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The effect of celecoxib on perioperative pain and fracture healing in children with fractures and its imaging study

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Abstract: **Background**: Pediatric fractures are common, with high postoperative moderate-to-severe pain incidence, hindering recovery. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has analgesic/anti-inflammatory effects, but its perioperative efficacy and impact on fracture healing in children remain understudied. **Objective**: To evaluate celecoxib's efficacy for perioperative pain management and its effects on fracture healing/imaging outcomes in children with fractures. This study aimed to evaluate the efficacy of celecoxib in children's fracture perioperative pain management and its impact on fracture healing and imaging outcomes. **Methods**: We employed a retrospective, consecutive sampling method to analyze medical records of 84 children who underwent surgery for fractures from January 2023 to December 2024. Postoperatively, they were divided into celecoxib (n=44) and tramadol hydrochloride (n=40) groups. Pain scores and healing times were monitored. In the celecoxib group, computed tomography (CT) images were compared to pre- and post-treatment. **Results**: Visual Analog Scale (VAS) scores decreased significantly from T0 (before medication) to T1 (4 weeks after operation) and T2 (3 months after operation) in both groups ($P<0.001$), more so in celecoxib ($P1=0.008$, $P2<0.001$). COX-2 and prostaglandin E2 (PGE2) levels also significantly dropped from T0 to T1 and T2 ($P<0.001$), with celecoxib showing greater reductions ($P1=0.036$, $P2=0.047$). Fracture healing times were comparable ($P>0.05$). Post-treatment CT images showed blurred fracture lines in the celecoxib group. Adverse reaction rates were similar (9.09% vs 15.00%; $P>0.05$). **Conclusion**: Celecoxib effectively alleviates pain and inflammation without hindering fracture healing in children, suggesting its potential as a perioperative analgesic.

Keywords: Celecoxib; Children fracture; Perioperative pain; Fracture healing; Imaging

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INTRODUCTION

Due to the poor safety awareness and self-protection ability of young children, coupled with the imperfect development of visual and proprioceptive functions, the risk of falls, impacts and other injuries is high, the integrity of the femur is easily destroyed and the incidence of femoral fractures is high. Surgery is an effective treatment for clinical fractures. However, due to the immature physical and mental development of children, it is difficult to effectively cope with stress events such as non-warning, sudden accidental injury stimulation, unfamiliar environment and invasive medical operations. The pain tolerance is weak and the fear of surgical treatment often shows negative emotions such as anxiety, fear and depression, which is not conducive to the smooth development of the operation and affects its rapid postoperative recovery (Ma *et al*., 2025, Engstrom *et al*., 2020). A study shows that 50% ~ 70% of children undergoing elective surgery have negative emotions and the incidence of moderate to severe pain in children after surgery is 60% ~ 80% (Vittinghoff *et al*., 2024). If not intervened, it can cause delayed wound healing, decreased immune function, which is not conducive to postoperative recovery and even negative behaviors such as loss of temper, nightmares and dietary degradation, affecting their quality of life (Noel *et al*., 2019, Powelson *et al*., 2022). Therefore, how to effectively control pain during the perioperative period and promote fracture healing is an important issue in current clinical practice.

Celecoxib, as a non-steroidal anti-inflammatory drug (NSAID), has multiple pharmacological effects such as analgesia and anti-inflammation. In recent years, it has been widely used in the pain management of osteoarthritis or rheumatoid arthritis (Obeid *et al*., 2022). Compared with traditional non-steroidal anti-inflammatory drugs, celecoxib has higher selectivity and can specifically inhibit cyclooxygenase-2 (COX-2) activity, thereby reducing the synthesis of prostaglandins, exerting strong analgesic and anti-inflammatory effects and has less irritation to the digestive tract mucosa (Cruz *et al*., 2022, Deng *et al*., 2024). Numerous studies have confirmed the efficacy of celecoxib in pediatric pain management. For instance, a randomized double-blind study conducted by Faramarzi *et al*. (Faramarzi *et al*., 2021) found that in the relief of pain after tonsillectomy in children, the average pain score in the celecoxib group was significantly lower than that in the acetaminophen group on the first postoperative day, although no significant difference was observed between the two groups in the following days. A randomized controlled trial by Giordan *et al*., (Giordan *et al*., 2023) using high-dose celecoxib for pain after pediatric

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tonsillectomy indicated that high-dose celecoxib was effective in controlling postoperative pain without increasing adverse effects. Although the analgesic effect of celecoxib is recognized, its safety and efficacy in the perioperative period of pediatric fractures, especially its impact on bone healing, still require further investigation. Researchers (Kigera *et al*., 2022) through constructing rat models of different ages, compared the effects of diclofenac and celecoxib on the histomorphometry of fracture callus tissue and found that celecoxib was associated with lower histological grades and bone ratios in older rats. However, there are significant differences between rats and children in terms of skeletal development and metabolism, which precludes direct extrapolation to children. Currently, specific studies on celecoxib in pediatric perioperative pain management, fracture healing and imaging are relatively scarce. Therefore, this study aims to explore the application effects of celecoxib in the perioperative period of pediatric fractures and to assess its advantages in pain relief, fracture healing and imaging performance compared to traditional analgesic drugs.

MATERIALS AND METHODS

Research subjects

Study settings: A retrospective cohort study design was adopted. We retrospectively reviewed the medical charts of 84 children with fracture diagnoses who received operative intervention at our institution from January 2023 through December 2024. According to different postoperative medication methods, the patients were divided into observation group (n = 44, celecoxib) and control group (n = 40, tramadol hydrochloride capsules). The data was retrospectively collected and analyzed the children who previously received two conventional analgesic regimens (celecoxib vs tramadol) and compared them.

Sample size calculation: This study utilized the formula for comparing two independent sample means to calculate the sample size (Clifton *et al*., 2018):

$$N = 2 \times \left[\frac{\left(Z_{1-\alpha/2} + Z_{1-\beta} \right) \times \sigma}{\delta} \right]^2 \quad \text{Eq. 1}$$

Based on the results of the preliminary experiment, the visual analog scale (VAS) scores at four weeks postoperatively were lower in the celecoxib group compared to the control group (celecoxib group 3.52±1.71, control group 4.34±1.20), with a combined standard deviation of 1.5 for both groups. Two mean [difference] test models using PASS V.11 software (NCSS，Kaysville，Utah，USA) (Yue *et al*., 2020), with an alpha level set at 0.05 and a beta level at 0.20, σ=1.5 (pooled standard deviation) and δ=0.8 (mean difference between groups), the calculation indicated that 35 subjects were needed in each group. Considering a 10% dropout rate, a minimum of 39 participants per group was required. To ensure the sample size was sufficient for analysis, this study ultimately included data from 84 patients.

Inclusion criteria

(1) Patients who had obvious fracture manifestations through imaging examination and met the indications of surgical treatment; (2) Underwent surgical treatment; (3) Conscious.

Exclusion criteria

(1) Combined with spinal tuberculosis, bone tumors and other diseases; (2) Patients with severe organic diseases; (3) Recently taking calcitonin, non-steroidal anti-inflammatory drugs, hormone drugs, etc.; (4) Bleeding tendency, gastrointestinal ulcer, etc. (5) Age≥18 years old, < 3 years old, allergic to research drugs; (6) Coagulation dysfunction; (7) Patients who could not complete the whole follow-up, may be lost to follow-up or discontinued treatment and incomplete data recording. This study has been examined and approved by the Medical Ethics Committee of The First Affiliated Hospital of Xinxiang Medical University, approval number [EC-023-019].

Methods

Both groups underwent general anesthesia and the intraoperative drugs were the same. Anesthesia: Midazolam (Jiangsu Enhua Pharmaceutical Co., Ltd., National Drug Approval Number H20247176) was administered intravenously with an initial dose of 0.03-0.04 mg/kg, followed by additional doses of 0.01-0.02 mg/kg every 5 minutes to maintain anesthesia, with a total dose not exceeding 0.1 mg/kg (Hong *et al*., 2021). Both groups received the same routine analgesic treatment preoperatively: Naproxen (Guangdong Yihe Pharmaceutical Co., Ltd., National Drug Approval Number H44023491), typically administered every 8 to 12 hours at a dose of 5-10 mg/kg, with a maximum daily dose of 20 mg/kg (Eccleston *et al*., 2017).

The control group received oral tramadol hydrochloride (Yangtze River Pharmaceutical; batch number: National Drug Approval Number H20010772) 2 hours before surgery, with the dose adjusted according to body weight, 1-2 mg/kg, with a maximum single dose of 100 mg (Umuroğlu *et al*., 2004). Postoperatively, tramadol was administered orally at a dose of 1.5 mg/kg every 8 hours for a duration of 7 days.

The observation group began receiving celecoxib (Sichuan Guowei Pharmaceutical Co., Ltd.; batch number: National Drug Approval Number H20203356) 2 hours before surgery at a dose of 1-2 mg/kg, administered every 12 hours. Postoperatively, they received 2 mg/kg twice daily (Hu *et al*., 2024) for a period of 7 days. Patients received discharge guidance education before discharge and were followed up for at least 3 months.

Observation indicators

Main outcome measures

(1) *Degree of pain*: A visual analogue scale (VAS) was used to evaluate the degree of pain in patients. Patients were

instructed to mark on a paper with a 0-10 scale according to their subjective pain perception. 0 indicates complete painlessness, 10 indicates unbearable severe pain and the staff recorded the degree of pain in patients according to the location of the mark (Orbach *et al*., 2018). VAS scores directly reflected pain intensity; the measurements were repeated at 48 h before operation (before medication, T0), 4 weeks after operation (during medication, T1) and 3 months after operation (after medication, T2). For children <5 years old, due to their limited expression ability, pain perception assessment is combined with behavioral observation (such as crying, physical activity, etc.) and parental feedback. (2) Fasting venous blood was collected 48 hours before operation (before medication, T0) and 3 days after operation (T1). Cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) concentrations were quantified using enzyme-linked immunosorbent assay (ELISA). (3) Fracture healing evaluation results: healing durations were recorded for both groups and inter-group differences were subsequently analyzed. The relevant criteria for fracture healing are that the fracture line is not clear and there is a continuous callus. At the same time, there are no symptoms such as percussion pain and tenderness and the local activity is normal. Following the surgery, the children in the observation group were regularly examined by computed tomography (CT) and other imaging examinations to observe the changes of fracture line and the formation of callus, which were independently evaluated by two experienced orthopedic surgeons. All imaging data were obtained with the informed consent of the patient's guardian.

Secondary indicators: safety evaluation: adverse reactions of the two groups were recorded 4 weeks after operation to evaluate the safety of celecoxib. The evaluation criteria of adverse reactions were based on the judgment and evaluation criteria of common adverse drug reactions (Smith *et al*., 2013). The adverse reactions in this study mainly included nausea and vomiting, dizziness, headache, abdominal distension and diarrhea. The total incidence of adverse reactions was calculated by the attending physician after diagnosis.

Statistical analysis

This study uses SPSS 26.0 statistical software to analyze the collected data. Before the statistical description and analysis of the measurement data, the Shapiro-Wilk test was used to determine whether it conformed to the normal distribution. If it conforms to the normal distribution (COX-2, PGE2 levels, etc.), it is described in the form of mean ± standard deviation ($\bar{x} \pm s$). An independent sample t-test was used for comparison between groups, and a paired t-test was used for comparison between T0, T1 and T2 in the group. If it does not conform to the normal distribution (age, VAS score), it is described in the form of median (interquartile range) [M (P25, P75)] and the nonparametric test method should be Wilcoxon signed rank test. At the same time, the multi-time point observation data were analyzed by repeated measures analysis of variance / Friedman test (Friedman test) + post hoc test (pairwise comparison between groups). The enumeration data such as gender, disease type and adverse reactions were expressed as the number of cases and rate (%). The $\chi 2$ test was used for comparison between groups. When the sample size was small ($n < 5$), Fisher 's exact test was used. When analyzing the results, the confidence level was 95 %. When $P < 0.05$, the difference was considered statistically significant.

RESULTS

General information

The comparison of baseline data between the two groups showed no significant statistical difference ($P > 0.05$), indicating that the two groups were comparable (Table 1).

VAS score changes

At T0, the VAS scores of the two groups did not differ significantly ([7.00(5.00, 9.00)] vs [7.00(5.00,9.00)], $P > 0.05$). Both groups exhibited markedly lower VAS scores at T1 and T2 relative to T0 ($P < 0.001$); however, the observation group's reductions were significantly greater than those of the control group at both time points ([4.00(4.00, 5.00)] vs [5.00(4.50,6.00)], P1=0.008; [3.00(2.00,4.00)] vs [4.00(4.00,4.00)], P2<0.001) (Fig. 1). Furthermore, the VAS scores in this study were non-normally distributed data. Repeated comparisons were conducted using generalized estimating equations and the results showed that the effect significance test, differences between treatment groups (group), differences in the indicator data measured multiple times (time) and interaction effects were statistically significant (P=0.000).

The levels of COX-2 and PGE2 in the two groups at T1, T2 were lower than those at T0 ($P < 0.001$) and the levels of COX-2 and PGE2 in the observation group were lower than those in the control group at T1, T2 (P1=0.036, P2=0.047, Fig. 2). COX-2 levels (spherical test P<0.05) showed significant effects (F1 = 6.607, P=0.012), the time effect was significant (F2=224.810, P<0.001) and there was no significant interaction between COX-2 levels and time (F3=0.904, P=0.409); PGE2 levels (spherical test P>0.05) showed significant effects (F1 = 4.127, P=0.045), the time effect was significant (F2=34.819, P<0.001) and there was no significant interaction between PGE2 levels and time (F3=1.688, P=0.189).

Fracture healing evaluation results

Table 2 demonstrates equivalent fracture healing times between the observation and control cohorts, with non-significant intergroup variation ($P > 0.05$).

Imaging data

The imaging examination showed that in the observation group treated with celecoxib, the CT examination before medication showed that the fracture line of the image was obvious, the fracture line existed during medication and the fracture line was blurred after medication (Fig. 3).

Table 1: Baseline characteristics of the groups

Groups	Sexuality [n(%)]		Age (years) [M (P25, P75)]	Disease type [n(%)]		
	Male	*Female*		*Tibial fracture*	*Fracture of rib*	*Others*
Observation group (n = 44)	26 (59.09)	18 (40.91)	7.00 (5.00,9.00)	12 (27.27)	15 (34.09)	17 (38.64)
Control group (n = 40)	19 (47.50)	21 (52.50)	6.50 (5.00,9.00)	13 (32.50)	17 (42.50)	10 (25.00)
χ^2/Z	1.132		0.012		1.793	
P	0.287		0.914		0.408	

Table 2: Comparison of fracture union times in two groups

Groups	Fracture healing time ($\bar{x}\pm s$, weeks)
Observation group (n=44)	10.26±1.43
Control group (n=40)	9.88±1.79
t	1.204
P	0.232

Table 3: Adverse-event profiles of the two groups

Groups	No appetite [n(%)]	Nausea and vomiting [n(%)]	Stomach dull pain [n(%)]	Dizziness [n(%)]	Total number of occurrences[n(%)]
Observation group (n=44)	2 (4.55)	0 (0)	1 (2.27)	1 (2.27)	4 (9.09)
Control group (n=40)	2 (5.00)	1 (2.50)	2 (5.00)	1 (2.50)	6 (15.00)
Fisher's exact test					0.699
P					0.508

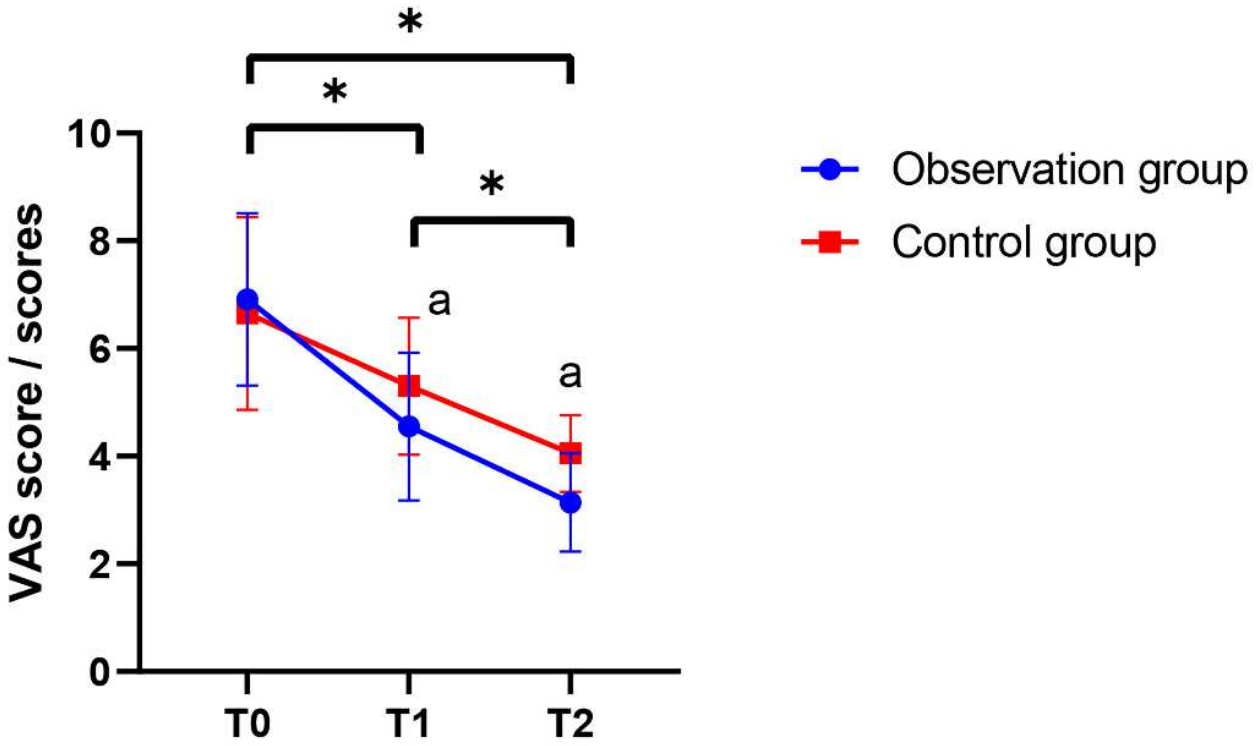

Fig. 1: Comparison of VAS scores between the two groups

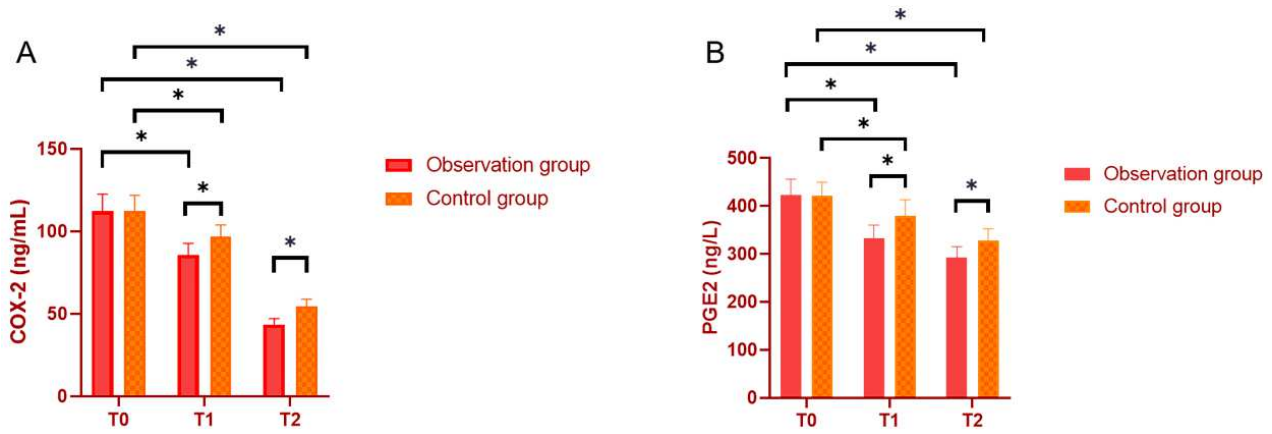

Fig. 2: Comparison of serum COX-2 and PGE2 levels between the two groups
(A) Serum COX-2 levels (ng/mL) in the celecoxib group and tramadol group at T0, T1, and T2; (B) Serum PGE2 levels (pg/mL) in the celecoxib group and tramadol group at T0, T1, and T2. Note: * $P < 0.05$; T0: 48 h preoperatively; T1: 3 days postoperatively; T2: 3 months postoperatively

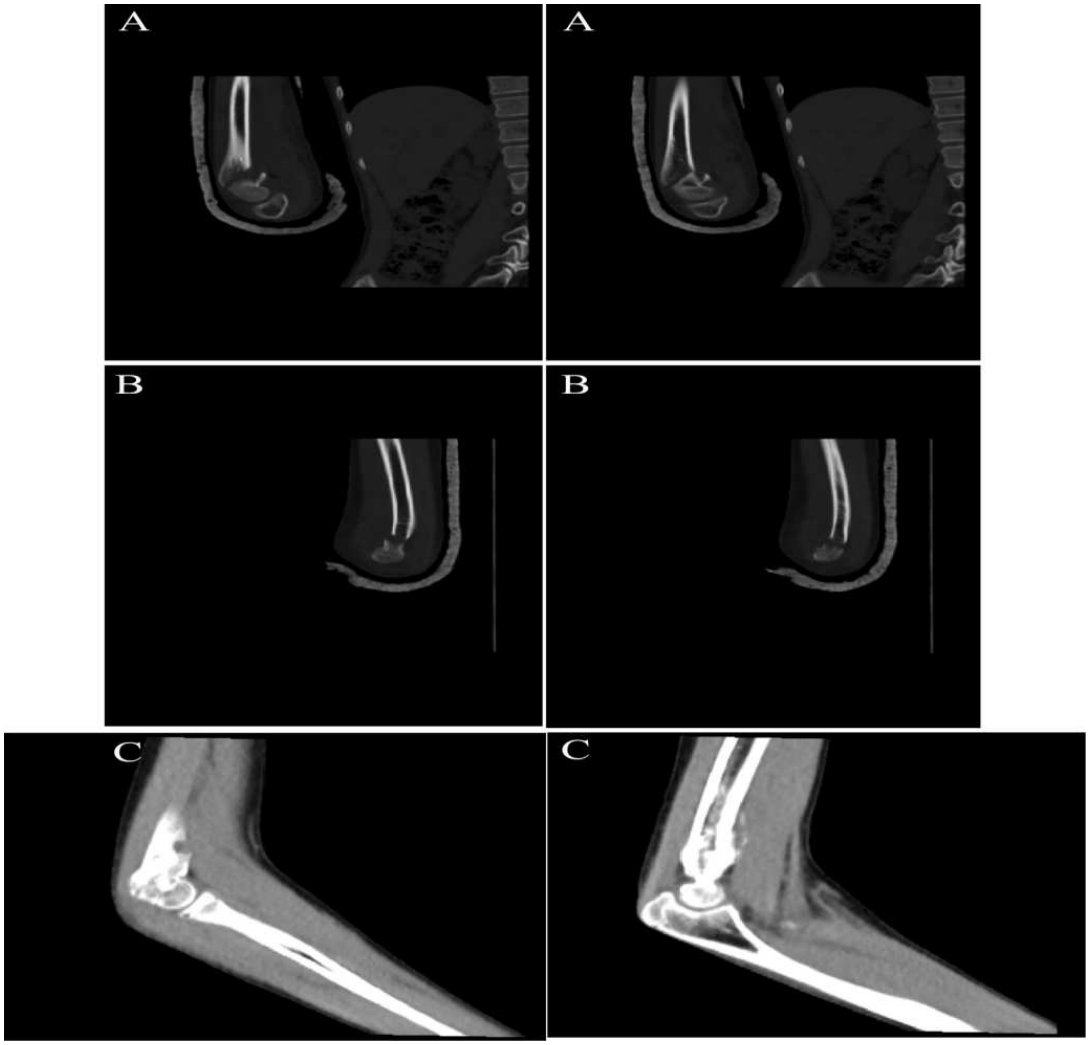

Fig. 3: CT examination pictures of a child with right humeral supracondylar fracture
(A) Pre-administration CT scan: Obvious fracture line was observed, with clear boundary between fracture fragments; (B) During-administration CT scan: Fracture line remained visible; (C) Post-administration CT scan: Fracture line was significantly blurred, indicating progressive union.

Comparison of adverse reactions between the two groups of children

There was no significant difference in the total incidence of adverse reactions between the observation group and the control group (9.09% vs 15.00%) ($P > 0.05$), as shown in table 3.

DISCUSSION

About 32.6 % of children in China are hospitalized due to traumatic fractures, especially in school-age children (Song *et al*., 2021). Pain, often referred to as the fifth vital sign, is a common stress response in patients with fractures and after surgery. After fracture, local swelling and broken end bleeding often occur in patients and postoperative external fixation leads to limited activity, which is prone to strong pain and bad psychology. Due to the active nature of children, children's pain and negative psychology are more serious. The long-term existence of pain not only affects the fracture healing of children, but also interferes with their postoperative functional exercise, which is not conducive to the improvement of surgical treatment effect. Children 's physical and mental health, sleep, etc., are also easily affected by pain, eventually resulting in slower recovery and even chronic pain (Hu *et al*., 2024). Hence, identifying and utilizing safe and effective analgesic medications holds considerable importance for the postoperative recovery of children suffering from fractures.

Non-steroidal anti-inflammatory drugs have antipyretic, analgesic and anti-inflammatory effects. Its analgesic effect is achieved by blocking cyclo-oxygenase activity, thereby curtailing the transformation of arachidonic acid into prostaglandins and thromboxanes (D'Arcy *et al*., 2021). Celecoxib, as a commonly used non-steroidal anti-inflammatory analgesic, can reduce the inflammatory response of local tissues and effectively relieve pain (Yang *et al*., 2024, Ni *et al*., 2022). In this study, by collecting and counting the data of the two groups, it can be seen that the postoperative pain intensity in the observation group was significantly reduced at T1 and T2 compared to controls ($p<0.01$ for both). This result suggests that celecoxib can effectively alleviate perioperative pain in children with fractures. Inflammatory response is an important factor affecting the postoperative recovery of fracture patients. Both COX-2 and PGE2 are inflammatory factors, which can stimulate the nerve root and induce a strong pain response. Inhibiting the expression of COX-2 and PGE2 is of positive significance for controlling pain (Xue *et al*., 2025, Chen *et al*., 2024, Liu *et al*., 2024). In this study, the levels of COX-2 and PGE2 in the observation group were lower than those in the control group, suggesting that the application of celecoxib can better stabilize the levels of serum COX-2 and PGE2 after operation and then control the pain degree of patients. According to the above two results, the reason may be that celecoxib can selectively inhibit the activity of COX-2, reduce the synthesis of prostaglandins, reduce the release of inflammatory mediators caused by trauma, thereby promoting the decrease of inflammatory factor levels and playing an analgesic role. Tramadol hydrochloride mainly exerts its analgesic effect through central mechanisms (such as activation of opioid receptors and modulation of neurotransmitter reuptake) (Barakat *et al*., 2019), which is different from the COX-2 inhibition pathway of celecoxib. This difference in mechanism may lead to a weaker effect on the downregulation of inflammatory factors (COX-2, PGE2), which is consistent with the lower levels of inflammatory factors observed in the observation group in this study. Clinical studies have pointed out that celecoxib is used as an analgesic drug in open surgery and its analgesic effect is good (Zhu *et al*., 2020). Other studies have confirmed that celecoxib has a certain effect on postoperative analgesia after total knee arthroplasty. The mechanism may be to reduce hyperalgesia and tactile induction at the surgical site by inhibiting the production of inflammatory mediators (Zhuang *et al*., 2020), a finding that aligns with this study.

Fracture healing represents a complicated regenerative process that resembles bone development, aside from the initial bleeding and inflammatory phases (ElHawary *et al*., 2021). From a biomechanical point of view, fracture healing means the recovery of mechanical properties such as strength and stiffness. Clinically, it is necessary to determine when the fracture heals in order to determine the weight-bearing state of the patient's limb, the level of activity and whether it is necessary to wear a brace. Although bone nonunion is closely related to clinical decision-making, there is still a lack of uniform standards in the current literature (Steppe *et al*., 2023). The clinical determination of fracture union involves sequential evaluation of three key components: clinical examination results, imaging-based healing indicators and the patient's subjective feelings. However, due to individual differences and different education levels of patients, the signs of palpable pain during physical examination are also very subjective and unreliable (Lopas *et al*., 2023). Although orthopedic surgeons cannot make diagnosis and clinical decisions based on imaging data alone, imaging data still play a key role in judging whether the fracture is healed or not. As the image thickness of CT scan is getting smaller and smaller, the imaging quality is getting higher and higher and it has become a practical tool for evaluating fracture healing. This study found that compared with before treatment, after treatment, the CT images of the right humeral supracondylar fracture of the child showed significant changes, the most obvious of which was the blurring of the fracture line. This change shows that with the passage of time and the therapeutic effect of drugs, the fracture site is gradually healing, bone regeneration and repair process is ongoing, showing the effect of drugs on clinical healing. The reason may be that the drug may create a more favorable microenvironment for fracture

healing by regulating the local inflammatory response and reducing the adverse effects of inflammatory factors on fracture repair.

Celecoxib, as a COX-2 inhibitor, may affect bone healing (Kigera *et al*., 2022). For example, it has been found that bone mineral density and new bone formation were significantly reduced in patients treated with COX-2 inhibitors, suggesting that COX-2 inhibitors can lead to impaired tendon-to-bone healing (Janssen *et al*., 2017). Similarly, it has been studied the reconstruction and shaping of lamellar bone in a rat tibial fracture model (Gregory and Forwood, 2007). The time to reach the peak bone mass in the celecoxib treatment group was delayed by one week compared with the control group. It is inferred that celecoxib does not significantly interfere with the mechanism of woven bone remodeling, but will prolong its healing time. It has been studied the closed fracture model of female SD rats (Bergenstock *et al*., 2005). In the histological sections, the quantity of chondrocytes in the group treated with celecoxib was markedly greater than in the control group. The biomechanical results showed that celecoxib significantly reduced the maximum shear stress of the healed femur. Histology also showed that the strength of fracture healing was reduced, indicating that celecoxib inhibited fracture healing. However, the above results are based on animal experiments. At present, there is no report on the adverse effects of celecoxib on fracture healing in clinical use. Clinical assessment revealed comparable fracture healing timelines in patients receiving celecoxib versus controls ($P > 0.05$), suggesting that celecoxib had no significant effect on fracture healing. Even if celecoxib has an inhibitory effect on human fractures, it can relieve patients' pain and promote early activity and weight-bearing, which can promote fracture healing. Celecoxib is a double-edged sword, with both advantages and disadvantages. Clinicians should have enough vigilance awareness, carefully measure the pros and cons, make correct clinical decisions and use them reasonably.

This study found that the two groups did not differ appreciably in adverse-event rates. It shows that oral celecoxib has high safety. Previous studies indicate that celecoxib capsule administration may induce mild gastrointestinal and neurological symptoms in certain patients, including nausea, vomiting and somnolence (He *et al*., 2022). Only a small proportion of patients experienced clinically significant hepatic or renal impairment, a finding that aligns with the present results. Although this study has achieved some results in exploring the effect of celecoxib on perioperative pain management and fracture healing in children, there are obvious limitations. First of all, this study is a retrospective study, relying on previous medical records, data collection may be biased or incomplete and it is difficult to clarify the causal relationship. Secondly, the sample size is small, affecting the extrapolation of the results; due to the short follow-up time, it is difficult to fully observe the long-term effect of celecoxib on fracture healing and potential long-term effects or adverse reactions may be missed. In addition, the lack of multi-center data, the results of the study may be affected by a single central factor. Future research should carry out multi-center prospective clinical trials to further expand the sample size and extend the follow-up time to more comprehensively evaluate the application value of celecoxib in the treatment of children's fractures.

CONCLUSION

In summary, celecoxib showed a significant pain relief effect in perioperative analgesia intervention of fractures in children. Although celecoxib had a slight and less adverse effect on fracture healing, considering the potential risks of celecoxib. Therefore, clinicians need to fully weigh the advantages and disadvantages in the application and formulate accurate medication plans according to the individual situation of children, so as to maximize the benefits and provide better medical services for the rehabilitation of children with fractures.

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Authors' contribution
Pengfei Yan: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions; Dawei Li: Participated in collecting, assessing and interpreting the data. Made significant contributions to date interpretation and manuscript preparation; Haibo Hu: Provided substantial intellectual input during the drafting and revision of the manuscript.

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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval
This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University (EC-023-019).

Conflict of interest
The authors declare that they have no financial conflicts of interest.

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