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The efficacy of celecoxib in preventing heterotopic ossification recurrence after open arthrolysis for post-traumatic elbow stiffness in adults

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Background: Heterotopic ossification (HO) recurrence after joint surgery is always a disturbing problem for patients and surgeons. Our study was performed to assess the efficacy and safety of celecoxib in preventing the recurrence of HO after open arthrolysis for post-traumatic elbow stiffness.

Methods: We retrospectively studied 152 patients with stiff elbows caused by post-traumatic HO. After surgery, 77 patients received celecoxib (200 mg once daily) for 28 days, whereas 75 did not. Radiographic evaluation was performed at 3, 6, and 9 months postoperatively. Univariate and multivariate analyses were performed to determine which factors affected HO recurrence.

Results: HO was both more common and more severe in the no-celecoxib group than in the celecoxib group at 3, 6, and 9 months after surgery. A significant difference was observed between the 2 groups in terms of postoperative extension ($P = .030$), flexion ($P = .008$), and pronation ($P = .005$); however, no significant difference in postoperative supination was noted ($P = .622$). Logistic regression analysis showed that taking celecoxib was the protective factor for HO recurrence, whereas overweight (body mass index > 25) and male gender were the risk factors.

Conclusions: A short course of celecoxib aids in the prevention of HO recurrence after open arthrolysis for elbow stiffness in adults and could be an effective and safe option.

Level of evidence: Level III, Retrospective Cohort Design, Treatment Study.

Keywords: Heterotopic ossification; celecoxib; elbow stiffness; open arthrolysis; risk factor; trauma

As a common complication after trauma, elbow stiffness is defined as a flexion-extension arc of $<100°$ or flexion contracture of $>30°$.[8] When nonoperative management fails after more than 6 months, patients whose lifestyle or vocation is greatly affected often request open arthrolysis to restore elbow function. However, because of the clinical recurrence of heterotopic ossification (HO) postoperatively, some patients may suffer from repeated elbow stiffness and

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have to undergo repetitive surgical interventions to excise new bone formation. A systematic review of published clinical results of surgeries for HO around the elbow found a clinical recurrence rate of HO of 13.7% after excision in post-traumatic elbows (with recurrence being defined as loss of motion or a reoperation due to HO).[11]

Clinicians have been searching for ways to prevent the occurrence of HO since the 1970s. Nonsteroidal anti-inflammatory drugs (NSAIDs)[3,4,10] and radiation therapy[15,17] are the 2 major measures reported to be effective in the prophylaxis of HO. Compared with radiation therapy, the use of NSAIDs, which inhibit the cyclooxygenase enzymes (COX-1 and COX-2), is regarded as an easier and more cost-effective method and is recommended as a general prophylactic in most hospitals, although it has side effects that must be taken into account.[19] Celecoxib, a selective COX-2 inhibitor, retains anti-inflammatory action but reduces the occurrence of side effects caused by other NSAIDs, especially on gastrointestinal toxicity[1] and hemostasis.[12] The majority of studies involving celecoxib have reported that it is effective in preventing ectopic bone formation after total hip arthroplasty with fewer side effects than with other NSAIDs.[10,20,23] However, to our knowledge, the independent effect of celecoxib in preventing HO recurrence after open arthrolysis for elbow stiffness has not yet been reported in the English-language literature. This study aimed to address this issue as well as to evaluate the impact of age, sex, body mass index (BMI), and preoperative Hastings and Graham classification on the development of HO after open elbow arthrolysis.

Materials and methods

This is a retrospective cohort study of 307 patients who suffered from elbow stiffness with HO and were then treated with open arthrolysis combined with a hinged external fixator by a single surgeon (C.F.) at our institution from January 2010 to April 2013. Patients were eligible for inclusion if (1) they were aged $\geq$18 years, (2) they suffered from post-traumatic elbow stiffness, or (3) they had a diagnosis of mature HO based on confirmation of cortical boundaries observed on serial radiographs. Patients were excluded if (1) their HO was the result of trauma caused by burns, central nervous system injury, or genetic disease; (2) they had a history of peptic ulceration, gastrointestinal bleeding, coagulation defects, cerebral or myocardial infarction, allergy to NSAIDs or sulfonamides, renal or hepatic insufficiency, or mental disorder; or (3) they failed to complete routine radiographic evaluation at 3, 6, and 9 months.

According to the inclusion and exclusion criteria, a total of 152 patients were included in our study. Specifically, 45 patients were excluded because of incomplete radiographic evaluation at 3, 6, and 9 months. The patients included were 69 men and 83 women, with an average age of 43.9 (18-82) years. Open elbow arthrolysis was performed >6 months after trauma or last surgery. The surgical approaches were based on the location of the HO and previous scars from past operations. The surgical techniques were similar to those described in previous studies.[13,21] A hinged external fixator was applied for 6 to 8 weeks in most cases to provide sufficient stability and to allow immediate postoperative rehabilitation. After surgery, the patients were divided into 2 groups: 77 patients who received celecoxib 200 mg once daily for 4 weeks for acute pain relief according to the physician's suggestions (celecoxib group) and 75 patients who were not willing to take celecoxib just for acute pain relief (no-celecoxib group). All patients were standardized to a rehabilitation program from the first postoperative day. A cycle of exercises including flexion, extension, and rotation were devised to guide all patients, gradually including active and passive exercises, which should be performed at least 4 times a day for 30 minutes each time. This progressive exercise program continued for at least 2 months after discharge.

Range of motion (ROM) of the elbow was measured with a hand-held goniometer. Radiographic follow-up consisted of anteroposterior and lateral radiographs obtained preoperatively and at 3, 6, and 9 months postoperatively. The presence of HO was assessed on these radiographs by 2 radiologists according to the classification system devised by Hastings and Graham.[5] Class I includes radiographically evident HO but without functional limitation. Class II includes limited yet functional range of elbow motion but radiographically demonstrable HO with functional limitation in 1 or more planes of motion, subdivided into IIA, IIB, and IIC. Limitation of flexion-extension constitutes subclass IIA, limitation of pronation-supination constitutes subclass IIB, and limitation in both planes forms subclass IIC. Class III includes complete ankylosis of the particular articulation. The 2 radiologists were blinded to each patient's treatment regimen. Any disagreement was resolved on the basis of the opinion of a third radiologist.

The Fisher exact test was used to evaluate the association between treatment with celecoxib and recurrence of HO at 3, 6, and 9 months. A rank sum test was used to assess the association between taking celecoxib at 3, 6, and 9 months and the severity of the disease based on the Hastings and Graham classification. ROM was analyzed by the unpaired Student t test. The association of age and BMI with HO was tested by unpaired Student t test, and the association of sex and preoperative Hastings and Graham classification with HO was tested by χ^2 analysis. Considering the interactions between the variables, a nonconditional logistic regression analysis was performed to analyze the relationship between and among variables at 9 months. A P value $<.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

As shown in Table I, there were no significant differences between the 2 groups with regard to sex, age, BMI, or Hastings and Graham classification preoperatively. Overall, the number of patients with HO recurrence (including class I, class II, and class III) was 63 (41.4%), among whom severe HO (class III) was found in 12 patients (7.9%) at 9 months after open arthrolysis.

HO recurrence was more common in the no-celecoxib group than in the celecoxib group at 3 months (30.7% vs. 10.4%; $P = .002$), 6 months (50.7% vs. 18.2%; $P < .001$),

Table I Patient demographics and preoperative evaluation of HO

	Sex, male (%)	Age (years)	BMI (kg/m^2)	Pre-HO classification *			
				IIA	IIB	IIC	III
Celecoxib	52.0	43.6 ± 15.1	24.3 ± 3.5	21	17	25	14
No-celecoxib	45.3	44.1 ± 12.3	24.9 ± 3.9	25	13	26	11
P value	.415	.820	.326	.559			

* Preoperative HO classification according to the Hastings and Graham classification.

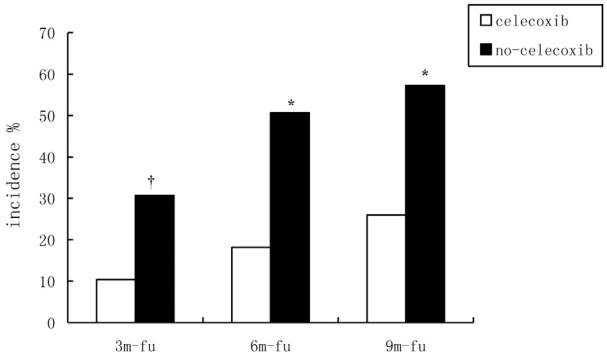

Figure 1 Incidence of HO in celecoxib and no-celecoxib groups at 3 months, 6 months, and 9 months of follow-up after surgery. $^{\dagger}P = .002$; $^{*}P < .001$.

and 9 months (57.3% vs. 26.0%; $P < .001$) postoperatively (Fig. 1). Similarly, comparison of the severity of HO between the 2 groups revealed that patients who did not take celecoxib were more likely to experience more severe HO based on the Hastings and Graham classification at 3 months ($P = .002$), 6 months ($P < .001$), and 9 months ($P < .001$) postoperatively. Moreover, 12 of the patients who did not receive celecoxib were found to have class III HO on radiographs at 9 months after surgery and were advised to undergo repeated arthrolysis when the HO became mature. No class III HO was seen in those patients who received celecoxib.

Data concerning preoperative and postoperative ROM of the elbow in the celecoxib and no-celecoxib groups are summarized in Table II. There were no significant intergroup differences with respect to preoperative mean range of extension ($P = .790$), flexion ($P = .179$), pronation ($P = .148$), and supination ($P = .350$). Despite the recurrence of HO, the final ROM was considerably improved. In the celecoxib group, the average postoperative extension and flexion were 7° (range, −5° to 56°) and 129° (range, 55°-155°), respectively, and the average postoperative pronation and supination were 71° (range, 0°-90°) and 71° (range, 30°-90°), respectively. In the control group, the average postoperative extension and flexion were 11° (range, 0°-40°) and 122° (range, 85°-145°), respectively, and the average postoperative pronation and supination were 63° (range, 0°-90°) and 72° (range, 20°-90°), respectively. A significant difference was observed between

Table II Preoperative and postoperative ROM

	Celecoxib	No-celecoxib	*P* value
Preoperative mean ROM (degrees)			
Extension	37 (0-90)	37 (0-80)	.790
Flexion	75 (15-140)	81 (30-130)	.179
Pronation	43 (0-90)	50 (0-90)	.148
Supination	55 (0-90)	60 (0-90)	.350
Postoperative mean ROM (degrees)			
Extension	7 (−5 to 56)	11 (0-40)	.030
Flexion	129 (55-155)	122 (85-145)	.008
Pronation	71 (0-90)	63 (0-90)	.005
Supination	71 (30-90)	72 (20-90)	.622

the 2 groups in terms of postoperative extension ($P = .030$), flexion ($P = .008$), and pronation ($P = .005$); however, no significant difference in postoperative supination was noted ($P = .622$).

Furthermore, univariate analysis showed that men had a higher incidence of HO compared with women at 9 months after arthrolysis (59.5% vs. 24.4%; $P < .001$; Table III). In addition, when focusing only on the no-celecoxib group, we found that 82.4% of men who did not receive celecoxib developed HO compared with 36.6% of women ($P < .001$). More interestingly, 40.0% of men who received celecoxib nevertheless developed HO, whereas only 10.8% of women developed HO ($P = .004$), indicating that celecoxib had a better prophylactic effect in female patients than in male patients. Analysis of BMI revealed that those who developed HO at 9 months had a higher BMI, with a mean value of 26.8 ± 2.9 kg/m^2 (19.7–33.3), compared with those who did not develop HO, in whom the mean BMI was significantly lower at 23.0 ± 3.5 kg/m^2 (17.4–30.6) ($P < .001$). No significant association was found between HO recurrence and other variables, including age ($P = .951$) and preoperative Hastings and Graham classification ($P = .467$). Similarly, nonconditional logistic regression analysis showed that taking celecoxib (odds ratio [OR], 0.152; $P < .001$) was a significantly protective factor for HO recurrence, whereas overweight (BMI > 25; OR, 1.404; $P < .001$) and male gender (OR, 2.741; $P = .038$) were risk factors.

There was no notable difference in the incidence of other postoperative complications, such as neuropathy, incomplete wound healing, or infection, between the 2 groups after open arthrolysis. Two patients in the celecoxib group

Table III Results by univariate analysis for the factors affecting HO recurrence at 9 months

Variable	No HO recurrence (n = 89)	HO recurrence (n = 63)	*P* value
Sex, N			<.001
Male	30	44	
Female	59	19	
BMI (mean ± SD)	23.0 ± 3.5	26.8 ± 2.9	<.001
Age (mean ± SD)	43.9 ± 14.0	43.7 ± 13.5	.951
Pre-HO classification, N			.467
II	76	51	
III	13	12	

complained of obvious nausea or gastrointestinal pyrosis at 14 and 16 days after surgery, respectively. Both symptoms were relieved by taking celecoxib in combination with a proton pump inhibitor, and this combination regimen was continued to the end of the treatment. No cardiovascular events were observed in patients taking celecoxib, and none of the patients discontinued the trial.

Discussion

As a common cause of elbow stiffness, HO is always a disturbing problem for patients and surgeons. In the upper extremity, HO frequently occurs after elbow trauma and can result in severe functional impairment, for which surgical treatment is necessary. Although arthroscopic arthrolysis of stiff elbows has been regarded as a surgical procedure with a much lower risk for occurrence of HO, it was best indicated in elbows without the presence of heterotopic bone or neuropathy. Open elbow arthrolysis was selected technically because it allowed complete excision of heterotopic bone while stability was maintained. However, the recurrence of HO around the elbow has been reported in previous studies after index surgical release.[9,18] When postoperative recurrence of HO leads to pain, neuropathy, or incapacitating restriction of ROM, further reoperation may be unavoidable. In our study, in the absence of prophylactic treatment, the incidence of HO recurrence at 9 months after open arthrolysis for post-traumatic elbow stiffness was 57.3%, and the incidence of severe HO was 16%. These incidence rates are relatively high, and of our study participants, at least 12 patients who did not receive celecoxib would require further surgical re-excision to resolve their limited elbow function.

As the recurrence of HO around the elbow after simple excision is surprisingly frequent, many surgeons have made every effort to prevent it, with NSAIDs and radiation therapy being the most common prophylactic treatments. During the past decades, NSAIDs have been shown to be effective in preventing HO after hip arthroplasty. NSAIDs act by modulating the release of inflammatory cytokines, in particular by lowering the level of prostaglandins, which are known to be potent costimulators, with bone morphogenetic proteins, in the induction of HO.[7]

A wide range of NSAIDs have been proposed as effective prophylactic therapy, with indomethacin being the most extensively studied drug. However, selection of the optimal prophylactic drug for HO was difficult, considering the efficacy and safety of available drugs. Romanò et al[20] reported that indomethacin induced gastrointestinal side effects, excessive bleeding, and mental confusion when it was used for the prevention of HO after hip replacement. Fortunately, celecoxib has the same efficacy as indomethacin with fewer side effects because it inhibits COX-2 alone, leaving COX-1 function intact. In our study, we found that celecoxib was associated with a significant reduction in the incidence of HO recurrence at 3 months, 6 months, and 9 months after open elbow arthrolysis. Furthermore, patients who took celecoxib were more likely to achieve better postoperative ROM of extension, flexion, and pronation than were those who did not. The lower incidence and severity level of HO recurrence could account for less restricted ROM and better functional outcomes for the patients in the celecoxib group. Considering the undesirable gastrointestinal and cardiovascular side effects of celecoxib,[25] we chose short-term (4 weeks) and low-dose (200 mg once a day for 28 days) treatment for HO prophylaxis. As a result, only 2 gastrointestinal events and no cardiovascular events were documented in our patients taking celecoxib. Accordingly, we consider our dosing schedule of celecoxib is ideal for HO prophylaxis after open arthrolysis for elbow stiffness.

Moreover, we confirmed that male gender and BMI are risk factors for the development of HO, in agreement with the findings reported in many studies of hip arthroplasty and acetabular fractures.[10,16] First, male gender was associated with more severe HO and a worse response to celecoxib in HO prevention compared with female gender. We presume that female sex hormones, including estrogen and progesterone, might have a beneficial effect in inhibiting HO by affecting the balance of osteoblasts and osteoclasts, as these hormones are well known to play a role in bone metabolism.[14,24] Second, we also found that overweight (BMI > 25) correlated with a higher rate of recurrence of HO. As other studies have reported,[6,16] patients with overweight (BMI > 25) showed a positive correlation with a high level of activated adipose tissue macrophages, which are important for secretion of inflammatory cytokines and adipokines. We therefore hypothesize that adipose tissue macrophages might contribute to heterotopic bone formation. In light of this, it is recommended that patients control their body weight before surgery. Further investigations are warranted to verify these 2 hypotheses. Our study showed that there were no differences in preoperative Hastings and Graham classification between patients with and without HO recurrence after surgery. This suggests that preoperative HO classification merely indicates the severity rather than the susceptibility of individuals to develop HO. This may also

partially support the findings reported by other authors that patients with partially or completely restricted ROM of the elbow due to HO could never recover comparable motion after surgical release.[2,22]

There are several limitations to our study. As it is a retrospective study, selection bias cannot be excluded. On the one hand, 45 patients were excluded because of incomplete radiographic evaluation. On the other hand, patients included in this study were divided into 2 groups according to whether they took celecoxib for postoperative pain relief. These 2 aspects may lead to potential selection bias. Besides, other confounding factors, such as nutrition, speed of bone metabolism, and other medical comorbidities, may influence the efficacy of celecoxib to some degree. Last, the gastrointestinal and cardiovascular side effects of celecoxib were recorded simply according to the related complaints or symptoms of the patients in our study. More objective tests, such as blood tests, electrocardiography, and endoscopy, should be carried out for a more comprehensive assessment of its safety. More and larger prospective trials should be performed to further elucidate the beneficial effects of celecoxib and to determine which combination of risk factors can be effectively ameliorated by celecoxib, thus providing guidance for standardized use and dosage of celecoxib when it is indicated for HO prophylaxis.

Conclusion

Our findings demonstrate that a short course of celecoxib (200 mg once daily) could be an effective and safe prophylactic treatment against HO recurrence after open arthrolysis for post-traumatic elbow stiffness in adults. In addition, we also found that male gender and obesity (BMI $>$ 25) were risk factors for the development of elbow HO postoperatively.

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