Heterotopic Ossification Following Spinal Cord Injury

Robert Teasell MD FRCPC
Amanda McIntyre MSc
Spencer Thompson BSc
Swati Mehta MA
Eldon Loh MD FRCPC
Key Points

Anti-inflammatory medications given early post spinal cord injury reduces development of heterotopic ossification.

Warfarin may inhibit the development of heterotopic ossification post spinal cord injury.

Etidronate can halt the progression of heterotopic ossification.

Pamidronate halts secondary progression of heterotopic ossification post-surgical excision.

Pulse low intensity electromagnetic field therapy is effective in preventing heterotopic ossification post spinal cord injury.

Radiotherapy can reduce the progression of heterotopic ossification.

Surgical resection of heterotopic ossification can improve hip range of motion.

Surgical resection and pamidronate treatment halts secondary heterotopic ossification progression.
Table of Contents

Abbreviations ............................................................................................................................... i
1.0 Introduction ........................................................................................................................... 1
2.0 Pathophysiology of Heterotopic Ossification .................................................................... 1
3.0 Risk Factors and Clinical Presentation .............................................................................. 2
4.0 Diagnosis ............................................................................................................................... 3
5.0 Treatment of Heterotopic Ossification ................................................................................ 3
  5.1 Non-Steroidal Anti-Inflammatory Drugs as Prophylaxis ...................................................... 4
  5.2 Warfarin as Prophylaxis ...................................................................................................... 5
  5.3 Bisphosphonates ................................................................................................................ 6
  5.4 Pulse Low Intensity Electromagnetic Field Therapy ........................................................... 9
  5.5 Radiation Therapy ............................................................................................................. 10
  5.6 Surgical Resection ............................................................................................................ 11
6.0 Summary .............................................................................................................................. 14
References ................................................................................................................................. 15

This review has been prepared based on the scientific and professional information available in 2013. The SCIRE information (print, CD or web site www.scireproject.com) is provided for informational and educational purposes only. If you have or suspect you have a health problem, you should consult your health care provider. The SCIRE editors, contributors and supporting partners shall not be liable for any damages, claims, liabilities, costs or obligations arising from the use or misuse of this material.


www.scireproject.com
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>HO</td>
<td>Heterotopic Ossification</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>PLIMF</td>
<td>Pulse Low Intensity Electromagnetic Field</td>
</tr>
<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
</tr>
</tbody>
</table>
Heterotopic Ossification
Following Spinal Cord Injury

1.0 Introduction
Heterotopic ossification (HO) is the formation of pathological bone in muscle or soft tissue. The incidence in individuals following a spinal cord injury (SCI) has been reported to vary greatly, ranging from 10% to 78% (Banovac 2001; van Kuijk et al. 2002). Banovac et al. (2001) noted that HO occurs most frequently in the first two months after SCI, below the level of paralysis. The etiology of HO is not fully understood; this creates challenges in determining appropriate diagnostic and therapeutic approaches.

2.0 Pathophysiology of Heterotopic Ossification
The mechanism underlying HO following spinal cord injury is not fully understood but it appears to be initiated by mesenchymal cells into bone precursor cells (Schuetz et al. 2005). Pape et al. (2004) has noted that mesenchymal stem cells can differentiate into osteogenic cells given the right stimuli and within the right environment (even soft tissue; Chalmers et al. 1975). These mesenchymal stem cells can generate cartilage, bone, muscles, tendons, ligaments or fat (Williams et al. 1999) and are thought to play a pivotal role in the development of HO (Pape et al. 2004). After mesenchymal cell differentiation to osteogenic cells, a protein mixture created by bone cells (osteoid) calcifies within a matter of weeks (Pape et al. 2001). Over the next few months, the calcified osteoid remodels and matures into well-organized trabecular bone (Pape et al. 2001). Months following the initial trauma, patients develop bone formation in muscle and soft tissues in a periarticular location with resultant restriction in range of motion, pain and ankylosis (Banovac & Gonzalez 1997; Garland et al. 1980). The bony lesion has a high metabolic rate, adding new bone at more than three times the rate of normal bone. Osteoclastic (bone removal cells) density is more than twice that found in healthy bone (Puzas et al. 1987). It is suspected there may be a neurogenic factor contributing to HO but the mechanism is poorly understood (Hurvitz et al. 1992; Pape et al. 2001; Pape et al. 2004).
A case-control study was performed by Citak et al. (2012) among 132 individuals with traumatic spinal cord injury and 132 controls to determine risk factors for HO. The authors reported that the presence of complete neurological deficit was a major risk factor for HO. Moreover, factors such as spasticity, pneumonia, thoracic trauma, tracheostomy, nicotine use, and urinary tract infection increase patients’ risk for HO (Citak et al. 2012). Contrary to previous belief, the authors reported that patients with fewer comorbidities were also at a higher risk for developing HO. The evaluation of the preceding factors, in combination with early intervention and diagnosis, may reduce incidence of HO or improve a patient’s recovery post-operatively (Citak et al. 2012).

Schuetz et al. (2005) have noted that the symptoms of HO appear 3-12 weeks after spinal cord injury. Individuals with SCI typically present with joint and muscle pain, parasthesias and tissue swelling in the involved region, accompanied by a mild fever (Thomas & Amstutz 1987; Orzel &
Rudd 1985; Smith 1998; Shehab et al. 2002). In the initial stages of HO, clinical signs of inflammation are nonspecific (Neal 2003).

4.0 Diagnosis

In the early phase of HO, triple phase bone scanning demonstrates increased uptake of osteotropic radionucleotides. Bone scanning has proven to be more sensitive than plain radiography in detecting early HO. Neurogenic HO becomes evident on plain radiography approximately two to six weeks after diagnosis using the triple phase bone scan (Orzel et al. 1985; Freed et al. 1982). However, bone scans have lower specificity than radiography (Freed et al. 1982). Computed tomography (CT) or magnetic resonance imaging (MRI) scanning may be a useful tool when considering surgery as it allows for better visualization of the heterotopic bone (Amendola et al. 1983). Some studies have examined diagnosis of HO through elevations in biochemical markers such as alkaline phosphatase (Singh et al. 2003; Tibone et al. 1978) and creatine phosphokinase (Singh et al. 2003; Welch et al. 1973; Rossier et al. 1973). The predictive value of alkaline phosphatase has not been validated (Singh et al. 2003; Welch et al. 1973; Rossier et al. 1973), although there is conflicting evidence of an association with HO and increased serum creatine phosphokinase levels (Singh et al. 2003; Welch et al. 1973). Schurch et al. (1997) studied individuals with acute SCI and found increases in the 24 hour prostaglandin E₂ (PGE₂) urinary excretion a valid indicator of early HO formation.

The Brooker Classification Scheme is typically used to diagnose HO in the pelvic region (Zychowicz 2013). The system is based on an anteroposterior radiograph of the pelvis which classifies HO into one of five classes. The classes are based on the progression of ossification: Class 0 – no presence of ossification, Class 1 - islands of bone within soft tissue of any size, Class 2 - bone spurs from pelvis or femur with at least 1 cm between opposing bone surfaces, Class 3 - bone spurs from pelvis and femur reducing space between opposing bone surfaces to less than 1 cm, and Class 4 - complete ankylosis of hip (Zychowicz 2013).

The Brooker Classification Scheme has been criticized by some clinicians and adjustments to the traditional classification system have been proposed. Mavrogenis et al (2012) have suggested focusing on the location of the HO formation around the hip joint using the following scheme: Type 1 – anterior, Type 2 – posterior, Type 3 – anteromedial, Type 4 - circumferential HO. The adjustments are based on locating the anatomical position of HO which permits an estimation of the prognosis regarding blood loss, transfusion requirements, and recurrence. The new classification system improves ease of use and provides the opportunity for more rapid post-operative planning for surgical approach, evaluation, and prognosis (Mavrogenis et al. 2012). However, Citak et al. (2012) suggested the use of ultrasound, CT or MRI rather than radiograph in order to improve diagnosis and reduce the use of methods with less sensitivity for early diagnosis.

5.0 Treatment of Heterotopic Ossification

The published literature on treatment of HO provides evidence for non-steroidal anti-inflammatory drugs, warfarin, bisphosphonates, pulse low-intensity electromagnetic field therapy, radiation and surgical excision.
Two systematic reviews examined the effectiveness of HO management interventions. Aubut et al. (2011) found that pharmacological interventions were effective in the prophylaxis of HO. Teasell et al. (2010) also found that rofecoxib and indomethacin were effective in preventing HO after SCI. However, only limited evidence supported the use of radiotherapy, warfarin, or Pulse low intensity electromagnetic field therapy (PLIMF) for the prevention of HO after SCI. Once HO developed, only surgical resection was found to be effective, while bisphosphonates such as Etidronate Disodium and pamidronate were supported by limited evidence.

### 5.1 Non-Steroidal Anti-Inflammatory Drugs as Prophylaxis

Indomethacin and Rofecoxib have both been evaluated in the treatment of HO post SCI.

#### Table 1 Anti-Inflammatory Drugs as a Prophylaxis for Heterotopic Ossification

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>PEDro Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banovac et al. 2004</td>
<td>Population: Gender: males=65,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. A significantly lower incidence of HO</td>
</tr>
</tbody>
</table>
**Discussion**

Two highly rated RCTs examined the use of non-steroidal anti-inflammatory drugs in the early phase after SCI in an attempt to reduce the incidence of HO. Banovac et al. (2001) randomized 33 SCI patients approximately three weeks post SCI and treated them prophylactically with either slow-release indomethacin 75 mg daily or placebo for a total of three weeks. Patients were carefully followed with regular clinical follow-up and bone scans. There was a significantly higher incidence of HO, diagnosed on bone scan and plain radiographs, in the placebo group when compared with the group receiving indomethacin (p<0.001). Banovac et al. (2004) randomized 76 patients in the early phase post SCI into either the treatment group (25 mg rofecoxib daily for two weeks) or a placebo group. A significantly lower incidence of HO was observed in the rofecoxib group (13.4%) than in the placebo group (33.3%; p<0.05). While both of these RCTs provided compelling evidence that anti-inflammatory drugs given prophylactically reduce the likelihood of developing HO post-SCI, Rofecoxib is no longer available due to cardiovascular side effects.

**Conclusions**

*There is strong Level 1a evidence (from 2 RCTs; Banovac et al. 2001; Banovac et al. 2004) that non-steroidal anti-inflammatory medications can reduce the incidence of heterotopic ossification when administered early after a spinal cord injury.*

---

**5.2 Warfarin as Prophylaxis**

Warfarin is a well-known anticoagulant which may also be useful in the prevention of HO post SCI.

**Table 2 Warfarin as a Prophylaxis for Heterotopic Ossification**
Discussion

There is only one observational retrospective study which noted an association between Warfarin use and HO post SCI. Buschbacher et al. (1992) studied 227 patients with SCI. None of the 33 patients treated with Warfarin post SCI were diagnosed with HO; among the remaining 193 patients, 34 were diagnosed with HO but not one of these individuals had been treated with Warfarin. The authors speculated that Warfarin provided a protective or inhibitory effect against HO.

Conclusion

There is Level 5 evidence (from 1 observational study; Buschbacher et al. 1992) that Warfarin inhibits the development of heterotopic ossification post spinal cord injury.

5.3 Bisphosphonates

Two bisphosphonates, Etidronate (didronel) and pamidronate, have been studied in the treatment of HO progression post SCI. Etidronate was introduced in the 1970s for the treatment of HO post SCI and is still commonly used today (Banovac et al. 1997; Fleisch 1991). Etidronate works by inhibiting the transformation of amorphous calcium phosphate into crystalline hydroxyapatite (Fleisch 1991; Fleisch et al. 1969; Banovac et al. 1997). Although commonly used, its efficacy in prophylaxis has been questioned (Finerman & Stover 1981). Pamidronate is a new generation nitrogen-containing bisphosphonate (Schuetz et al. 2005).

Table 3 Bisphosphonates for Treatment of Heterotopic Ossification

<table>
<thead>
<tr>
<th>Author Year Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banovac et al. 1993</td>
<td>USA</td>
<td>Prospective Controlled Trial</td>
<td>N=27</td>
<td>Population: SCI; Age range=15-64 yr; Gender: males=25, females=2; Severity of injury: Frankel Class: A=15, B=12; Time since injury=2-6 wk. Treatment: 300mg IV Etidronate</td>
<td>1. After initial IV therapy, 20 patients showed prompt reduction in swelling over the first 48 hr, while seven patients had no change or an increase in swelling.</td>
</tr>
<tr>
<td>Study</td>
<td>year</td>
<td>Country</td>
<td>Study Design</td>
<td>N</td>
<td>Population</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------</td>
<td>---------</td>
<td>--------------</td>
<td>---</td>
<td>------------</td>
</tr>
</tbody>
</table>
| Garland et al. 1983         | USA      | Case series | N=14         |   | SCI: Mean age=25 yr; Gender: males=9, females=5; Level of injury: cervical=6, thoracic=5; Severity of injury: complete=7, incomplete=2. | Bisphosphonate treatment was administered for 2 wk at 20 mg/kg/day and then for 2 yr at 10 mg/kg/day. | Outcome Measures: Effectiveness of treatment and adverse effects. | 1. 8/9 pretreatment patients had HO in 10 hips.  
2. Post-treatment all patients showed evidence of HO.  
3. Of the 9 minimal graded hips, only 1 stayed at the minimal grade, whereas others increased (5 mild, 3 moderate, 5 severe).  
4. No adverse effects were observed. |
| Subbarao et al. 1987        | USA      | Case Series | N=5          |   | SCI: Age range=29-41 yr; Time since injury=18-197 mo. | Didronel given 10 d -2 wk preoperatively, medication withheld for immediate postop period (72 hr) and continued for a minimum of 3 mo. All patients underwent wedge resection at hip to permit free movement of hip in flexion. | Outcome Measures: Effects of treatment. | 1. All patients at last follow-up were able to function independently in their wheelchairs except one, who was able to function independently in a semi reclining wheelchair.  
2. Patients had severe restriction of range of motion in involved joints. |
| Stover 1987                 | USA      | Pre-Post | N_initial=169; N_final=87 |   | Acute SCI; Age= >16 yr. | Didronel therapy. Four subgroups: 1) 3 mo therapy, early; 2) 6 mo therapy, early; 3) 3 mo therapy, late; 4) 6 mo therapy, late. | Outcome Measures: X-ray of hips at baseline, post treatment, 1 yr follow-up. | 1. There was no difference in development of HO between those receiving therapy for 3 mo versus 6 mo.  
2. Regardless of duration of Didronel, early treatment worked better than later treatment. |
| Banovac et al. 1997         | USA      | Prospective Controlled Trial | N=46         |   | SCI: Age range=16-55 yr; Gender: males=44, females=2; Severity of injury: AIS: A-C; Time since injury=2-5 wk. | 3 hr IV Etidronate Disodium on day of HO diagnosis and continued for 3 successive days followed by PO Etidronate for 6 mo. | Outcome Measures: Degree of HO. | 1. Group 1 (positive bone scan and negative x-ray for HO, n=33): five patients discontinued therapy and showed gradual development of HO; of the remaining 28 patients, 22 had no x-ray evidence of HO while 6 developed x-ray diagnosis of HO by follow-up.  
2. Group 2 (positive bone scan and x-ray, n=13): six patients' progression of soft tissue ossification was inhibited by Etidronate Disodium while the remaining seven did not respond to treatment, demonstrated further progression of HO. |
| Banovac 2000                | Denmark  | Case Series | N=40         |   | SCI: Mean age=23 yr; Gender: males=39, females=1; Severity of injury: AIS A-B; Time since injury=2-5 wk. | All patients with positive clinical findings and positive bone scan were treated with IV Etidronate Disodium, then PO Etidronate 20 mg/kg/day for 6 mo. | Outcome Measures: Prevalence of HO. | 1. No statistical results reported.  
2. 11/40 patients developed radiographic evidence of HO from 1.5 to 6 yr post treatment.  
3. In 95% of cases, recurrent HO in developed in different areas involving different joints. |
| Schuetz et al. 2005         | Switzerland | Population: SCI: Age range=47-68 yr; Gender: males=7; Level of injury: | No statistical results reported. |   | | | | 1. None of the patients treated with |
Case Series
N=7

| thoracic=1, tetraplegia=2. | Treatment: All patients underwent excision surgery for removal of HO. Pamidronate was administered IV peri- and post-op, starting at a dose level of 120 mg for the first 12 hr, gradually increasing for a total of 6-14 days. | pamidronate showed clinical, x-ray or lab signs of HO recurrence or new forming HO at 5-54 mo follow-up. |

Outcome Measures: Prevalence of HO.

Note: AIS=ASIA Impairment Scale

Discussion

Banovac et al. (1993) provided intravenous Etidronate for three-five days followed by oral Etidronate for six months to 27 patients with SCI following a diagnosis of HO; outcomes were compared to 11 SCI patients treated with only oral Etidronate Disodium for six months. After the initial intravenous therapy, 20 patients showed prompt reduction in swelling over the first 48 hours while seven patients had no change or an increase in swelling. Overall, treatment reduced swelling (p<0.01); there was no significant difference in effect between the intravenous and orally treated groups on HO.

Garland et al. (1983) assessed the effectiveness of Etidronate treatment on SCI patients with clinical signs of HO over a two-year period. Ossification appeared to plateau in only one of nine patients, while an increase in HO was reported to varying degrees in the remaining patients.

Banovac et al. (1997) studied 46 patients (five excluded due to discontinuation of therapy) treated with three days of intravenous Etidronate Disodium followed by oral Etidronate for six months. Of the 33 patients with a positive bone scan but a negative x-ray for HO, five discontinued treatment and showed gradual progression of HO. In the remaining 28 patients, 22 had no x-ray evidence of HO while six developed HO on x-ray. Among 13 patients who had a positive bone scan and a positive x-ray for HO, progression of soft tissue ossification was inhibited by Etidronate in six of these patients, while the remaining seven did not respond to treatment and showed further progression of HO.

Banovac (2000) studied 40 patients with SCI and HO, who were diagnosed early with positive bone scan but negative x-rays, and were treated with Etidronate (intravenous for three days, then oral for six months). Of the 40, 11 individuals (27.5%) developed radiographic evidence of HO 1.5-6.0 years post initiation of therapy.

Stover et al. (1987) conducted a pre-post trial of 87 adult SCI patients and found that there was no difference between patients treated with Etidronate Disodium for three months versus those receiving therapy for six months. However, those who received earlier treatment did better on x-rays.

Secondary prevention of HO post surgical excision was examined by Subbarao et al. (1987, N=5) and Schuetz et al. (2005, N=7). Subbarao et al. (1987) examined Etidronate treatment pre- and post-surgical hip wedge resection and found that patients still had severe restriction in their range of motion at follow-up. Schuetz et al. (2005) reported that pamidronate was administered pre- and post-surgical removal of HO among individuals with SCI and had no recurrences. It is important to note that sample sizes in both studies were small.

The lack of RCTs and variable treatment regimens make it difficult to form definitive conclusions. It appears that Etidronate is able to delay or inhibit HO progression once it is diagnosed and it tends to work better when given earlier after diagnosis.
Conclusions

There is Level 2 evidence (from 2 prospective controlled trials; Banovac et al. 1993; Banovac et al. 1997) that Etidronate can stop the progression of heterotopic ossification once the diagnosis is made; it is most effective if treatment is provided when the bone scan is positive but the radiographs are negative.

There is Level 2 evidence (from 1 prospective controlled trial; Banovac et al. 1997) that Etidronate is not effective once radiographs are positive for HO.

There is Level 4 evidence (from 1 case series; Schuetz et al. 2005) that pamidronate effectively halts secondary HO progression after surgical resection of HO.

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>PEDro Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durovic et al. 2009</td>
<td>Italy</td>
<td>PEDro=6</td>
<td>RCT</td>
<td>N=29</td>
<td>Population: Age range=18-45 yr. Treatment: Patients were randomly divided into experimental and control groups. Treatment group received 30 min Pulse low intensity electromagnetic field therapy (PLIMF) therapy (25 Hz, 10 mT) for 4 wk, approximately 7 wk post SCI. Outcome measures: Incidence of HO; Brooker classification.</td>
<td>1. Significant differences were found in the incidence of HO between the treatment and control groups. 2. 33% of individuals in the control group had incidence of HO; 0 cases of HO in the treatment group. 3. Among control groups individuals with HO post intervention, 2 progressed grade 1, 2 to grade 2, and 1 to grade 3 on the Brooker classification. 4. Significant differences were found in the incidence of HO between the treatment and control group (p&lt;0.04).</td>
</tr>
</tbody>
</table>

Discussion

Durovic et al. (2009) randomly assigned 29 SCI patients to a control group or treatment group. Both received range of motion and exercise therapy; however, only the treatment group received PLIMF therapy an average of seven weeks post injury for four weeks. The study showed no incidence of HO in the treatment group yet a 33% incidence in the control group (p<0.04).

Conclusion

Etidronate can halt the progression of heterotopic ossification.
Pamidronate halts secondary progression of heterotopic ossification post-surgical excision.

5.4 Pulse Low Intensity Electromagnetic Field Therapy

PLIMF therapy uses magnetic fields to increase oxygen levels and decrease toxic by-products of inflammation by increasing local blood flow (Durovic et al. 2009).
There is Level 1b evidence (from 1 RCT; Durovic et al. 2009) that Pulse Low Intensity Electromagnetic Field therapy is an effective prophylaxis of HO post SCI

Pulse low intensity electromagnetic field therapy is effective in preventing heterotopic ossification post spinal cord injury.

5.5 Radiation Therapy

Radiation therapy or radiotherapy, which is the use of ionizing radiation for therapeutic ends, has been proposed as a possible adjunct treatment for HO.

Table 5 Radiation Therapy for Treatment of Heterotopic Ossification

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sautter-Bihl et al. 2001</td>
<td>Germany</td>
<td>Case series</td>
<td>N=52</td>
<td>Population: Mean age=33 yr; Gender: males=44, females=8; Treatment: Patients received a single dose of radiotherapy 2-10 Gy through a linear accelerator at 6-8 MV photons. Outcome Measures: Efficacy, Brooker classification, and adverse effects.</td>
<td>1. Prevention of HO was seen in 71% of (41 primarily treated, 9 resected) joints. 2. Radiotherapy treatment did not result in a regression of the Brooker score in any patient. 3. An increase in two Brooker score grades was seen in two joints (1 knee, 1 hip) 4. No adverse effects due to therapy occurred. 5. 16 of 32 hips treated only with radiotherapy (50%) did not show any abnormalities on follow-up. 6. No progression of HO was noted in 30/36 subjects (83%). 7. Re-ossification after therapy which led to a decrease in joint mobility was noted in three subjects.</td>
</tr>
<tr>
<td>Sautter-Bihl et al. 2000</td>
<td>Germany</td>
<td>Case series</td>
<td>N=36</td>
<td>Population: Age range=17-59 yr; Gender: males=32, females=4; Follow-up=4-98 mo. Treatment: 25/36 subjects received 10 Gy radiotherapy in fraction of 2-2.5Gy, while four patients received higher doses. In phase 2 seven subjects received a single does of irradiation with 8Gy. In total, 46 joints were irradiated. Outcome Measures: Progression of HO and complications.</td>
<td>1. No statistically significant results were reported. 2. 16 of the 32 hips treated with radiotherapy only did not show any abnormalities on follow-up. 3. No progression of HO was noted in 30/36 subjects. 4. Re-ossification after therapy, which led to a decrease in joint mobility was noted in three subjects.</td>
</tr>
</tbody>
</table>

Discussion

Sautter-Bihl et al. (2000) studied 36 patients with HO of whom 27 patients (32 joints) received radiotherapy when ossification was minimal. 11 patients (13 joints) had obvious ossifications, which had to be resected. Post-op radiotherapy was performed 24-36 hours post-operatively. Two patients received radiotherapy both before and after surgery. Mean duration of follow-up was 23.6 months. 30 of the 36 irradiated patients showed no progression of HO. In 3 patients, reossification after therapy resulted in a moderate decrease in joint mobility.
In the follow-up case series by Sautter-Bihl et al. (2001), the authors examined the effectiveness of radiotherapy administered to 52 SCI patients. Radiotherapy effectively prevented primary and secondary HO post-surgical excision in 71% of patients. However, treatment did not result in regression of HO once developed, as measured by the Brooker scale. Two joints increased in Brooker score, although neither of them developed any functional impairment.

**Conclusion**

*There is limited Level 4 evidence (from 2 case series studies; Sautter-Bihl et al. 2000; Sautter-Bihl et al. 2001) that radiotherapy reduces the progression of heterotopic ossification.*

Radiotherapy can reduce the progression of heterotopic ossification.

### 5.6 Surgical Resection

Surgical resection of HO post SCI is a well-established treatment but still somewhat controversial.

**Table 6 Surgical Resection for Treatment of Heterotopic Ossification**

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>PEDro Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genet et al. 2011</td>
<td>France</td>
<td>Case series</td>
<td>N=86</td>
<td><strong>Population</strong>: Gender: male=81%; Mean age: 27.1 yr; Mean time post SCI: 13.1 mo. <strong>Treatment</strong>: Charts of patients who underwent surgical resection for HO were examined. <strong>Outcome Measures</strong>: Recurrence of HO</td>
<td>1. Most common site of HO was hips (74.4%). 2. HO recurrence was seen in 5.8% of patients. 3. Sepsis was a common side effect post-surgery. 4. Recurrence was not associated with etiology of injury (p=0.46) or sex (p=1.00). 1. A significant association was found between recurrence and delay until first surgery for SCI (p&lt;0.01).</td>
<td></td>
</tr>
<tr>
<td>Garland &amp; Orwin 1989</td>
<td>USA</td>
<td>Case Series</td>
<td>N=19</td>
<td><strong>Population</strong>: Mean age=22.5 yr; Level of injury: paraplegia=8, tetraplegia=11; Severity of injury: complete 12, incomplete 7. <strong>Intervention</strong>: Records of those who underwent hip resection for HO between 1970 and 1985 were reviewed. <strong>Outcome Measures</strong>: Range of motion, recurrence rate, and adverse effects.</td>
<td>2. Of 24 hips operated on, three had similar or less motion when compared with preoperative motion, 15 had 10-39° improvement, and 6 had &gt;40° improvement. 3. Total recurrence rate was 92% (22 of 24 hips). 4. A high number of complications, infections and blood loss occurred.</td>
<td></td>
</tr>
<tr>
<td>Meiners et al. 1997</td>
<td>Germany</td>
<td>Case Series</td>
<td>N=31 (43 hips); N=29 (41 hips)</td>
<td><strong>Population</strong>: Mean age=37.87 yr; Gender: males=28, females=1; Level of injury: paraplegia=19, tetraplegia=10; Severity of injury: complete 22, incomplete 7; Time since injury=17-298 mo; Hip side: l=16, r=23. <strong>Intervention</strong>: Resection of HO of the hip via ventral approach. Post-operation: Wk</td>
<td>1. Mean range of motion improved from 21.95° pre-operatively to 94.51° intra-operatively, to 82.68° post-operatively (mean=4.2 yr).</td>
<td></td>
</tr>
<tr>
<td>Author Year</td>
<td>Country</td>
<td>PEDro Score</td>
<td>Research Design</td>
<td>Total Sample Size</td>
<td>Methods</td>
<td>Outcome</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Schuetz et al. 2005</td>
<td>Switzerland</td>
<td></td>
<td>Case Series</td>
<td>N=7</td>
<td>1–irradiation of hip with a linear accelerator; Day 15–passive movement exercises implemented.</td>
<td>1. No statistical results were reported. 2. None of the patients treated with pamidronate showed clinical, x-ray or lab signs of HO recurrence or new HO at time of F/U (5-54 mo post-op).</td>
</tr>
<tr>
<td>Subbarao et al. 1987</td>
<td>USA</td>
<td></td>
<td>Case Series</td>
<td>N=5</td>
<td>Population: SCI: Age=47-68 yr; Gender: males=7; Level of injury: thoracic=1, tetraplegia=2. Treatment: All patients underwent excision-surgery for removal of HO. Pamidronate was administered IV peri- and post-op, starting at a dose level of 120 mg for 1st 12 hrs and gradually increasing for a total of 6-14 days.</td>
<td>1. All patients at last follow-up were able to function independently in their wheelchairs except one (was able to function independently in a semi-reclining wheelchair). 2. Patients had severe restriction of range of motion in involved joints.</td>
</tr>
</tbody>
</table>

**Discussion**

Meiners et al. (1997) reported a case series of 29 individuals (10 with quadriplegia and 19 with paraplegia) who underwent HO resection at the hip followed by irradiation and eventually passive range of motion exercises. Mean hip range of motion increased from 21.95° pre-operatively to 94.51° intra-operatively and 82.68° at 4 year (mean) follow-up.

Garland and Orwin (1989) examined the effect of HO excision to improve range of motion in 19 individuals with SCI. They found that the largest gain of function occurred intra-operatively followed by a large loss of function within the first six months. At final follow-up (6 yr post-surgery), 3 of 24 hip joints where HO was surgically excised had similar or less motion when compared with preoperative motion, 15 improved between 10° and 39°, while six showed greater than 40° improvement.

The effectiveness of surgical excision followed by bisphosphonates was examined in two case series (Schuetz et al. 2005; Subbarao et al. 1987). Etidronate treatment post-surgical excision showed that patients were able to function independently in a wheelchair; however, they had severe restrictions in their range of motion (Subbarao et al. 1987). Surgical excision supplemented with pamidronate treatment resulted in no recurrence of HO post surgery (Schuetz et al. 2005).

**Conclusion**
There is level 4 evidence that resection of HO about the hip post SCI can dramatically improve restricted hip range of motion.

There is Level 4 evidence that surgical resection combined with pamidronate treatment effectively halts secondary HO progression.

Surgical resection of heterotopic ossification can improve hip range of motion.

Surgical resection and pamidronate treatment halts secondary heterotopic ossification progression.
6.0 Summary

There is strong Level 1a evidence (from 2 RCTs; Banovac et al. 2001; Banovac et al. 2004) that non-steroidal anti-inflammatory medications can reduce the incidence of heterotopic ossification when administered early after a spinal cord injury.

There is Level 5 evidence (from 1 observational study; Buschbacher et al. 1992) that Warfarin inhibits the development of heterotopic ossification post spinal cord injury.

There is Level 2 evidence (from 2 prospective controlled trials; Banovac et al. 1993; Banovac et al. 1997) that Etidronate can stop the progression of heterotopic ossification once the diagnosis is made; it is most effective if treatment is provided when the bone scan is positive but the radiographs are negative.

There is Level 2 evidence (from 1 prospective controlled trial; Banovac et al. 1997) that Etidronate is not effective once radiographs are positive for HO.

There is Level 4 evidence (from 1 case series; Schuetz et al. 2005) that pamidronate effectively halts secondary HO progression after surgical resection of HO.

There is Level 1b evidence (from 1 RCT; Durovic et al. 2009) that Pulse Low Intensity Electromagnetic Field therapy is an effective prophylaxis of HO post SCI

There is limited Level 4 evidence (from 2 case series studies; Sautter-Bihl et al. 2000; Sautter-Bihl et al. 2001) that radiotherapy reduces the progression of heterotopic ossification.

There is level 4 evidence (from 3 case series studies; Genet et al. 2011; Garland & Orwin 1989; Meiners et al. 1997) that resection of HO about the hip post SCI can dramatically improve restricted hip range of motion.

There is Level 4 evidence (from 1 case series study; Schuetz et al. 2005) that surgical resection combined with pamidronate treatment effectively halts secondary HO progression.
References


Freed JH, Hahn H, Menter R, Dillon T. The use of the three-phase bone scan in the early diagnosis of heterotopic ossification (HO) and in the evaluation of didronel therapy. Paraplegia 1982;208-16.


