

## Original Article

# Prevention of heterotopic ossification after spinal cord injury with COX-2 selective inhibitor (rofecoxib)

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**Study design:** A randomized, prospective, double-blind, placebo-controlled clinical trial.

**Objectives:** To determine the effect of COX-2-selective inhibitor on the prevention of heterotopic ossification (HO) after spinal cord injury (SCI).

**Setting:** County and University Teaching Hospital, Miami, FL, USA.

**Methods:** A total of 76 patients were enrolled in the study. Among them, 39 patients received placebo, and 37 received COX-2-selective inhibitor rofecoxib 25 mg daily for a period of 4 weeks. Prevention was started 3 weeks after spinal cord injury (SCI). In both groups of patients there was similar age as well as the level of SCI and ASIA impairment scale. Two methods were used to diagnose early HO, clinical symptoms and bone scintigraphy. Radiography was used for diagnosis of late stages of HO development.

**Results:** A significantly lower incidence of HO was found in the rofecoxib group (13.4%) than in the placebo group (33.3%;  $P < 0.05$ ). In patients receiving rofecoxib, there was a 2.5 times lower relative risk of developing HO than in the placebo group (95% CI, 2.3–6). There were no patients who discontinued the study due to adverse effects of medication.

**Conclusion:** Our data suggest that COX-2-selective inhibitor rofecoxib is an effective medication in prevention of HO after SCI.

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## Introduction

Heterotopic ossification (HO) is one of the most common orthopedic complications after spinal cord injury (SCI). Incidence of HO after SCI is 40–50%;<sup>1–4</sup> in 10–20% of these patients HO develops in a more severe form, which usually needs surgical treatment.<sup>5,6</sup> The etiology of HO remains unknown. Based on the results obtained from experiments in animal models, it seems that mesenchymal cells play an important role in the development of HO. These cells may, under various systemic or local stimuli, differentiate ectopically into osteoblasts, the cells responsible for bone formation.<sup>7,8</sup> Since the etiology of HO is uncertain, it is difficult to design an effective prevention. However, it is well known that nonsteroidal anti-inflammatory drugs (NSAID) have significant preventive effect on the development of HO after total hip arthroplasty (THA).<sup>9,10</sup> Based on

these positive results in orthopedic patients, we conducted a study where NSAID indomethacin was used in the prevention of HO after SCI.<sup>11</sup> The results of that study showed a significant three-fold reduction in the incidence of HO in indomethacin-treated patients. Since indomethacin belongs to a group of nonselective NSAID with significant gastrointestinal toxicity that appears to be related to cyclooxygenase 1 (COX-1) inhibition,<sup>12</sup> the goal in the present study was to evaluate the effect of COX-2-selective inhibitor that is known to have significantly lower incidence of gastrotoxicity than nonselective NSAID.

## Methods

The study was an evaluation of the effect of COX-2-selective inhibitor rofecoxib on prevention of HO after SCI. Patients involved in the study were admitted to the rehabilitation center and randomly divided into two groups. Exclusion criteria were history of peptic ulcer

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disease or gastrointestinal bleeding, age of patient outside the range of 18–60 years and pregnancy. There was no concomitant use of any other NSAID during the study. One group received oral rofecoxib (Vioxx, Merck, Rahway, NJ, USA) 25 mg daily and the other group placebo for a period of 4 weeks. An informed consent form, approved by institutional review board, was obtained from all patients prior to the study. The number of patients in each group, age, gender and time period after injury are shown in Table 1. Table 2 summarizes clinical characteristics, level of spinal cord injury and ASIA impairment scale.

Patients in the rofecoxib group were started in the study  $25 \pm 7$  days after SCI, and those in the placebo group were started  $23 \pm 5$  days postinjury. Diagnosis of HO was based on clinical symptoms and signs (local edema, fever and decreased joint range of motion) and bone scintigraphy by clinician and radiologist without the knowledge of patient group selection. A three-phase bone scintigraphy was used as reported earlier.<sup>13</sup> The following diagnostic algorithm was used: All patients on the study medication (COX-2-selective inhibitor or placebo) were followed clinically until they developed swelling of joint(s), with or without fever or reduction of ROM. Prior to bone scintigraphy, radiographic studies and compression ultrasonography were obtained to rule out trauma or vein thrombosis of affected extremity. In patients with positive bone scintigraphy for HO, the study was discontinued and treatment was started with disodium etidronate (Didronel, Proctor&Gamble Pharmaceuticals Inc., Mason, OH, USA) as reported earlier.<sup>14</sup>

The significance of differences between the groups was statistically evaluated by  $\chi^2$ -test.

## Results

Table 1 illustrates similar age, gender and the postinjury period. Also, there were similar clinical characteristics; the level of paralysis and ASIA impairment scale (Table 2).

Table 3 summarizes the results of the study. In the control group of patients taking placebo, 33.3% developed HO that was statistically higher than 13.4% taking rofecoxib ( $P < 0.05$ ).

Also, there was a higher risk for developing HO in placebo group; RR = 2.5 (95% CI, 2.3–6). In the present study, there were no patients in either group who had significant gastrointestinal adverse effects due to experimental drug.

**Table 1** Groups of SCI patients

Drug	Number of patients	Age (years)	Postinjury (days)	Female	Male
Rofecoxib	37	$28 \pm 13$	$25 \pm 7$	2	35
Placebo	39	$36 \pm 10$	$23 \pm 5$	9	30

**Table 2** Clinical characteristics of patients

Drug	Paraplegia	Tetraplegia	ASIA Score			
			A	B	C	D
Rofecoxib	24	13	28	8	1	0
Placebo	21	18	27	8	4	0

**Table 3** Incidence of HO after prevention with COX-2 inhibitor

	Positive	Negative
Rofecoxib	5 (13.4%)	32 (86.6%)
Placebo	13 (33.3%)	26 (66.7%)
Statistical significance <sup>a</sup>	$P < 0.05$	

<sup>a</sup>Chi square *t*-test

**Table 4** Comparison of results of prevention with two different NSAID

Drug	Decreased incidence of HO
Nonselective NSAID (indomethacin <sup>a</sup> )	2.7 times
COX-2 selective inhibitor (rofecoxib)	2.5 times

<sup>a</sup>Data previously published<sup>11</sup>

## Discussion

The prevention of HO with NSAID in patients who have had THA has been investigated extensively and showed to be effective.<sup>8,9,15,16</sup> Numerous studies in orthopedic patients have documented that the incidence of HO after THA is significantly reduced by oral indomethacin (25 mg three times daily for 6 weeks postoperatively). These observations stimulated our first study in SCI patients, where we evaluated the effect of indomethacin on the incidence of HO after SCI.<sup>11</sup> We found 2–3 times lower incidence of HO after indomethacin prevention. However, nowadays there has been some reservation in using indomethacin and other similar NSAID. Indomethacin belongs to a group of nonselective NSAID, which is known to be associated with higher incidence of adverse effects on gastrointestinal (GI) tract than COX-2-selective inhibitors.<sup>17–19</sup> Owing to beneficial pharmacological characteristics of COX-2-selective inhibitors, we designed the present study where we evaluated rofecoxib. As illustrated in Table 4, similar to the first double-blind study with indomethacin, rofecoxib had similar effectiveness in the prevention of HO after SCI.

The results of our studies with indomethacin and rofecoxib confirm previous reports on beneficial effect of NSAID on development of HO when they were used in 'secondary' prevention after surgical removal of HO.<sup>20–22</sup> It appears that inflammation plays an important role in the genesis of HO in the early stages after SCI as well as after surgical resection of HO.

The mechanism of action of NSAID on the prevention of HO remains to be determined, but it seems that these drugs have inhibitory effects on the expression of factors that trigger the ectopic osteogenesis. At the site of bone formation, the crucial events are the recruitment, proliferation and differentiation of mesenchymal stem cells (MSCs).<sup>23</sup> These cells are primitive precursors capable of differentiating in many cell types including osteoblasts, chondroblasts, adipocytes, fibroblasts and smooth muscle cells.<sup>24,25</sup> Recent studies have shown that prostaglandins regulate MSC differentiation into osteoblastic cells and are critically involved in new bone formation.<sup>26</sup> Another factor important in formation of HO are bone morphogenic proteins (BMPs).<sup>27,28</sup> Among the BMPs, BMP-2, -4, -7 have been recognized as potent bone inducers.<sup>29,30</sup> It is not clear as to what is the functional relationship between prostaglandins and BMPs, but it seems that prostaglandins have more 'upstream' function and are able to induce BMP expression in soft tissue.<sup>26</sup> Based on the present knowledge on new bone formation, the effect of NSAID on HO is in the earliest stages, at the time of recruitment and proliferation of precursors of bone-forming cells. Blocking the synthesis of prostaglandins by NSAID inactivation of COX-2 enzymes the early processes of bone formations are inhibited.

Our study was not designed to determine the effect of COX-2-selective inhibitors on GI toxicity; however, based on the data from large clinical trials on GI effects of COX-2-selective inhibitors, in our opinion, COX-2-selective inhibitors are preferred in prevention of HO after SCI. These drugs have similar efficacy to non-selective NSAID but better tolerability and less adverse effects.<sup>31-34</sup>

## Conclusion

The present study indicates that COX-2-selective inhibitor rofecoxib is an effective drug in the prevention of HO after SCI. In patients receiving rofecoxib, there was 2.5 times lower incidence of HO based on clinical and scintigraphic diagnosis. Our data also suggest that inflammation is an early clinical sign in the development of HO after SCI and that NSAID may have significant inhibitory effect on formation of ectopic bone. If the future clinical investigation confirms our results, the use of NSAID in early periods after SCI might be recommended as a standard of care for SCI patients.

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