in pain, joint range of motion, stability, walking, and stair climbing domains was noted in both cohorts (P<0.05), with higher AKSS scores in the research group (across dimensions and the global scale) versus controls (P<0.05).

Comparison of serum inflammatory biomarkers

This study measured serum inflammatory biomarkers by ELISA, with the results visualized in

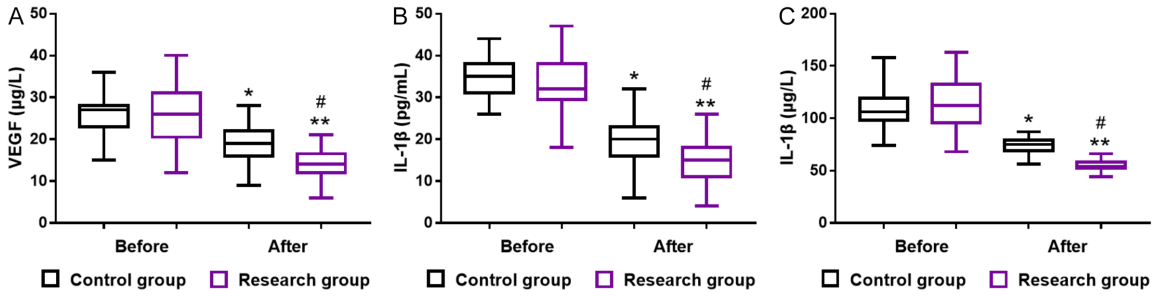

Figure 2. Comparative analysis of serum inflammatory indicators. A. VEGF levels before and after treatment. B. Pre- and post-treatment IL-1β levels. C. TNF-α alterations before and after treatment. Note: *P<0.05, **P<0.01 (within-group comparison vs. pre-treatment); #P<0.05 (between-group comparison vs. control group). VEGF, vascular endothelial growth factor; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-alpha.

Table 4. Comparative analysis of sleep quality

Indicators	Control group (n=55)	Research group (n=61)	Z	P
Sleep duration (points)				
Before	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	-0.172	0.864
After	1.00 (1.00, 2.00)	1.00 (0.00, 1.00)	-2.566	0.010
Sleep latency (points)				
Before	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	-0.995	0.320
After	1.00 (1.00, 1.00)	1.00 (0.00, 1.00)	-3.607	<0.001
Sleep disturbances (points)				
Before	2.00 (1.00, 2.00)	1.00 (1.00, 2.00)	-1.605	0.287
After	1.00 (1.00, 1.00)	1.00 (0.50, 1.00)	-2.741	0.006
Sleep quality (points)				
Before	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	-1.521	0.128
After	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	-2.122	0.034

Table 5. Comparative analysis of the incidence of adverse events

Indicators	Control group (n=55)	Research group (n=61)	χ^2	P
Vomiting	1 (1.82)	2 (3.28)		
Nausea	1 (1.82)	3 (4.92)		
Dizziness	3 (5.45)	2 (3.28)		
Total	5 (9.09)	7 (11.48)	0.595	0.766

Figure 2. VEGF, IL-1β, and TNF-α were comparable at baseline (P>0.05); all these indices exhibited a dramatic reduction after treatment (P<0.05), demonstrating lower levels in the research group compared to the control group (P<0.05).

Comparative sleep quality assessment

As shown in **Table 4**, patients' sleep quality was evaluated in four dimensions by PSQI. All dimensions, while comparable between groups prior to treatment (P>0.05), decreased post-treatment (P<0.05), with a greater amplitude of reduction in the research group (P<0.05).

Adverse event comparison

We monitored the occurrence of vomiting, nausea, and dizziness across the groups, with the results summarized in **Table 5**. No marked difference was identified between the research and control groups in the total incidence of adverse events (11.48% vs. 9.09%; P>0.05).

Analysis of efficacy-associated determinants in KOA patients

Through univariate analysis (**Table 6**), we identified gender, age, disease duration, lesion site, K-L classification, educational level, and several scale scores (VAS, AKSS, and VEGF) as factors non-significantly related to curative effica-

Table 6. Factors influencing KOA patients' curative effects (univariate analysis)

Indicators	Ineffective group (n=20)	Effective group (n=96)	χ^2	P
Sex			0.044	0.834
Male	8 (40.00)	36 (37.50)		
Female	12 (60.00)	60 (62.50)		
Age (years)			0.075	0.784
<60	9 (45.00)	40 (41.67)		
≥60	11 (55.00)	56 (58.33)		
Disease duration (months)			0.023	0.879
<30	11 (55.00)	51 (53.13)		
≥30	9 (45.00)	45 (46.88)		
Lesion location			3.806	0.051
Left knee	12 (60.00)	35 (36.46)		
Right knee	8 (40.00)	61 (63.54)		
K-L classification			1.612	0.204
I-II 67	9 (45.00)	58 (60.42)		
III-IV 49	11 (55.00)	38 (39.58)		
Educational level			0.007	0.932
< senior high school	10 (50.00)	49 (51.04)		
≥ senior high school	10 (50.00)	47 (48.96)		
VAS (points)			0.660	0.416
<7	5 (25.00)	33 (34.38)		
≥7	15 (75.00)	63 (65.63)		
AKSS (points)			1.913	0.167
<145	14 (70.00)	51 (53.13)		
≥145	6 (30.00)	45 (46.88)		
VEGF (μg/L)			0.405	0.524
<25	7 (35.00)	41 (42.71)		
≥25	13 (65.00)	55 (57.29)		
IL-1β (pg/mL)			4.945	0.026
<35	6 (30.00)	55 (57.29)		
≥35	14 (70.00)	41 (42.71)		
TNF-α (μg/L)			4.208	0.040
<110	6 (30.00)	53 (55.21)		
≥110	14 (70.00)	43 (44.79)		
Treatment modality			7.376	0.007
Pregabalin+celecoxib	5 (25.00)	56 (58.33)		
Celecoxib	15 (75.00)	40 (41.67)		

Note: KOA, knee osteoarthritis; VAS, Visual Analogue Scale; AKSS, American Knee Society Knee Score; VEGF, vascular endothelial growth factor; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-alpha.

cy (P>0.05). However, IL-1β, TNF-α, and treatment modality all showed a significant relationship with curative effects (P<0.05).

Through further mining by multivariate analysis (**Table 7**), IL-1β lost significance (P>0.05), while TNF-α (≥110 μg/L) and single celecoxib use were confirmed as independent risk factors (P<0.05).

Discussion

KOA is pathologically characterized by articular cartilage degeneration, subchondral bone disease, and synovitis. The disease primarily manifests as knee pain and tenderness in the early stage, but as limited joint movement, muscular atrophy, and knee varus deformity when progressed to an advanced stage, with a disability

Table 7. Efficacy determinants in KOA patients (multivariate analysis)

Indicators	B	Standard error	Wald	P	OR	95% CI
IL-1β (pg/mL)	0.891	0.557	2.558	0.110	2.437	0.818-7.256
TNF-α (μg/L)	1.093	0.555	3.877	0.049	2.982	1.005-8.848
Treatment modality	1.343	0.579	5.384	0.020	3.829	1.232-11.901

Note: KOA, knee osteoarthritis; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-alpha.

rate reaching 53% [18]. To effectively curb KOA progression and minimize disability risk, this study verified the clinical effect of pregabalin plus celecoxib in KOA management, which is hereby reported in detail.

We found that pregabalin+celecoxib was highly effective in KOA patients (effective rate: nearly 92%), suggesting the ability of the combined medication to effectively relieve knee pain and swelling and promote joint mobility. This might be due to the different pain-relieving mechanisms of the two. This allows for the synergistic enhancement of pain relief for KOA patients through diverse mechanisms. Compared to celecoxib alone, pregabalin addition in KOA patients contributed to a more potent analgesic effect and superior knee function recovery. In the report of Zhou et al. [19], pregabalin+celecoxib in post-total knee replacement (TKA) patients exerts a more prominent pain relief effect 6-48 h following the procedure while effectively improving knee ROM, similar to our observations. In the report of Li et al. [20], pregabalin shows higher efficacy in attenuating pain at rest for 24 and 48 hours and enhancing the knee flexion, further supporting our results. According to ELISA results, VEGF, IL-1β, and TNF-α levels were more markedly suppressed under pregabalin+celecoxib therapy. As an angiogenic factor, VEGF not only acts as a mediator of KOA onset but also correlates strongly with cruciate ligament degeneration in KOA patients [21]. Its abnormally high levels are also indicative of unfavorable clinical and functional outcomes in KOA [22]. L-1β and TNF-α are also highly involved in KOA progression. They will be over-released under the stimulation of articular cartilage damage and wear, disrupting the inflammatory microenvironment balance in the joint. As a consequence, synovitis (synovial membrane inflammation) and hyperosteogeny are induced, causing discomfort symptoms such as joint pain, swelling, and dysfunction [23]. The anti-inflammatory mechanism of pregabalin may be partly attributed to its inhibition of the cytoplasmic translocation of high mobility group box 1 (HMGB1), thus effectively alleviating inflammatory responses and inhibiting proinflammatory factor (e.g., IL-1β and TNF-α) release [24].

On the other hand, PSQI evaluation revealed better sleep quality in KOA patients managed with pregabalin plus celecoxib. In previous research, pregabalin used in elective neurosurgery is associated with greater pain alleviation and superior sleep quality enhancement (via relieving preoperative anxiety), aligning with our study results [25]. Further safety evaluation indicated a non-significant elevation in the overall risk of adverse events in KOA patients when pregabalin was administered alongside celecoxib, confirming the combination therapy's tolerability and safety. In patients with chronic low back pain, Romanò et al. [26] similarly reported the advantage of pregabalin-celecoxib co-administration over single drug treatment in terms of clinical safety. Lubis et al. [27] noted the effectiveness and good tolerability of pregabalin plus celecoxib in post-TKA patients, effectively relieving postoperative acute pain without inducing any obvious side effects, validating the results of this study. Finally, regression analysis confirmed TNF-α and treatment modality as the significant and independent determinants of curative effects in KOA patients. To be specific, high TNF-α (≥110 μg/L) and single celecoxib use increase the risk of ineffective treatment in such patients.

This study has the following limitations: (1) The sample size is limited, and multicenter samples across regions should be included in the future to improve the extrapolation of our conclusions; (2) The economic benefits of the two therapies have not been evaluated- therefore supplementing relevant health economics evaluations may help promote the pregabalin+celecoxib combination; (3) There is no risk stratification prediction tool for evaluating the curative effect

of KOA patients; supplementary in-depth analysis is helpful to provide more useful references for clinical guidance; (4) Additionally, our efficacy assessment primarily relied on subjective clinical scales and patient-reported outcomes. Future studies could be strengthened by incorporating more objective and quantifiable measures. For instance, leveraging advanced imaging analysis techniques, such as the radiomics and machine learning-based automatic Kellgren-Lawrence grading method [28], could provide a more precise and reproducible evaluation of structural changes in response to treatment. Integrating such objective imaging biomarkers with clinical phenotypes may facilitate the development of personalized treatment strategies and better prediction of therapeutic outcomes. Based on the above findings, this study will be continuously improved in the future.

To sum up, pregabalin plus celecoxib outperforms celecoxib alone in KOA treatment. While ensuring certain safety, the combination therapy significantly enhances curative effects, promotes knee function recovery, inhibits serum inflammation, and improves sleep quality. In addition, a higher risk of ineffective treatment is observed in KOA patients with TNF-α up-regulation (≥110 μg/L) and those receiving celecoxib alone. This underscores the importance of closer clinical attention for patients with such characteristics and timely adjustment of the treatment regimen.

Disclosure of conflict of interest

None.

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