REVIEW

A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury

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Study design: Systematic review.

Objective: To conduct a systematic review of the effectiveness of interventions used to prevent and treat heterotopic ossification (HO) after spinal cord injury (SCI).

Setting: St Joseph's Parkwood Hospital, London, Ontario, Canada.

Methods: MEDLINE, CINAHL, EMBASE and PsycINFO databases were searched for articles addressing the treatment of HO after SCI. Studies were selected by two reviewers and were only included for analysis if at least 50% of the subjects had an SCI, there were at least three SCI subjects and if the study subjects participated in a treatment or intervention. Study quality was assessed by two independent reviewers using the Downs and Black evaluation tool for all studies, as well as the PEDro assessment scale for randomized control trials only. Levels of evidence were assigned using a modified Sackett scale.

Results: A total of 13 studies met the inclusion criteria. The selected articles were divided into prevention or treatment of post-SCI HO. Nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and pulse low-intensity electromagnetic field (PLIMF) therapy were reviewed as prophylactic measures. Bisphosphonates, radiotherapy and excision were reviewed as treatments of post-SCI HO.

Conclusions: Pharmacological treatments of HO after SCI had the highest level of research evidence supporting their use. Of these, NSAIDs showed greatest efficacy in the prevention of HO when administered early after an SCI, whereas bisphosphonates were the intervention with strongest supportive evidence once HO had developed. Of the non-pharmacological interventions, PLIMF was supported by the highest level of evidence; however, more research is needed to fully understand its role.

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Introduction

Heterotopic ossification (HO) or ectopic ossification is associated with several medical conditions, including spinal cord injuries (SCIs), traumatic brain injuries and hip arthroplasties. It is commonly reported after SCI in which it involves the formation of mature lamellar bone in soft tissues, usually para-articularly.¹ Reported incidence varies greatly in the SCI population, ranging from 10–53%.^{2,3} HO begins to develop most frequently within the first 2–3 weeks after SCI and occurs below the level of paralysis, usually at the hip (70–97%) and followed by the knee.^{2,3} In patients

with SCI with clinically significant HO, 20–30% present with a reduction in joint range of motion, whereas only 3–8% develop ankylosis.²

Initial clinical features of HO may include joint and muscle pain, decreased range of motion, tissue swelling, redness and heat in the involved region, as well as a low-grade fever.² Diagnostic testing can be helpful; in the early phase of HO, three-phase nuclear bone scanning is positive with increased uptake of osteotropic radionuclides. Nuclear bone scans have proven to be more sensitive than plain radiography in detecting early HO with neurogenic HO becoming evident in the first and second phase of the three-phase bone scan 2–6 weeks before diagnosis on plain radiographs.^{4,5} Computed tomography scanning may be a useful tool in the later stages when considering surgery as it allows better visualization of the heterotopic bone.⁶ The use

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of sonography has also been assessed to diagnose HO before radiographic evidence.⁷ Some studies have looked into diagnosing HO through elevations of biochemical markers such as alkaline phosphatase^{8,9} and creatine phosphokinase.^{8,10,11} The predictive value of alkaline phosphatase has not been validated,^{8,10,11} although there is conflicting evidence of an association of HO with increased serum creatine phosphokinase levels.^{8,10} Schurch *et al.*¹² studied individuals with acute SCI and found increases in the 24-h prostaglandin E₂ urinary excretion a valid indicator of early HO formation.

Various clinical factors have been associated with neurogenic HO, including degree of completeness of the SCI and the presence of pressure sores, urinary tract infections, deep venous thrombosis, severe spasticity, and trauma.^{13–16} A causal relationship between these factors and the development of HO after SCI has yet to be determined.

HO may be a significant complication for individuals who have suffered an SCI; despite this, no critical review of HO interventions in SCI has been conducted. The purpose of this systematic review was to examine the effectiveness of treatments that used to prevent and treat HO in the SCI population. This review was conducted as part of the Spinal Cord Injury Rehabilitation Evidence project (<http://www.icord.org/scire>),¹⁷ an evidence-based review of the literature assessing rehabilitation interventions in patients with SCI.

Methods

Literature search strategy

A systematic review of all relevant literature, published from 1980 to April 2009, was conducted using multiple databases (MEDLINE, CINAHL, EMBASE and PsycINFO). Keywords included heterotopic ossification, HO, ectopic ossification; excision surgery, etidronate, pharmacological, non-pharmacological, medication, radiation, treatment and intervention. All references were scanned for relevant citations and assessed against inclusion criteria. References of selected articles were reviewed for pertinent articles.

Study selection

The literature search and secondary hand search resulted in a total of 194 studies. Studies were selected on the basis of previously established Spinal Cord Injury Rehabilitation Evidence methodology.¹⁸ Studies were only included for analysis if at least 50% of subjects had an SCI, there were at least three SCI subjects and if there was a definable intervention being studied. Only studies published in English language were included. A total of 13 articles were identified as research interventions for HO after SCI. Excluded articles included: (1) review articles, (2) noninterventional studies, (3) pediatric studies, (4) non-SCI populations (hip arthroplasty, brain injury, multiple sclerosis and Guillain-Barre syndrome).

This review included randomized controlled trials (RCTs) and nonrandomized controlled trials (nonRCTs), including prospective controlled trial, cohort, case-control, pre-post, post-test and case series.

Table 1 Levels of evidence modified from Sackett scale

Level 1	RCTs with a PEDro score ≥ 6
Level 2	RCTs with a PEDro score < 6 , cohort and prospective controlled trials
Level 3	Case-control studies
Level 4	Pre-post or post-interventions and case series
Level 5	Case reports, clinical consensus or observational studies

Abbreviations: PEDro, Physiotherapy Evidence Database rating scale score; RCTs, randomized controlled trials.

Straus *et al.*²¹

Study appraisal

A quality assessment was conducted for each RCT study by two reviewers, using the Physiotherapy Evidence Database (PEDro) scoring¹⁹ system. Discrepancy in scoring was resolved by a third-blind reviewer. The PEDro tool¹⁹ consists of 11 questions with a maximum score of 10; higher score indicating a better methodological study with scores from 10 to 6 rating excellent to good and < 5 fair to poor. Downs and Black (D&B) tool²⁰ was used in the assessment of nonRCTs. The D&B tool²⁰ contains 27 items with a maximum score of 28; again higher scores reflect a higher methodological quality of the rated study.

Data synthesis

Data from each of the studies were extracted and put into a table; investigations involving similar interventions were grouped. Data extracted included the type of study, a brief summary of intervention outcomes, study results and methodological quality (PEDro¹⁹ or Downs and Black score²⁰). A modified Sackett scale rated the strength of evidence for each category of intervention²¹ (see Table 1).

Results

There were 13 studies that met the inclusion criteria; this included four prophylaxis^{1,3,22,23} and nine treatment^{24–35} studies of HO. Three of these intervention studies had Level 1,^{3,22,23} two Level 2,^{24,25} seven Level 4^{26–29,32–35} and one Level 5¹ evidence.

Prophylaxis of HO

Interventions studied included primary prevention of HO shortly after SCI onset and later secondary prevention after surgical removal of the heterotopic bone. These include pharmacological and electromagnetic field treatment (Table 2).

NSAIDs drugs as a prophylaxis. There were two studies that investigated nonsteroidal anti-inflammatory drugs (NSAIDs) in the prevention of HO early after SCI. Banovac *et al.*²² randomized 76 patients early after SCI into two groups; a treatment group, in which subjects received 25 mg rofecoxib daily for 4 weeks, and a nontreatment control group. After 1 month, there was a significantly lower likelihood of developing clinical and radiographic evidence of HO in the rofecoxib group (13.4%) when compared with the placebo group (33.3%) ($P < 0.05$). The most common adverse effect of

Table 2 Prevention of heterotopic ossification after SCI

Study	Eligibility criteria	Methods	Outcome measures	Results
NSAIDs				
<i>Rofecoxib</i> Banovac <i>et al.</i> ²² USA PEDro = 10	<i>Inclusion:</i> patients with SCI, ~24 days after injury, on average 32 years old. 11 females and 65 males. <i>Exclusion:</i> history of peptic ulcer disease or gastrointestinal bleeding, age < 18 or > 60 years, pregnancy.	<i>RCT:</i> 76 patients were randomized to one of the two groups (treatment vs control). The treatment group received rofecoxib 25 mg daily × 4 weeks.	Incidence of HO. Signs and symptoms of HO were edema, fever and decreased joint range of motion.	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.
Indomethacin				
<i>Banovac et al.</i> ³ USA PEDro = 9	<i>Inclusion:</i> patients with SCI, mean age ~33 years old, 17 paraplegics and 16 tetraplegics, roughly 21 days after injury. <i>Exclusion:</i> not specified.	<i>RCT:</i> 33 patients were included in the study. Treatment was slow-release indomethacin 7.5 mg daily vs placebo × 3 weeks. Patients were followed up clinically until they showed signs and symptoms of HO; all were monitored with x-rays q2mos for 6 months. In case patients had evidence of a positive nuclear bone scan for HO, the study was discontinued and the patient initiated on disodium etidronate.	Incidence of HO	There was a significantly higher incidence of early HO, diagnosed on nuclear bone scan, in the placebo group (11/17; 65%) than in the group taking indomethacin (4/16; 25%) ($P < 0.001$). In the placebo group, 7/17 (41%) patients developed x-ray evidence of HO vs 2/16 (13%) in the indomethacin-treated group ($P < 0.001$).
Warfarin				
<i>Buschbacher et al.</i> ¹ USA D&B = 9	<i>Inclusion:</i> patients with acute SCI, adequate medical records, injury resulting from a gunshot wound, motor vehicle accident, or stabbing. Participants were on average 34 years old; 6% were females and 94% males. <i>Exclusion:</i> slowly progressive lesions such as syringomyelia, spinal stenosis and tumors.	<i>Observational:</i> 227 patient charts were reviewed. Patients had been treated with warfarin for 5.4 weeks (mean time) after SCI for DVT with no x-rays taken to rule out HO. HO diagnostic tests were completed only if clinical signs suggested it.	Not specified	Warfarin administration and the development of HO were found to be significantly inversely related ($P < 0.01$). None of the patients treated with warfarin ($n = 33$) developed HO, and none of the patients with HO ($n = 34$) had been treated with warfarin. 17.5% not treated with warfarin were diagnosed with HO.
PLIMF				
<i>Durovic et al.</i> ²³ Italy PEDro = 6	<i>Inclusion:</i> patients with SCI between the age of 18–45 years, traumatic SCI, no HO in 2 months after SCI, not taking any medications that influence HO. <i>Exclusion:</i> patients with pressure ulcer or severe spasticity because of these conditions are positively related to the formation of HO.	<i>RCT:</i> 29 patients were randomly divided into the experimental and control groups. The treatment group received PLIMF therapy for 4 weeks, about 7 weeks after injury. Therapy characteristics included induction of 10 mT, frequency of 25 Hz and duration of 30 min.	Incidence of HO; Brooker class	Significant differences were found in the incidence of HO between the treatment and control groups. No one in the treatment group had HO (remained at Brooker grade 0), whereas 33% of individuals in control group had incidence of HO. Of these, 2 individuals progressed to Brooker grade 1, 2 to grade 2, and 1 to grade 3. Significant differences were found in the incidence of HO between the treatment and control group, $P < 0.04$.

Abbreviations: D&B, Downs and Black quality assessment scale score;²⁰ DVT, deep venous thrombosis; HO, heterotopic ossification; NSAIDs, nonsteroidal anti-inflammatory drugs; PEDro, Physiotherapy Evidence Database rating scale score;¹⁹ PLIMF, pulse low-intensity electromagnetic field; RCT, randomized controlled trial; SCI, spinal cord injury.

rofecoxib was upper gastrointestinal symptoms.²² Owing to a reported increased risk of cardiovascular side effects of rofecoxib (Vioxx) in other populations, it is no longer available as a treatment.

Banovac *et al.*³ randomized 33 patients with an SCI ~3 weeks after injury into prophylactic treatment with either slow-release indomethacin (75 mg daily) or a placebo control for a total of 3 weeks. Patients were followed up carefully with regular clinical follow-up and nuclear bone scans. After 3 weeks, there was a significantly higher incidence of HO (diagnosed through clinical signs and nuclear bone scan and/or radiographs) in the placebo group (64.7%) when compared with the group taking indomethacin (25.0%) ($P < 0.001$). Patients receiving the indomethacin also experienced HO symptoms later than those in the placebo group (31.7 vs 19.2 days ($P < 0.048$)). Upper abdominal discomfort was the most common symptom in both groups; however, this did not result in any patient discontinuing the medication.

In conclusion, there was Level 1 evidence (on the basis of two positive RCTs)^{3,22} that NSAIDs, rofecoxib and indomethacin, reduced the incidence of HO when administered early (3 weeks) after SCI.

Warfarin as a prophylaxis. Warfarin is a well-known anticoagulant that has been observed to reduce the development of HO after SCI. A single observational retrospective study examined the association between warfarin use and HO after SCI.¹ Buschbacher *et al.*¹ reviewed 227 patients with SCI. Diagnosis of HO was made through bone scans, x-rays and clinical signs. None of the 33 patients treated with warfarin (for an average of 5.4 weeks after SCI) were diagnosed with HO, whereas 34 of the remaining 194 patients (17.5%) not treated with warfarin were diagnosed with HO on an average of 12.5 weeks after injury.

In conclusion, there was only Level 5 evidence that warfarin is associated with a reduction in the incidence of HO after SCI.¹

PLIMF. Pulse low-intensity electromagnetic field (PLIMF) therapy uses magnetic fields to increase oxygen levels and decrease toxic by-products of inflammation by increasing local blood flow into the area.²³ Durovic *et al.*²³ conducted an RCT examining the effect of PLIMF therapy as a prophylaxis for HO in individuals with SCI. Diagnosis of HO was through plain radiography and the Brooker's grading system. Both the control and treatment groups received a range of motion and exercise therapy. Individuals in the treatment group ($n = 14$) also received 4 weeks of PLIMF therapy at a mean of 7 weeks after injury. The study showed significant differences in the incidence of HO between the two groups ($P = 0.04$). None of the individuals in the treatment group developed HO, although HO progressed in 33% of individuals in the control group as measured by Brooker grades and radiographs.

On the basis of a single RCT, there was Level 1 evidence, supporting the efficacy of PLIMF in prophylaxis of HO after SCI.²³

Treatment of HO

Bisphosphonates. Six studies reported on the efficacy of bisphosphonates in the treatment of HO, once diagnosed (Table 3). Banovac *et al.*²⁴ studied 46 patients with SCI with HO treated for 3 days with intravenous disodium etidronate, followed by oral etidronate for 6 months. Patients were subsequently categorized as being in one of the two groups. Group 1 ($n = 33$) had positive bone scintigraphy but negative radiographic findings for HO; of these, five discontinued treatment and experienced a gradual progression of their HO. Of the remaining 28 patients, 22 continued to have no radiographic evidence of HO. Group 2 ($n = 13$) tested positive on both bone scintigraphy and radiographs. Within this group, there was no further progression of soft-tissue ossification with etidronate in six patients, whereas the remaining seven exhibited progression of HO despite treatment.²⁴ The authors concluded that once the bone scan was positive, discontinuation of treatment, regardless of radiographic findings, resulted in progression of HO; furthermore, once radiographic changes were present, there was a high probability that HO would progress regardless of whether treatment was continued or not.

Banovac *et al.*²⁵ treated 27 patients diagnosed with HO based on radiographs and the three-phase nuclear bone scan after SCI, with intravenous etidronate for 3–5 days, followed by oral etidronate for 6 months. These 27 subjects were compared with 11 patients treated with oral etidronate alone for a period of 6 months. After the initial intravenous etidronate therapy, 20 of the 27 patients (74.1%) showed a reduction in swelling over the first 48 h, whereas 7 patients (25.9%) had either no change or increased swelling. Overall, it was determined that treatment reduced swelling from baseline ($P < 0.01$). No significant difference was noted in the development of HO between those who had received etidronate both intravenously and orally and those treated with the oral drug alone.²⁵

Banovac²⁶ again studied patients with SCI with HO ($n = 40$), diagnosed early (3–6 weeks after SCI) with positive bone scans and negative radiographs, who were treated with etidronate (intravenous for 3 days and then orally for 6 months). These patients were then followed over an extended period of time (6 years). In all, 11 of the 40 patients (27.5%) developed radiographic evidence of HO between 1.5 and 6 years after the initiation of therapy.

Garland *et al.*²⁷ assessed 14 patients with SCI with clinical signs of HO and found no evidence of improvement in patients who were administered etidronate. In one patient, ossification appeared to plateau at the end of the treatment, whereas ossification continued to increase in the remaining patients to varying degrees.

In two small case series, each involving five individuals with an SCI, no recurrence of HO was found following surgical removal and subsequent treatment. Subbarao *et al.*²⁸ used disodium edridonate before and after surgical hip wedge resection, whereas Schuetz *et al.*²⁹ used pamidronate before and after HO surgical removal.

In conclusion, there was Level 2 evidence that etidronate can halt the progression of HO once the diagnosis is made, if initiated earlier (3–6 weeks).²⁵ It seems to be most effective if

Table 3 Treatment of heterotopic ossification after SCI

Study	Eligibility criteria	Methods	Outcome measures	Results
Bisphosphonates				
Etidronate				
Banavac <i>et al.</i> ²⁵ USA D&B = 12	<i>Inclusion:</i> no specific inclusion criteria listed. Patients with SCI admitted to the rehabilitation center 2–6 weeks after injury. There were 2 females and 25 males, ranging in age from 16 to 54 years, who were either paraplegics or tetraplegics. <i>Exclusion:</i> not specified.	<i>Prospective control trial:</i> 27 patients participated. 300 mg etidronate disodium was administered i.v. over a 3-h period daily for 3–5 days. After parenteral therapy, 20 mg of etidronate was administered orally for 6 months. 11 controls received oral etidronate alone for 6 months.	Observed swelling	After initial i.v. therapy, 20 patients showed prompt reduction in swelling over initial 48 h, whereas 7 patients had no change or an increase in swelling. Overall, treatment reduced swelling ($P < 0.01$). No significant differences noted between those who had received both i.v. and oral etidronate and those who had received oral etidronate alone, with respect to the effect on HO. 8/9 pretreatment patients had HO in 10 hips. The 9th patient had a positive bone scan but no radiographic evidence of HO. Post-treatment all patients showed evidence of HO. After treatment of the 9 minimal graded hips, only 1 stayed at the minimal grade, whereas others increased (5 mild, 3 moderate, 5 severe). No adverse effects were seen.
Garland <i>et al.</i> ²⁷ USA D&B = 9	<i>Inclusion:</i> patients with SCI with clinical signs of HO. Mean age = 25 years; gender: males = 9; level of injury: cervical = 6, thoracic = 5; severity of injury: complete = 7, incomplete = 2; etiology of injury: diving accident = 3, motor vehicle accident = 1, gunshot wound = 1, motorcycle accident = 1, hand-gliding accident = 1. <i>Exclusion:</i> not specified.	<i>Case series:</i> 14 patients participated. Once HO was diagnosed in patients, bisphosphonate therapy was administered at a dosage of 20 mg kg ⁻¹ day ⁻¹ for 2 weeks and then at a dosage of 10 mg kg ⁻¹ day ⁻¹ for 2 years.	Effectiveness of treatment, adverse effects	
Subbarao <i>et al.</i> ²⁸ USA D&B = 8	<i>Inclusion:</i> specific inclusion criteria not listed; however, participants were between the ages of 34 and 41 years, and were 77–197 months after injury; duration of follow-up ranged from 8 to 35 months. <i>Exclusion:</i> not specified.	<i>Case series:</i> etidronate (20 mg kg ⁻¹ per body weight) was given 10–14 days preoperatively; medication was withheld for a postoperative period of 72 h, but then continued (10 mg kg ⁻¹ per body weight) for a minimum of 3 months. All 5 patients underwent wedge resection at hip to permit free movement of hip in flexion. <i>Prospective control trial:</i> 46 patients participated.	Not specified	At last follow-up, all patients were able to function independently in their wheelchairs, except for one who functioned independently in a semi-reclining wheelchair. Patients had severe restriction of ROM in the involved joints.
Banavac <i>et al.</i> ²⁴ USA D&B = 7	<i>Inclusion:</i> not explicitly stated. A likely diagnosis of HO based on clinical signs and symptoms and positive bone scintigraphy in patients with SCI. Those who participated were admitted to the rehabilitation centre 2–5 weeks after injury, and ranged in age from 16 to 55 years. 2 were female and 44 were male. 24 patients were paraplegic and 22 were tetraplegic <i>Exclusion:</i> not specified.	3 h of i.v. disodium etidronate on the day of HO diagnosis, continued for 3 successive days, followed by etidronate for 6 months.	Degree of HO was determined radiographically: grade 1 = minimal, grade 2 = mild, grade 3 = moderate, grade 4 = severe, grade 5 = ankylosis	Group 1 (positive bone scan and negative x-ray for HO, $n = 33$), 5 patients discontinued therapy and showed gradual development of HO. Of the remaining 28 patients, 22 had no x-ray evidence of HO, whereas 6 had developed an x-ray diagnosis of HO at follow-up. Group 2 (positive bone scan and x-ray, $n = 13$): Progression of soft-tissue ossification was inhibited by etidronate in 1 of 6 patients, whereas the remaining 7 did not respond to treatment, with progression of HO. 11/40 (28%) patients with SCI developed radiographic evidence of HO from 1.5 to 6 years post-treatment. 9.5% of cases of recurrent HO developed in different areas, involving different joints.
Banovac ²⁶ Denmark D&B = 7	<i>Inclusion:</i> no specific inclusion criteria listed; however, participants had been admitted to the rehabilitation center 2–5 weeks after injury. 39 males and 1 females; mean age 23 years. 18 with tetraplegia and 22 with paraplegia. <i>Exclusion:</i> not specified.	<i>Case series:</i> 40 patients with positive clinical findings and positive nuclear bone scan were treated with i.v. etidronate sodium, followed by 20 mg kg ⁻¹ day ⁻¹ given orally for 6 months.	Not specified	
Pamidronate Schuetz <i>et al.</i> ²⁹ Switzerland D&B = 9	<i>Inclusion:</i> no specific inclusion criteria stated; however, all were male and between the ages of 47 and 68 years. <i>Exclusion:</i> not specified.	<i>Case study:</i> 5 patients underwent excision surgery for removal of HO. Pamidronate administered i.v. peri- and post-operation, starting at 120 mg for the 1st 12 h, gradually increasing the dose over a total of 6–14 days.	Not specified	None of the patients treated with pamidronate exhibited clinical, x-ray or laboratory signs of HO recurrence or new HO at the time of follow-up, 5–54 months post-operation.

Table 3 Continued

Study	Eligibility criteria	Methods	Outcome measures	Results
Radiotherapy Sautter-Bihl <i>et al.</i> ³² Germany D&B = 12	Inclusion: patients with SCI showing primary clinical signs of HO between December 1989 and March 2000 were included. Mean age = 33 years; gender: males = 44, females = 8. Exclusion: not stated.	Case series: 52 patients. Radiotherapy was used to treat HO and manifestation of heterotopic bone formation after resection in patients with SCI. A linear accelerator at 6–8 MV photons with single doses between 2 to 10 Gy was used.	Efficacy, Brooker score, adverse effects	Prevention of HO was seen in 71% (41 primarily treated and 9 resected) of joints. Radiotherapy treatment did not result in a regression of the Brooker score in any patient. An increase in two Brooker score grades was seen in two joints (1 knee, 1 hip). No adverse effects due to therapy occurred. 16 of the 32 hips treated only with radiotherapy (50%) did not show any abnormalities on follow-up. No progression of HO was noted in 30/36 subjects (83%). Reossification after therapy, which led to a decrease in joint mobility, was noted in 3 subjects.
Sautter-Bihl <i>et al.</i> ³³ Germany D&B = 9	Inclusion: Although no specific inclusion criteria were stated, participants were between the ages of 17 and 59 years, and duration of follow-up was 4–98 months. Exclusion: not specified.	Case series: 25/36 patients received 10 Gy in increments of 2–2.5 Gy, whereas 4 patients received higher doses. In phase 2, 7 patients received a single dose of irradiation with 8 Gy. In total, 46 joints were irradiated in 36 patients.	Not specified	
Excision Garland and Orwin ³⁵ USA D&B = 14	Inclusion: no specific inclusion criteria were listed. Participants were individuals with SCI with mean age = 22.5 years; level of injury: paraplegia = 8, tetraplegia = 11. Severity of injury: complete = 12, incomplete = 7. Exclusion: not specified.	Case series: records of 19 SCI individuals who underwent hip resection for HO between 1970 and 1985 were reviewed.	Range of motion, reoccurrence rate, adverse effects	3 of 24 hips operated on had similar or less motion when compared with preoperative motion, 15 had 10–39° improvement, and 6 had >40 degrees improvement. Total recurrence rate was 92% (22 of 24 hips). A high number of complications, infections and blood loss were present.
Meiners <i>et al.</i> ³⁴ Germany D&B = 12	Inclusion: specific inclusion criteria not listed; however, participants had a mean age of 37.87 years; males = 28, females = 1. Exclusion: not specified.	Case series: resection of HO of the hip through ventral approach. Post-operation: week 1, irradiation of hip with a linear accelerator; day 15, passive movement exercises implemented. Case study: 5 patients underwent excision surgery for removal of HO.	ROM, flexion and extension; preoperatively, postoperatively, intraoperatively and at follow-up	Mean ROM preoperatively = 21.95°. Mean ROM intraoperatively = 94.51°. Mean ROM at follow-up (M = 4.2 years) = 82.68°.
Schuetz <i>et al.</i> ²⁹ Switzerland D&B = 9	Inclusion: no specific inclusion criteria stated; however, all were male and between the ages of 47 and 68 years. Exclusion: not specified.	Pamidronate administered i.v. peri- and post-operation, starting at 120 mg for the 1st 12 h, gradually increasing the dose over a total of 6–14 days. Case series: etidronate (20 mg kg ⁻¹ per body weight) was given 10–14 days preoperatively; medication was withheld for a postoperative period of 72 h, but then continued (10 mg kg ⁻¹ per body weight) for a minimum of 3 months. All 5 patients underwent wedge resection at hip to permit free movement of hip in flexion.	Not specified	None of the patients treated with pamidronate exhibited clinical, x-ray or laboratory signs of HO recurrence or new HO at the time of follow-up, 5–54 months post-operation.
Subbarao <i>et al.</i> ²⁸ USA D&B = 8	Inclusion: specific inclusion criteria not listed; however, participants were between the ages of 34 and 41 years, and were 77–197 months after injury; duration of follow-up ranged from 8 to 35 months. Exclusion: not specified.			At the last follow-up, all patients were able to function independently in their wheelchairs, except for one who functioned independently in a semi-reclining wheelchair. Patients had severe restriction of ROM in the involved joints.

Abbreviations: D&B, Downs and Black quality assessment scale score;²⁰ HO, heterotopic ossification; i.v., intravenously; ROM, range of motion; SCI, spinal cord injury.

the treatment is initiated earlier when the nuclear bone scan is positive and radiographs are normal.²⁶ Once radiographs were positive, there was Level 4 evidence that bisphosphonates are not as effective. There was Level 4 (at a case series level) evidence that bisphosphonates effectively halt secondary HO progression after surgical resection of HO.^{28,29}

Radiotherapy. Radiotherapy involves the irradiation of pluripotential mesenchymal cells, which may be responsible for the formation of heterotopic bone.³¹ Sautter-Bihl *et al.*³² reported on 52 patients with SCI, some of whom already had HO, who were treated with radiotherapy with single doses between 2 to 10 Gy. The study found neither a progression nor recurrence of the resected bone in 71% of joints. Regression in the Brooker grading score was not seen in any of the patients. Two joints increased in Brooker grades; one patient's hip went from a Brooker grade I to III and another patient's knee went from grade 0 to II. However, neither of them developed any associated functional impairments.

Sautter-Bihl *et al.*³³ studied 36 patients with SCI diagnosed with HO, 3 of whom were subsequently lost to follow-up. In 11 of 33 patients (13 joints), radiotherapy treatment was used 24–36 h after surgical resection of heterotopic bone. Two of the 33 patients received radiotherapy both before and after surgery. The mean duration of follow-up was 23.6 months. In all, 30 of the 33 irradiated patients (90.9%) experienced no progression of HO and had normal mobilization and rehabilitation. In three patients, ossification after radiotherapy resulted in a moderate decrease in joint mobility with progression in the Brooker grade. No relevant adverse effects were seen due to irradiation.

In conclusion, there was Level 4 evidence that radiotherapy stops primary and secondary progression of HO.^{32,33}

Excision. Meiners *et al.*³⁴ reported on a case series of 10 quadriplegics and 19 paraplegics who underwent HO resection at the hip followed by irradiation and passive range of motion exercises. Mean hip range of motion increased from 21.95° preoperatively to 94.51° intraoperatively and 82.68° at 4-year (mean) follow-up. Garland and Orwin³⁵ in a case series, examined the effect of HO excision to improve range of motion in 19 individuals with SCI. The study found that the largest gain of function occurred intraoperatively followed by a large loss of function within the first 6 months. At final follow-up (6 years after surgery) of the 24 hips excised, 3 had similar or less motion compared with preoperative motion, 15 improved between 10 and 39° and 6 showed >40° improvement.

In two case series (mentioned previously in the bisphosphonate section), excision and bisphosphonate treatment (etidronate,²⁸ pamidronate²⁹) was effective in preventing secondary HO formation.

In conclusion, there was Level 4 evidence that resection of HO about the hip after SCI can improve restricted hip range of motion.^{34,35} There was Level 4 evidence that resection combined with bisphosphonate treatment halts the recurrence of HO.^{28,29}

Figure 1 Mechanism of HO intervention action after SCI.

Discussion

Our review focused on interventions designed to either prevent or treat primary or secondary HO development after SCI. Figure 1 outlines the known mechanisms of action for those interventions involved in the treatment of HO after SCI. Only three of the interventional studies reviewed were rated as high-quality RCTs.^{3,22,23} Two of these RCTs evaluated NSAIDs,^{3,22} whereas one showed the effectiveness of PLIMF therapy in the prevention of HO.²³ Treatment studies tended to involve smaller numbers of patients and were of lower quality when compared with prevention studies.

There was strong evidence that NSAIDs (rofecoxib and indomethacin) prevented the development of HO when provided early after SCI. Inflammation seems to have an important role in neurogenic HO and NSAIDs have been shown to prevent HO by reducing inflammation and blocking prostaglandin synthesis.²² Macfarlane *et al.*³⁶ reported that the systemic inhibition of prostaglandins, especially with the use of indomethacin, reduced the incidence of HO significantly following hip and acetabular surgery in non-SCI populations. Prostaglandins regulate mesenchymal cell differentiation into osteoblastic cells, which are important for new bone formation.^{37,38} These prostaglandins may be indirectly responsible for bone morphogenic protein expression in soft tissue, which is another factor in HO development. NSAIDs, by inhibiting COX enzymes, block prostaglandin synthesis which in turn is thought to inhibit heterotopic bone formation.^{3,22}

Both of the NSAID studies examining prophylaxis^{3,22} were Level 1 studies, used the same diagnostic tools for HO (three-phase scintigraphy and radiography), and initiated treatment around 20–25 days after SCI; both reduced the incidence of HO when compared with placebo. However,

patients treated with rofecoxib, a selective COX-2 inhibitor, suffered less gastrointestinal side effects than those treated with indomethacin. Indomethacin is a nonselective COX inhibitor²² and has long been associated with a greater side-effect profile. Furthermore, rofecoxib is no longer used in clinical practice because of its cardiovascular adverse effects. Another NSAID used in HO prevention, celecoxib, has been shown in other populations to be as effective an anti-inflammatory medication as indomethacin with fewer gastrointestinal adverse effects.³⁹ Hence, it is reasonable to assume that it may be as effective in patients with SCI and should be further studied in this population.

Radiotherapy for prevention of HO after SCI also acts through the inhibition of mesenchymal cell differentiation. Given radiotherapy has been successful in the treatment of HO after hip arthroplasty,^{40,41} it has been suggested that it may also be an appropriate treatment for other high-risk populations such as traumatic individuals with SCI; however, there is only limited published research evidence on the use of radiation in the prevention of HO in the SCI population.^{32,33} Although there have been studies suggesting that it was effective in preventing or treating HO progression, all were of low methodological quality and more research needs to be conducted to be more confident regarding its effectiveness in the treatment and prevention of HO after SCI.

PLIMF therapy was supported by a small single Level 1 study.²³ It seems to help prevent HO by increasing blood flow and oxygenation to the treated area. This may in turn remove the neurogenic stimulus that activates the HO pathway, thereby preventing HO formation. The study found a significant difference in the incidence of HO between the treatment and control groups at the end of the study period. However, bone formation may take longer than 2–3 months to form; therefore, further follow-up results are required to assess its true effectiveness in preventing HO after SCI. Research involving larger populations and longer follow-ups are needed to evaluate its clinical relevance.

Radiotherapy and the use of PLIMF therapy as a prophylaxis involves radiating or treating all patients with SCI, which makes it clinically less appealing given the costs and equipment training involved. Radiotherapy specifically may also result in other secondary complications such as carcinogenesis in treated individuals and therefore must be performed cautiously.³³

The first-generation bisphosphonates (that is, etidronate) are analogs of inorganic pyrophosphate.²⁹ Several studies have looked at etidronate in the treatment of HO ($n=5$);^{24–29} however, the methodological quality of the research was not strong. Furthermore, many studies involved treatments for short duration and had dosage levels below normal treatment levels to effectively evaluate the effect of treatment. The lack of RCTs makes definitive statements difficult; nonetheless, research to date suggests etidronate delays or inhibits HO progression once diagnosed, and seems to be more effective when given earlier rather than later after an SCI. As etidronate inhibits the transformation of amorphous calcium phosphate into crystalline hydroxyapatite and thus blocks the mineralization of the bone matrix, it seems to act

later in the HO developmental pathway than NSAIDs or radiotherapy.⁴² Hence, etidronate does not inhibit the production of the protein matrix but rather the mineralization of calcium phosphate on the matrix.¹ Furthermore, it has been known to be difficult for patients to administer and is poorly tolerated due to adverse effects. Hence, etidronate may not be the optimal treatment choice in individuals with SCI because of the apparent need to continue it indefinitely.

The new-generation nitrogen-containing bisphosphonates such as pamidronate are more potent and result in less adverse effects. However, only one Level 4 study (with a small sample size) assessed the effectiveness of pamidronate in secondary prevention of HO.²⁹ Further research is needed.

Warfarin as prophylaxis for HO after SCI has been suggested on the basis of the results of a single but intriguing observational study, which reported a significant association between warfarin administration and failure to develop HO. The mode of action of warfarin is likely early on through inhibition of bone matrix formation.¹ Further investigation into the efficacy of warfarin in preventing HO after SCI is required before recommending its use because of concerns about the potential side effects, in particular, the increased risk of hemorrhage. Furthermore, studies involving stronger methodological quality and longer follow-up time are required to assess its clinical effectiveness.

Surgical resection of heterotopic bone was evaluated in four Level 4 studies.^{28,29,34,35} Studies indicated that the optimal time for surgical resection of HO is after the bone matures. However, at present, there is no definitive clinical sign or test to assess the maturity of the heterotopic bone and whether the HO process is completed.^{28,29,34} Radiographs combined with clinical judgment are generally used to determine when HO is complete. Although surgical excision has been regarded as the best clinical option, all studies reviewed involved the use of additional treatment in conjunction with surgical resection.

An important limitation in assessing the effectiveness of interventions was the lack of standardization in diagnosing HO after SCI. HO was diagnosed using nuclear bone scans, radiographs, clinical symptoms and Brooker grades in various studies. To effectively compare the results of various interventions, a standardized tool for diagnosing HO must be used in future studies. Furthermore, most prophylactic studies diagnosed HO based on radiographic evidence; however, the clinical relevance was not assessed. The clinical relevance of a diagnostic tool is important to take into account the effectiveness of any prophylactic treatment.

Conclusions

HO can have a negative impact on the quality of life of individuals with SCI. For the prevention of HO after SCI, there was Level 1 evidence that NSAIDs (rofecoxib and indomethacin) and PLIMF prevented the development of HO after SCI. However, clinical application of these treatments may be complicated by adverse effects or limited by feasibility. However, these adverse effects may be small when compared with the negative impact of HO development.

There was only Level 4 evidence that radiotherapy prevented the progression of HO after SCI, indicating the need for more research. One interesting observation (Level 4 evidence) was the absence of HO when warfarin was used. For the treatment of HO, once diagnosed, there was Level 2 evidence that bisphosphonates stop the progression of HO; however, it seems to have no effect on the deposition of the bone matrix and only stops bone mineralization while the patient is taking the medication. Hence, once treatment is stopped, mineralization may subsequently progress. Furthermore, dangerous adverse effects have been reported with high doses of bisphosphonates. Surgical excision of HO along with supplemental therapies was supported by four case series. Overall, owing to the generally poor quality of the studies, more research is needed into the various clinical interventions used to prevent and treat HO in patients with SCI before definitive recommendations can be made.

Conflict of interest

The authors declare no conflict of interest.

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