J Shoulder Elbow Surg (2019) 28, 2379–2385

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

Celecoxib cannot inhibit the progression of initiated traumatic heterotopic ossification

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Background and hypothesis: Heterotopic ossification (HO) is a recognized sequela after trauma and arthroplasty. The purpose of this study was to evaluate the therapeutic effect of celecoxib on HO. We hypothesized that celecoxib may inhibit the progression of initiated HO.

Methods: We performed a retrospective review of 37 patients who underwent elbow joint surgery between January 2014 and June 2018. Seventeen patients were prescribed orally administered celecoxib (200 mg/dose, twice daily) for 2 months after the diagnosis of HO, whereas the remaining 20 patients were administered celecoxib for 1 month starting immediately after surgery. HO progression was evaluated by plain radiographs. By use of an Achilles tendon puncture-induced HO mouse model, the curative effect of celecoxib was illustrated at different HO progression stages. The mice were assigned to 1 of 4 groups: sham group, vehicle group, group receiving celecoxib on day 1, and group receiving celecoxib in week 6. Achilles tendons were analyzed by micro-computed tomography and histochemistry after 12 weeks.

Results: Celecoxib did not inhibit the progression of initiated HO in the patients in whom HO was diagnosed, whereas those who received celecoxib after surgery had lower morbidity. Achilles tendon puncture effectively induced typical HO in mice. The ectopic bone volume was significantly reduced in the day 1 celecoxib group compared with the vehicle group; however, the difference was not statistically significant in the week 6 celecoxib group.

Conclusions: Administration of celecoxib starting immediately after surgery can significantly inhibit the formation of HO. Once HO is visible on plain radiographs or micro-computed tomography, celecoxib cannot effectively attenuate further progression of HO in humans and mice.

Level of evidence: Level III; Retrospective Cohort Design; Treatment Study and Basic Science Study; In Vivo Animal Model

Keywords: Heterotopic ossification; elbow joint; celecoxib; NSAID; prostaglandin E2; trauma

The Wuxi 9th People's Hospital Affiliated to Soochow University Institutional Review Board approved this study (no. 20171219-01). All experimental procedures were approved by the Institutional Animal Review Committee.

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1058-2746/$ - see front matter
https://doi.org/10.1016/j.jse.2019.08.013

Heterotopic ossification (HO) is a pathologic process in which new lamellar bone forms in the adjunct soft tissues of joints. It often occurs in the elbow, hip, or knee joint following limb trauma, total elbow arthroplasty (TEA), arthrosis surgery, spinal cord injury, and severe burns.[22] Because of its location and size, HO can impede normal body functions and physical mobility and result in significant pain, joint ankylosis, swelling, pressure ulcers, and other complications, severely reducing quality of life.[35]

Prior analysis found that HO was radiographically present in 10% of TEA patients and was symptomatic in 3% of 2256 TEA patients.[19] Following elective and traumatic elbow arthroplasty, the overall incidence of HO was 84%; the incidence was higher in the trauma group than in the elective arthroplasty group.[27] Celecoxib, a selective cyclooxygenase 2 receptor antagonist, was shown to effectively inhibit the formation of traumatic HO.[17] The efficacy of celecoxib is equivalent to that of indomethacin but with fewer gastrointestinal side effects.[16,28] However, in many patients with elbow joint trauma, celecoxib is not administered in the early stage, and HO is often found when re-examined by radiography 1 month later. The efficacy of oral administration of celecoxib to inhibit further development of HO is still controversial. The objective of this research was to evaluate the inhibitory effect of celecoxib on initiated HO in humans and mice.

Materials and methods

Patients

We performed a retrospective study of 37 patients who underwent elbow joint surgery between January 2014 and June 2018. The patients consisted of 21 men and 16 women, aged 20 to 71 years, and were classified into 1 of 2 groups (Table I). The first group, comprising 17 patients, was administered celecoxib (200 mg/dose, twice daily; Pfizer, New York, NY, USA) for 2 months after the diagnosis of HO. The second group, comprising 20 patients, was administered celecoxib for 1 month starting immediately after surgery. All patients were re-examined after 1 to 3 months by radiography, and the follow-up period was 8 to 12 months. The degree of clinical and radiographic severity of HO was assessed on these radiographs by 2 radiologists according to the classification scale devised by Hastings and Graham.[13]

Animals

A trauma-induced HO mouse model with percutaneous Achilles tendon puncture was used to illustrate the curative effect of celecoxib. Forty-eight 10-week-old C57BL/6J mice were purchased from the Shanghai Laboratory Animal Center (Chinese Academy of Sciences, Shanghai, China). The mice were divided into 4 groups at random, with 12 mice in each group: sham group, vehicle group, group receiving celecoxib on day 1, and group receiving celecoxib in week 6. For this HO model,[20] mice were anesthetized beforehand by ketamine and xylazine, and the Achilles tendon was punctured from the lateral aspect percutaneously with a 27-gauge needle; this process was repeated 5 times in different parts of the Achilles tendon in each mouse. The mice in the day 1 celecoxib group were administered celecoxib 3 hours after puncture by oral gavage (8 mg/kg) once daily for 12 weeks. The mice in the week 6 celecoxib group were administered celecoxib starting at week 6 after puncture by oral gavage (8 mg/kg) once daily until week 12. For the sham group, the needle punctured the skin without touching the Achilles tendon. For the vehicle group, the Achilles tendon was punctured according to the aforementioned procedure but was treated with an identical volume of normal saline solution.

Specimen collection

At week 12, the mice were killed humanely by carbon dioxide inhalation. The ankle with the Achilles tendon was dissected and fixed in 10% buffered formalin for 48 hours, and the specimens were embedded in paraffin after being decalcified in EDTA 10% (VWR 0105, pH 7.6; VWR International, Radnor, PA, USA) for 2 weeks.

Micro-computed tomography analysis and histochemistry

Achilles tendons with the calcaneus and lower tibia from mice were fixed in formalin 10% and analyzed by high-resolution micro-computed tomography (SkyScan 1176; Aartselaar, Belgium). The scan voltage was 60 kV, and the resolution was 18 μm/pixel. CT Vol (version 2.0), CT An (version 1.9), and NRecon (version 1.6) were used to visualize the reconstructed images, and the bone volume of HO was analyzed. After scanning, the Achilles tendons were decalcified and sectioned at 4-μm intervals using a paraffin microtome. We processed 4-μm-thick sections of bone for hematoxylin-eosin staining and viewed the slides using an optical microscope (VanoxAH-2; Olympus, Tokyo, Japan).

Statistical analysis

Data for continuous variables were expressed as mean ± standard deviation. Demographic data and functional outcomes were compared by the Student t test. Radiographic characteristics and categorical variables were expressed as numbers and percentages and analyzed with the χ^2 test. Differences among the 4 groups of mice were analyzed by 1-way analysis of variance. All statistical analyses were performed using SPSS software (version 24.0; IBM, Armonk, NY, USA), and all figures were created by GraphPad Prism software (version 8.0; GraphPad Software, San Diego, CA, USA). For all analyses, $P < .05$ was considered statistically significant.

Results

Clinical outcome

We studied 37 subjects who were categorized into 1 of 2 groups based on the timing of celecoxib administration.

Table I Descriptive data for patient characteristics

Variable	Celecoxib received after HO diagnosis (n = 17)	Celecoxib received after surgery (n = 20)	*P* value
Age, mean ± SD, yr	46.5 ± 11.4	43.1 ± 13.1	.398
Sex, n (%)			.815
Male	10 (59)	11 (55)	
Female	7 (41)	9 (45)	
BMI, mean ± SD, kg/m^2	24.6 ± 3.0	23.9 ± 3.1	.461
ASA grade I/II/III, n	16/1/0	18/2/0	.647
Comorbidity, n (%)	3 (18)	3 (15)	.828
Type of injury, n			.894
Distal humeral fracture	1	2	
Proximal radial or ulnar fracture	14	16	
Elbow dislocation or fracture-dislocation	2	2	
Previous surgery, n	0	1	.350
Initial treatment, n			.272
Nonoperative	1	0	
Operative	16	20	
Postoperative complications, n (%)	3 (18)	4 (20)	.855
Follow-up time, mean ± SD, mo	8.7 ± 1.4	9.2 ± 1.7	.391
HO classification, I/II/III, n	4/13/0	2/0/0	.028*

HO, heterotopic ossification; *SD*, standard deviation; *BMI*, body mass index; *ASA*, American Society of Anesthesiologists.
* Statistically significant.

As shown in Table I, no significant difference between the 2 groups was found for age, sex, body mass index, American Society of Anesthesiologists grade, comorbidity, type of injury, or postoperative complications. However, patients who received celecoxib after the diagnosis of HO had a higher HO classification level than those administered celecoxib starting immediately after surgery ($P = .028$).

Case 1 and case 2 in Figure 1 are representative elbow joints of patients who received celecoxib for 2 months after the diagnosis of HO. Case 1 had typical HO adjacent to the elbow joint (Fig. 1, *A*). A small number of ectopic bones were visible in the left posterior elbow joint 1 month after recovery following a dislocation. The bone volume of HO tissue significantly increased after 3 and 5 months. At 8 months, the heterotopic bone tissue was completely fused to the olecranon and distal dorsal humerus. Case 2 was an elbow joint with HO after fracture of the radius (Fig. 1, *B*). On re-examination by radiography at 1 month, a few bones appeared in the posterior region of the elbow joint and gradually enlarged and densified, finally turning into typical heterotopic bone tissue after 8 months (Fig. 1). Ectopic bone was not found in the elbow joints of patients who received celecoxib after surgery during the follow-up period of 1 to 8 months (Fig. 2). In summary, as shown by the patient characteristics and plain radiographs, treatment with celecoxib when HO was visible could not effectively suppress further progression whereas administering celecoxib in a timely manner after surgery could remarkably inhibit the initiation of HO.

Animal trial outcome

As shown in Figure 3, the imaging examination of the Achilles tendons by micro-computed tomography indicated that puncture could effectively induce typical HO in these tendons. Heterotopic bone formed and continued to enlarge in the trauma area in the mouse model 12 weeks after puncture (Fig. 3, *A*), and a mature cancellous bone structure with bone marrow could be observed (Fig. 3, *B*). On day 1 after puncture, oral administration of celecoxib could inhibit the formation of HO tissue. The bone volume of heterotopic bone in the day 1 celecoxib group was significantly reduced compared with the vehicle group ($P = .01$, Fig. 4), and the heterotopic bone had an immature bone marrow cavity and large collagenous fibers (Fig. 3, *B*). When celecoxib was administered 6 weeks after puncture, there was no observable inhibitory effect on the progression of HO. The bone volume in the week 6 celecoxib group was slightly decreased compared with the vehicle group, but the difference was not statistically significant ($P = .68$, Fig. 4), showing a mature cancellous bone structure with bone marrow. Collectively, these results demonstrated that the propagation of HO could be attenuated by

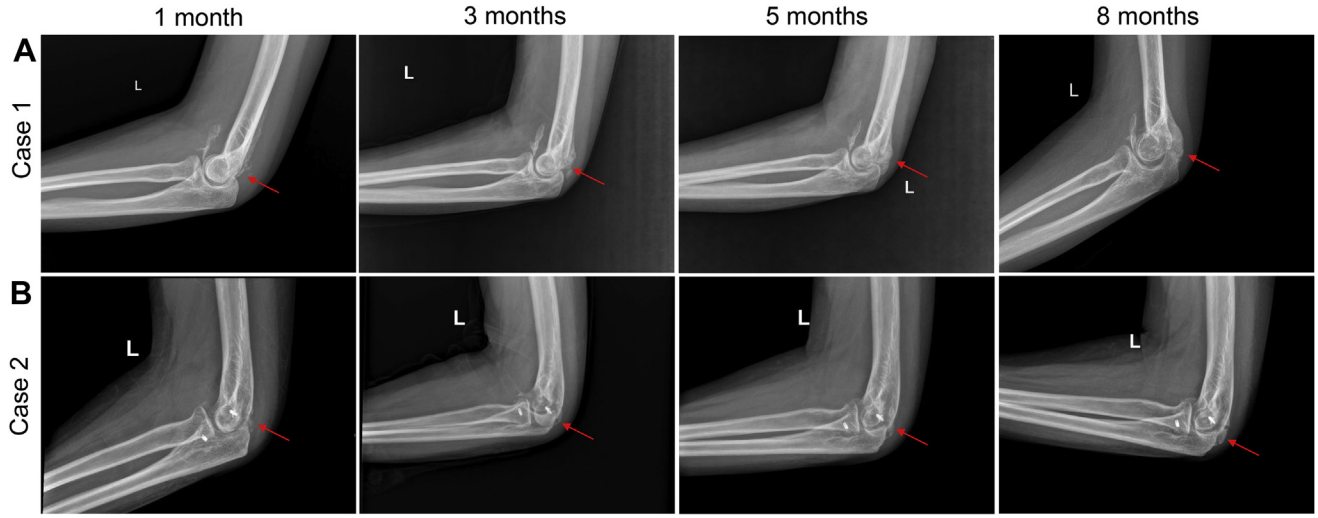

Figure 1 Post-traumatic heterotopic ossification (HO) development in human patients. Case 1 (**A**) and case 2 (**B**) are representative left (L) elbow joints of patients who received celecoxib after the diagnosis of HO. The ↑ indicate the HO lesions.

celecoxib in the early stage of HO. Once the progression of ectopic bone was initiated, the administration of celecoxib could not effectively mitigate the further formation of HO in mice.

Discussion

HO is an ectopic formation of mature bone within extraskeletal tissues in which bone normally does not exist. Currently used prophylaxis for HO is restricted to systemic administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose radiotherapy.[3,4,23,39] The effectiveness of these strategies for preventing HO after hip fracture, elbow trauma, and spinal cord injury has been confirmed by numerous studies.[1,6,11,14,26] However, long-term use of NSAIDs in the early stage of fracture healing may inhibit new bone formation and increase the risk of cardiovascular and gastrointestinal disease.[8,30] Once the ectopic bone is visible, it is impractical to remove it without surgery. Until now, no research has reported whether administration of NSAIDs, such as celecoxib, can inhibit the development of HO that is already initiated. Celecoxib is a cyclooxygenase 2 receptor antagonist, and its inhibitory effect on traumatic HO in the inflammatory stage has been confirmed.[17] The efficacy of celecoxib is comparable to that of indomethacin; however, the gastrointestinal side effects are much less severe.[16,28] Thus, celecoxib is recommended as a priority

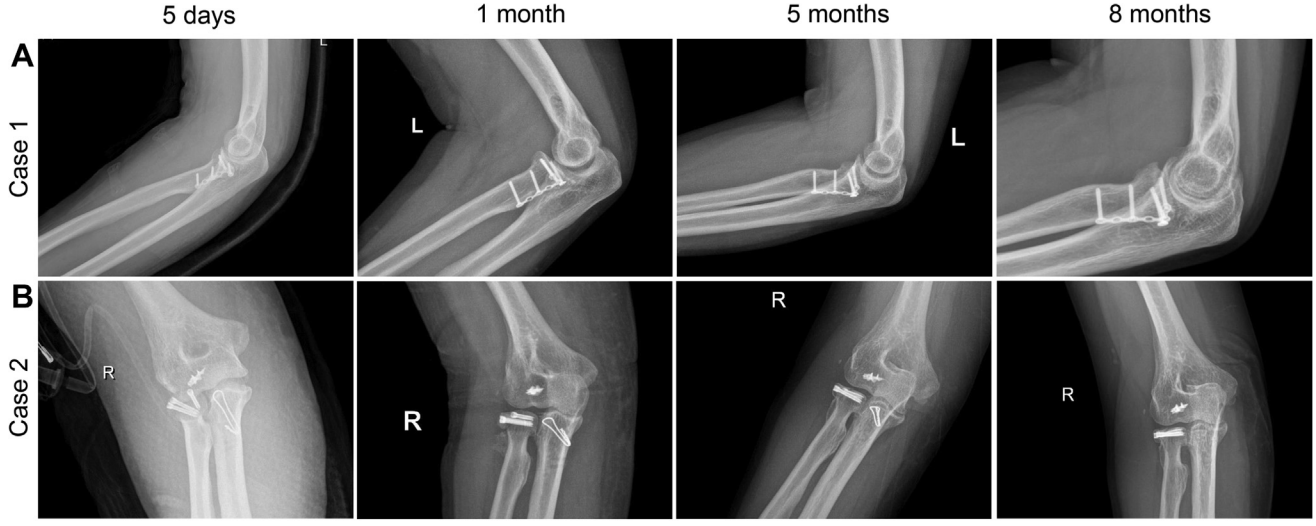

Figure 2 Plain radiographs of elbow joints in human patients after surgery. Case 1 (**A**) and case 2 (**B**) are respectively representative left (L) and right (R) elbow joints of patients who received celecoxib for 1 month after surgery.

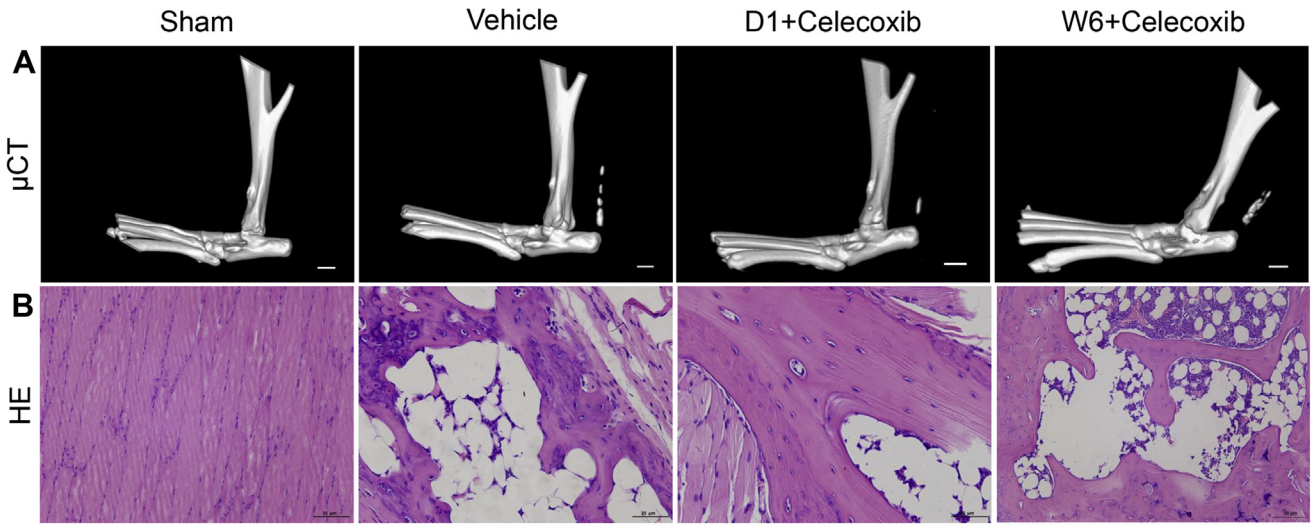

Figure 3 Progression of heterotopic ossification in trauma-induced mouse model with celecoxib treatment (n = 12 per group). (**A**) Representative imageological examination of Achilles tendons by micro-computed tomography *(μCT)*. The *scale bar* measures 10 mm. (**B**) Hematoxylin-eosin *(HE)* staining of Achilles tendons. The *scale bar* measures 25 μm. *D1*, day 1; *W6*, week 6.

selection in patients without cardiovascular disease. In this study, we investigated whether celecoxib could inhibit the progression of initiated HO.

We retrospectively analyzed 17 post-traumatic patients in whom HO was diagnosed and 20 patients treated with celecoxib after surgery. Ectopic ossification appeared at 1 or 2 months in the patients who did not receive celecoxib after surgery. After HO was diagnosed by plain radiographs, these patients were administered celecoxib orally, and the results indicated that celecoxib could not inhibit the further development of initiated HO. However, the patients who received celecoxib immediately after surgery had a comparatively low incidence of HO. Similarly, the animal experiments showed that the administration of celecoxib starting immediately after surgery could significantly attenuate the progression of HO, but the delayed treatment had no significant suppression effect. These results are consistent with what we have inferred previously. A reliable interpretation of this conclusion may be related to the mechanism of celecoxib to inhibit the initiation of HO. Celecoxib is an analgesic that can inhibit HO through prostaglandin E2,[2,5,37] which is an important factor in promoting bone development, bone healing, and osteogenesis.[7,15,29,31,36] Treatment with NSAIDs in the early stage can inhibit the differentiation of osteoprogenitor cells into osteoblasts by inhibiting prostaglandin E2 activity and can mitigate the progression of HO finally.[9,10] When HO is visible, the osteoprogenitor cells have differentiated into osteoblasts, with proliferation and differentiation of osteoblasts into osteocytes, matrix secretion, and mineralization, so the development of HO in the osteogenesis stage cannot be ceased by celecoxib via depressing prostaglandin E2. Thus, an NSAID will exert the best efficacy if it is given as early as possible.[18]

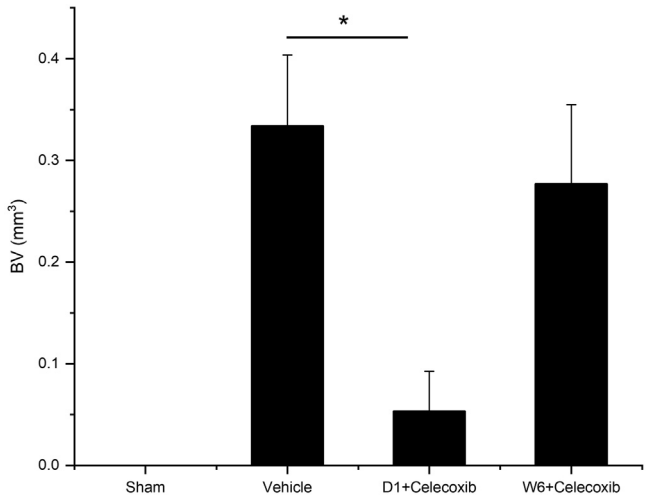

Figure 4 Bone volume *(BV)* of heterotopic ossification in different groups of mice (n = 12 per group). Data are presented as mean ± standard deviation. *$P = .01$. *D1*, day 1; *W6*, week 6.

Once HO has formed, the common prophylaxis protocols mentioned earlier are not relatively effective, so surgical excision of non-genetic HO is often necessary to remove the HO tissue masses, increase joint mobility, and restore functional outcomes.[34] However, complete ectopic bone excision is not always practical or feasible as HO does not respect the natural anatomic structures invariably, and surgical resection requires further hospitalization and may cause complications including inflammation, blood loss, and enlargement of the lesion, as well as an increase in the risk of another occurrence of HO. We previously reported that HO progression is due to the excessive activation of transforming growth factor β and the recruitment of

mesenchymal stem or progenitor cells for osteogenesis coupled with type H vessel formation, and oral administration of celecoxib on the day of surgery could effectively inhibit the recurrence of heterotopic bone in the elbow joint after resection.[33,38] Because the reappearance of HO after resection is largely identical to new bone formation, prophylactic strategies such as NSAIDs and radiotherapy are also valid to prevent the resurgence of HO,[21] as NSAIDs inhibit the production and release of both physiological and inflammatory prostaglandins in muscles and soft tissues and radiation therapy inhibits the differentiation of HO progenitor cells into chondrocytes or osteoblasts.[12,25,32] NSAIDs are as effective as radiotherapy in the prevention of HO occurrence and recurrence; their combination will be more effective.[24]

Our study demonstrated that celecoxib could inhibit the initiation of HO but could not suppress the propagation of HO. Further research to elucidate the mechanism of HO formation is essential, and the exploitation of drugs that can eliminate already formed HO would have clinical significance. Studying an early-warning index with high specificity and sensitivity in the early stage after trauma to help clinicians determine whether NSAIDs should possibly be used before initiation of HO will also be very meaningful.

Conclusion

Our retrospective study and animal experiment both showed that immediate administration of celecoxib after surgery could significantly inhibit the formation of HO, which was consistent with our clinical manifestations. However, if the heterotopic bone was visible by imaging diagnosis, the administration of celecoxib could not effectively inhibit the progression of HO.

Disclaimer

This study was supported by the National Natural Science Foundation of China (81672164) and the Key Research Project of the Health and Family Planning Commission of Wuxi City (Z201714).

The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

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