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Original Article

Prevention of heterotopic ossification after spinal cord injury with indomethacin

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Study design: A randomized, prospective, double-blind, placebo-controlled clinical trial.
Objectives: To determine the effect of indomethacin on the prevention of heterotopic ossification (HO) following spinal cord injury (SCI).
Setting: County Hospital, Miami, Florida, USA.
Methods: Sixteen patients were treated with slow-release indomethacin 75 mg daily and 17 patients received placebo for a period of 3 weeks. Prevention was started 21 ± 14 days after SCI. In both groups of patients there was similar age of the patients as well as the level of SCI and ASIA impairment scale. Two methods were used to diagnose HO, bone scintigraphy and radiographic examination. Bone scintigraphy with technetium labeled methylene-diphosphonate was used for diagnosis of early stage, while radiography was used for diagnosis of late stage of HO development.
Results: A significantly lower incidence of early HO was found in the indomethacin group (25%) than in the placebo group (65%; $P<0.001$). Similarly there was a significant reduction of late HO in the indomethacin group (12.5%) as compared to the placebo group (41%; $P<0.001$).
Conclusion: Our data suggest that indomethacin used during the first 2 months after SCI is effective in prevention of HO in a significant number of patients.
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Keywords: heterotopic ossification; spinal cord injury; NSAID

Introduction

HO is a frequent complication after SCI. The incidence of HO, based on the retrospective studies, varies from 16 to 78%.[1–5] Prospective evaluations of HO showed an incidence of approximately 50%.[6–9] HO occurs most frequently in the first 2 months after SCI below the level of paralysis.[8–10] It forms adjacent to the major joints and in severe cases causes reduction of joint mobility. In addition, there is also comorbidity of HO with deep vein thrombosis (DVT)[11–13] and decubitus ulcers[14–17] in the same anatomical region. The etiology of HO is unknown which represents difficulties in designing preventive and therapeutic protocols. Today there is no effective prevention of neurogenic HO. The prevention of HO with etidronate after SCI had an effect mainly on the reduction of progression of ectopic bone than on the incidence of this complication.[18,19]

The effect of NSAIDs on the prevention of HO following total hip arthroplasty (THA) is well accepted.[20,21] In only a few patients with SCI these drugs have been used as a 'secondary' prevention after surgical removal of HO. The effect of NSAIDs in the 'primary' prevention of HO after SCI has not been evaluated. The goal of the present study was to determine the effect of indomethacin, a NSAID, on the prevention of HO in the early stages following SCI.

Methods

The study was an evaluation of NSAID effect on prevention of HO after SCI in the early stage of rehabilitation using a randomized, prospective, double-blind, placebo-controlled design. Patients involved in the study were admitted to the rehabilitation center and randomly divided into two groups. One group received slow release oral indomethacin (Indocin SR, MSD, Division of Merck & Co. Inc., West Point, PA, USA) 75 mg daily, the other group of patients received placebo for 3 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, level of spinal cord injury and ASIA impairment scale are shown in Table 1. Patients

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Table 1 The groups of SCI patients

	Age (years)	*Paraplegia ASIA scale*				*Tetraplegia ASIA scale*				*Number of patients*	*Post-injury (days)*
		A	*B*	*C*	*D*	*A*	*B*	*C*	*D*		
NSAIDs	34±12	7	0	2	0	5	1	0	1	16	20±14
Placebo	32±11	8	0	0	0	7	1	1	0	17	23±15

in the indomethacin group were started in the study 20±14 days after SCI, and those in the placebo group were started 23±18 days post-injury. Both groups of patients were given oral misoprotol (Cytotec, C.D. Searle & Co., Chicago, IL, USA) 200 μg four times daily as a prevention of gastric ulceration caused by NSAIDs. Because of the abortifacient property of misoprostol, female patients were excluded from this study.

Two methods were used for diagnosis of HO. Bone scintigraphy was used to demonstrate the early stage of HO development, while radiography was used in the diagnosis of late stage ossification. The early diagnosis of HO, prior to radiographic findings of ossification in soft tissue, was also based on the presence of clinical signs and symptoms (local erythema, swelling, loss of joint range of motion and fever). The following diagnostic algorithm was used: All patients on the study medication (NSAID or placebo) were followed clinically until they developed swelling of joint(s), with or without fever or reduction of ROM. The onset of clinical symptoms in the indomethacin treated group was on average 30 days later while in the placebo group it was 20 days. Prior to bone scintigraphy, radiographic studies and compression ultrasonography were obtained to rule out trauma or DVT of affected extremity. A three phase scintigraphy was used with technetium 99m labeled methylene diphosphate (99mTc-MCP) as reported earlier.[8,22] In patients with positive bone scintigraphy for HO, the study was discontinued and treatment was started with disodium etidronate (Didronel, Procter & Gamble Pharmaceuticals, Inc., Mason, OH, USA) as previously described.[9,22] In brief, patients initially received intravenous etidronate 300 mg daily for three successive days followed by oral etidronate 20 mg/kg/day for 6 months. Follow up of patients consisted of radiographic examinations every 2 months for the first 6 months to determine the incidence of late stage heterotopic bone formation. During the study both groups of patients were on a routine rehabilitation program and continued with a home exercise program after discharge from the hospital.

Statistical significance of differences between the groups was determined by Chi square test and Student's *t*-test.

Results

Table 1 illustrates similar age in both groups studied as well as similar level of disability based on ASIA scale system. Also, there was a similar post-injury time of the patients into the study. Tables 2 and 3 summarize the results of the study. There was a significantly higher incidence of early HO, diagnosed by bone scintigraphy, in the placebo group (65%) than in the group of patients taking indomethacin (25%) ($P<0.001$). We also found differences in the onset of clinical symptoms. In the indomethacin group the onset of symptoms was later (31.7±7 days) than in the placebo group 19.2±11 days); this difference in time of HO development was statistically significant ($P=0.048$). In the group of patients receiving indomethacin, the inflammatory reactions, ie swelling, erythema and fever were of a lesser degree than in the placebo group. Patients with positive HO on bone scintigraphy in both groups underwent identical treatment with etidronate for 6 months. The results of radiographic follow up of these patients are shown on Table 3. In the placebo group, seven patients (41%) developed radiographic evidence of HO, significantly higher than two patients (12.5%) in the indomethacin group ($P<0.001$). The radiographic analysis of HO showed that in the placebo group, four patients had solitary location, while in the remaining three patients HO developed around two or more joints, with larger bone masses than patients receiving indomethacin. The patients in the indomethacin group had solitary lesions

Table 2 The incidence of heterotopic ossification diagnosed in early stage by bone scintigraphy

	Negative	*Positive*	*Onset (days)*
NSAIDs	12 (75%)	4 (25%)	32±7
Placebo	6 (35%)	11 (65%)	19±11
Statistical significance		$P<0.001$*	$P<0.05$**

*Indicates statistical significance by Chi square test, **by Student *t*-test

Table 3 The incidence of heterotopic ossification diagnosed in later stage by radiography

	Negative	*Positive*	*Onset (months)*
NSAIDs	14 (87.3%)	2 (12.5%)	1.5 (range: 1–2)
Placebo	10 (59%)	7 (41%)	7 (range: 1–12)
Statistical significance		$P<0.001$*	

*Chi square test

with a small island of bone in soft tissue. In both group of patients the most common gastrointestinal symptom was upper abdominal discomfort; the symptoms or signs of gastrointestinal bleeding or any other serious complications of NSAIDs were not noted. There were no patients who discontinued the study due to adverse effects of medication.

Discussion

Prevention of HO after SCI has been evaluated in a limited number of studies. 'Primary' prevention was evaluated in patients following acute SCI while 'secondary' prevention was studied after surgical removal of HO in an attempt to reduce recurrence of HO. 'Primary' prevention was studied by Stover and coworkers in a prospective, double blind clinical trial using oral etidronate.[18,19] The rationale was that etidronate inhibits the transformation of amorphous calcium phosphate into crystalline hydroxyapatite, and through this effect blocks the mineralization of bone matrix. A total of 149 patients completed this study, 79 patients received placebo and 70 etidronate. The clinical trial was initiated 20 to 121 days after injury, at the time when 25% of patients in the placebo group and 16% of patients in the etidronate group already had radiographic evidence of HO. After 3 months, the incidence of HO in the placebo group increased 16% while in the etidronate group the increase was 8%. The authors also studied the degree of new bone formation and concluded that the effect of etidronate in the prevention of HO was mainly on the extent of formation of heterotopic bone mass.

More recently, the role of warfarin was evaluated in 'primary' prevention of HO.[23] In a retrospective study of 33 patients with SCI treated with warfarin for DVT, the authors did not find clinical HO as long as 10 years after SCI. It is known that by inhibition of vitamin K action, warfarin has an effect on blood coagulation, similarly by blocking the effect of vitamin K action, warfarin may also inhibit synthesis of osteocalcin, a protein important in the mineralization of bone matrix. A drawback in warfarin use in prevention of HO after SCI is the fact that after injury all patients would require anticoagulation for several months regardless of clinical diagnosis of DVT which is approximately 20 to 30% at this period after SCI. To determine clinical applicability and side effects of warfarin in prevention of HO, further studies are needed with a different epidemiological design.

Several groups of investigators report on 'secondary' prevention of HO or the prevention of recurrence of HO after surgical resection. Different preventive protocols have been used, such as etidronate,[24,25] NSAIDs in combination with etidronate and radiation therapy,[26] NSAIDs alone[27,28] or with etidronate.[29] Garland *et al* used etidronate in nine patients after surgical resection of HO and were not able to determine its benefits against recurrence of HO.[24] Subbarao *et al*[25] reported five patients and suggested that the functional improvement after surgery could in part be attributed to postoperative administration of etidronate minimizing the recurrence of HO.

Based on the experience with etidronate in 'primary' and 'secondary' prevention of HO after SCI, it has been generally accepted that this drug has a partial preventive effect on the incidence of HO. The main beneficial effect of etidronate is seen in the prevention of growth of HO.

There are a number of clinical studies supporting the beneficial effect of different NSAIDs in the prevention of HO following THA.[20,21] However, it is less known what the effect of NSAIDs is in the prevention of HO after SCI. The only available data in SCI population are on the 'secondary' prevention of HO when NSAIDs were used to prevent recurrent surgery of HO. These studies are based on a limited number of patients involving one,[26] two[27,28] or three patients[28] after surgery and showed conflicting results. Our clinical trial evaluated the effect of NSAIDs on primary prevention of HO after SCI. We used indomethacin which, similar to other members of the NSAIDs family, has therapeutic effects from blocking the formation of prostaglandins (PG).[31] It has been known that PGs are potent regulators of bone metabolism, especially the members of the PGE subgroup. PGE-1 or PGE-2 stimulate bone resorption and formation in favor of formation, and are regulated in skeletal tissue by many different factors such as mechanical forces, hormones, cytokines, and growth factors.[32,33] The efficacy of NSAIDs in prevention of HO after THA or acetabular fracture is thought to be through the inhibitory effect of these drugs on cyclooxygenases (COX), a group of enzymes important in PG synthesis. Our study suggests that indomethacin is an effective drug in primary prevention of HO after SCI if started during the first 2 months following injury. We found a significantly lower incidence of early HO in patients treated with indomethacin than in the placebo group (25% *vs* 65%). The later appearance of ossification documented on radiography was also found less often in the indomethacin group (12.5%) as compared to 41% in the placebo group. Interestingly, Schmidt *et al*[30], in a similarly designed prospective, placebo-controlled, double-blind study, used indomethacin in patients after THA and obtained similar results. This study found positive HO on radiographic examination in 15% of indomethacin-treated patients and 75% in the placebo group. As expected, our study also showed a beneficial effect of indomethacin on the inflammatory reaction associated with acute HO. The effect of NSAIDs on swelling in the early stage of HO development may present diagnostic difficulties by masking an important clinical sign of early HO. In the indomethacin group we found a delayed onset of HO and milder forms of bone mass formation. Although the number of our patients did not allow a more detailed quantitative evaluation and statistical analy-

sis, it seems that indomethacin might have an effect on the extent of HO development. Our patients in the placebo group developed larger heterotopic bone mass than indomethacin-treated patients, in agreement with previously reported results after THA.[30] Our study was initiated prior to clinical availability of COX-2 inhibitors. Today, these agents are used more often because of a lower incidence of adverse side effects than with nonselective NSAIDs inhibitors of COX. If found effective in the prevention of HO after SCI, COX-2 inhibitors would have an important role in the early management of patients following injury.

Conclusion

The present study indicates that nonselective NSAID indomethacin is an effective drug in the prevention of HO after SCI in a significant number of patients. In patients receiving indomethacin there was a 2.7-fold decrease of incidence of HO diagnosed by bone scintigraphy and a 3.3-fold reduction of late HO diagnosed by radiography.

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