

SCORE

SPINAL CORD INJURY REHABILITATION EVIDENCE

Heterotopic Ossification Following Spinal Cord Injury

Fatimah Alibrahim MD
Amanda McIntyre RN MSc
Jonathan Serrato MSc
Swati Mehta PhD
Eldon Loh MD FRCPC
Robert Teasell 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.

Alendronate does not prevent the development of heterotopic ossification and may cause contractures.

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 but it may reoccur in a large number of individuals.

Surgical resection and pamidronate treatment halts secondary heterotopic ossification progression.

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Abbreviations

CT	Computed Tomography
HO	Heterotopic Ossification
MRI	Magnetic Resonance Imaging
PLIMF	Pulse Low Intensity Electromagnetic Field
SCI	Spinal Cord Injury

Heterotopic Ossification Following Spinal Cord Injury

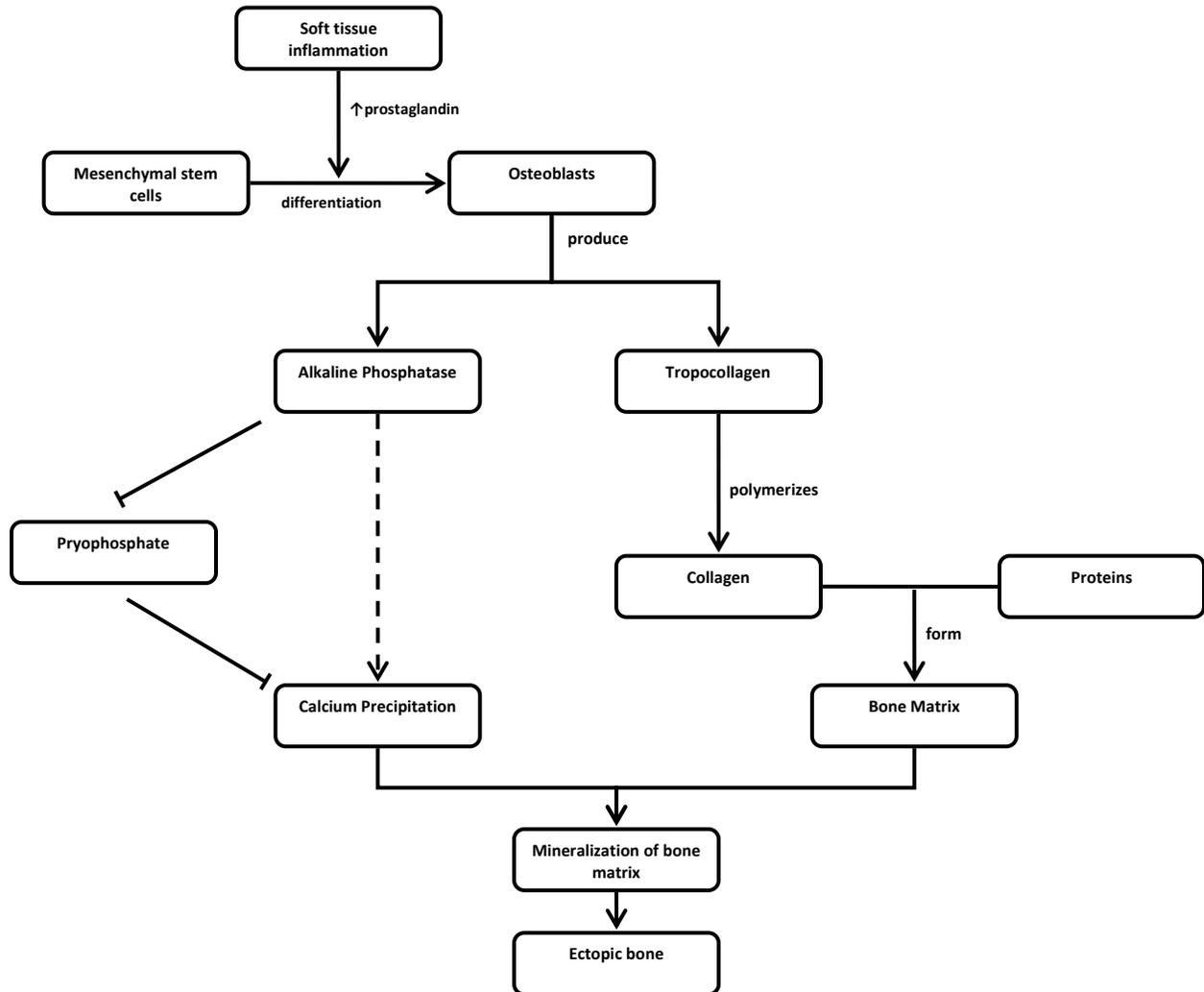
1.0 Introduction

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, Ranganathan et al. 2015). HO occurs most frequently in the first two months after SCI, below the level of paralysis (Banovac et al. 2001) and most commonly forms in the hip but rarely in the peripheral joints (Ranganathan et al. 2015).

2.0 Pathophysiology of Heterotopic Ossification

The mechanism underlying HO following spinal cord injury is not fully understood creating challenges in early diagnostic and therapeutic interventions. It appears to be initiated by metaplasia of mesenchymal cells in the peri articular hematoma and micro-hematoma into bone precursor cells (Schuetz et al. 2005). With time after a SCI, these cells calcify and ossify into bone cells (Emami Razavi et al. 2015). 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, muscles, tendons, ligaments or fat, besides bone (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).

Figure 1



3.0 Risk Factors and Clinical Presentation

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 less 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).

Krauss et al. (2014) reported that males were five times more likely to develop HO and SCI severity is also a risk factor with AIS A patients at greater risk than AIS D patients. Injury severity was also highlighted by Ranganathan et al. (2015) whose literature review revealed that severity and level of injury with injuries to the thoracic and cervical spine are greater risk of

developing HO. However, both gender and injury severity as risk factors have been disputed in the literature (Krauss et al. 2014).

Krauss et al. (2014) also investigated the role of hyper-coagulable states and related blood markers as risk factors in the development of HO. D-Dimer was elevated in 24 out of 32 patients with SCI and concurrent HO. Following this, the role of deep vein thrombosis (DVT) and pulmonary embolism (PE) have also been linked to the development of HO. Reznik et al. (2014) also reported that DVT/PE were significant predictors of HO along with multiple pressure ulcers and AIS B severity score. Reznik et al. (2014) propose that the association of HO and DVT/PE is due to the link between trauma, surgery and fractures and thrombogenic factors such as thromboplastin or factor III in the body becoming stimulated and increased. Regarding the association of HO and pressure ulcers, it is postulated to be due to pressure ulcer infection deep enough to reach the bone along with tissue hypoxia, prolonged immobilization and muscle trauma (Emami Razavi et al. 2015). Further research is required to establish the relationship between HO and pressures sores/ulcers.

After three-12 weeks, symptoms of HO start to appear (Schuetz et al. (2005). The initial clinical signs of inflammation are non-specific for HO (Neal 2003). Individuals typically present with joint and muscle pain, paresthesias and tissue swelling in the involved region, accompanied by a mild fever (Thomas & Amstutz 1987; Orzel & Rudd 1985; Smith 1998; Shehab et al. 2002). Conversely, some SCI patients do not experience any pain. Skeletal bio-markers can help detect development of HO, in particular, ALP serum, CPK, C-reactive protein, prostaglandin E₂, and erythrocyte sedimentation rate which have been to be associated with HO after SCI (Ploumis et al. 2015).

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 one 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 suggest 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.

A new classification has been proposed by Arduini et al. (2015) based on the use of a 3D-CT reconstruction scan. The authors propose that this method allows the surgeon to observe the bone bridge in its entirety, can assist in assessing the relationship between neurovascular structures and the HO, and can identify the site of discontinuity therefore allowing the surgeon to plan the best surgical approach. Arduini et al. (2015) contend that their approach is more advantageous in comparison to the Brooker Classification, which they believe is inadequate at classifying the anatomy of the HO, and Mavrogenis et al. (2012)'s proposal, which the authors argue cannot give precise details regarding the continuity of the bone bridge or the extent to which surrounding muscles and soft-tissues are being affected. Genêt et al. (2015) also highlight that the Brooker Classification cannot be used to determine the potential drawbacks of surgery and gives pessimistic results of hip range of motion with some hips classified as III or IV despite no clinical ankylosis found. Arduini et al. (2015) state that their classification system has reproducible high intra- and inter-observer reliability and that previous methods including Garland's radiological classification and Mavrogenis et al. (2012) CT approach have not been validated. However, it is also important to note that Arduini et al. (2015) used a mixed population of SCI and TBI with SCI accounting for 29% of the sample. Although their approach is of interest, further research is required with an all-SCI, or at least SCI-majority, group of patients.

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.

Table 1 Reviews examining the effectiveness of pharmacological, non-pharmacological and surgical management of HO after SCI

Author(s) Country Date included in the review AMSTAR score Number of articles	Method: Level of evidence Questions	Conclusions
Aubut et al. 2011 Canada Review of published articles between 1980-2010 AMSTAR=8 N=26	Method: Comprehensive literature search of English RCT, Cohort studies, case series, and review articles of traumatic SCI in adult age group (≥18yr). Databases: MEDLINE, EMBASE, CINAHL, PsycInfo. Level of evidence: <i>Moderate quality:</i> Downgraded high quality studies, non-randomized trials, prospective cohort studies; <i>Low quality:</i> Retrospective	<ol style="list-style-type: none"> 1. ABI population usually required multicomponent treatments compared to the SCI population. 2. There are more level 1 and level 2 evidence for the SCI literature in supporting HO treatment, while the literature for the ABI population is weaker with mainly level 4 evidence. 3. HO in SCI patients was mostly seen in the hip while the ABI patients had

	<p>observational, retrospective cohort and case-control studies; <i>Very low quality</i>: Case series, case reports, reviews and others.</p> <p>Questions/measures/hypothesis:</p> <p>1. Examine the effectiveness of pharmacological, non-pharmacological and surgical management of HO after ABI and SCI.</p>	<p>more varied location of HO including hip, knee and elbow.</p> <p>4. Etidronate and indomethacin post-surgery suggested for both populations to reduce the risk for HO.</p>
<p>Teasell et al. 2010 Canada Review of published articles between 1980-2009 AMSTAR=8 N=13</p>	<p>Method: Comprehensive literature search of English RCT, Cohort studies, case series, and review articles of traumatic SCI in adult age group (≥18yr).</p> <p>Databases: MEDLINE, EMBASE, CINAHL, PsycInfo.</p> <p>Level of evidence: <i>Moderate quality</i>: Downgraded high quality studies, non-randomized trials, prospective cohort studies; <i>Low quality</i>: Retrospective observational, retrospective cohort and case-control studies; <i>Very low quality</i>: Case series, case reports, reviews and others.</p> <p>Questions/measures/hypothesis: Examine the effectiveness of pharmacological, non-pharmacological and surgical management of HO after SCI.</p>	<p>1. There was strong evidence that early prophylactic treatment was efficacious in preventing HO, in which NSAIDs showed greatest effectiveness (level 1 evidence).</p> <p>2. Bisphosphonates had the strongest evidence for treatment of HO (level)</p> <p>3. There is some evidence for the use of Pulse low intensity electromagnetic field therapy (PLIMF), however, further research is needed.</p>

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 2 Anti-Inflammatory Drugs as a Prophylaxis for Heterotopic Ossification

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
<p>Banovac et al. 2004 USA RCT PEDro=10 N=76</p>	<p>Population: Gender: males=65, females=11; Severity of injury: complete, incomplete, AIS: A-C; Mean time since injury: 24 days.</p> <p>Interventions: The treatment group received oral rofecoxib 25mg daily x4/wk.</p> <p>Outcome Measures: Incidence of HO and swelling of joints.</p>	<p>1. A significantly lower incidence of HO was found in the rofecoxib group (13.4%) than in the placebo group (33.3%, p<0.05).</p> <p>2. In patients receiving rofecoxib, there was 2.5x lower relative risk of developing HO than in the placebo group.</p>
<p>Banovac et al. 2001 USA</p>	<p>Population: Mean age: 33 yr; Gender: males=33, females=0; Severity of injury:</p>	<p>1. There was a significantly higher incidence of early HO, diagnosed on</p>

<p>RCT PEDro=9 N=33</p>	<p>AIS: A-D; Groups: treatment=16, placebo=17. Treatment: Treatment was slow-release indomethacin 75 mg daily versus placebo x3/wk. Patients were followed up clinically until they showed signs and symptoms of HO; all were followed up with x-rays at 2 mo and 6 mo. Where patients had a positive bone scan for HO, the study was D/C and patient was initiated on Etidronate Disodium. Outcomes Measures: The effect of indomethacin administration on the incidence of HO.</p>	<p>bone scan, in the placebo group (11/17) than in the group taking indomethacin (4/16) (p<0.001). 2. In the placebo group, 7/17 patients developed x-ray evidence of HO as did 2/16 in the indomethacin treated group (p<0.001).</p>
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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 two 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.

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

5.2 Warfarin as Prophylaxis

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

Table 3 Warfarin as a Prophylaxis for Heterotopic Ossification

<p>Author Year Country Research Design Score Total Sample Size</p>	<p>Methods</p>	<p>Outcome</p>
<p>Buschbacher et al. 1992 USA Observational</p>	<p>Population: Age range: 17-75 yr; Gender: males=213, females=14; Severity of injury: complete, incomplete. Treatment: Patients treated with</p>	<p>1. Warfarin administration and development of HO were found to be significantly related (p<0.01). 2. None of the patients treated with</p>

N=227	warfarin for a mean of 5.4 wk post SCI for deep vein thrombosis; no X-rays taken to rule out HO. HO, diagnostic tests done only if clinical signs were suggestive. Outcome Measures: Prevalence of HO.	Warfarin (n=33) developed HO and none of the patients with HO (n=34) had been treated with Warfarin.
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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 one observational study; Buschbacher et al. 1992) that Warfarin inhibits the development of heterotopic ossification post spinal cord injury.

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

5.3 Bisphosphonates

Three bisphosphonates, Alendronate, Etidronate (didronel) and pamidronate, have been studied in the treatment of HO progression post SCI. Alendronate is a potent N-containing second generation bisphosphonate and is thought to inhibit bone resorption, have a small effect on mineralization and has been observed to reduce the rate of HO (Ploumis et al. 2015). 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 4 Bisphosphonates for Treatment of Heterotopic Ossification

Author Year Country Research Design Score Total Sample Size	Methods	Results
Alendronate		
Ploumis et al. 2015 USA Prospective Controlled Trial N=299	Population: Alendronate (ALN, N=125): Mean age: 40.6 yr; Gender: males=86, females=39. <i>Non-ALN</i> (N=174): Mean age: 44.2 yr; Gender: males=140, females=34. Treatment: 70 mg ALN was prescribed weekly to patients who could tolerate sitting in an upright position and able to receive oral medications. Patients used ALN for a mean period of 267 days. Outcome Measures: Documentation and presence of HO.	<ol style="list-style-type: none"> 1. No significant correlation between diagnosis of HO and ALN intake was found. 2. A significant correlation was found between HO appearance and ALP serum abnormality (p<0.001). Further, normal ALP serum levels were significantly correlated with ALN intake (p<0.05) whilst abnormal ALP serum levels was significantly correlated with no

		ALN intake. 3. Significantly more patients receiving ALN developed contractures (p<0.001).
Etidronate		
Banovac 2000 Denmark Case Series N=40	Population: Mean age: 23 yr; Gender: males=39, females=1; Injury etiology: SCI=40; Severity of injury: AIS A-B; Time since injury range: 2-5wk. Treatment: 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.
Banovac et al. 1997 USA Prospective Controlled Trial N=46	Population: Age range: 16-55 yr; Gender: males=44, females=2; Injury etiology: SCI=46; Severity of injury: AIS: A-C; Time since injury range: 2-5 wk. Treatment: 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): 6 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 et al. 1993 USA Prospective Controlled Trial N=27	Population: Age range: 15-64 yr; Gender: males=25, females=2; Injury etiology: SCI=27; Severity of injury: Frankel Class: A=15, B=12; Time since injury range: 2-6 wk. Treatment: 300mg IV Etidronate Disodium was administered over 3 hr for 3-5 days. After parenteral therapy, 20 mg PO Etidronate was administered for 6 mo. The second group received Etidronate PO only. Outcome Measures: Swelling.	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. 2. Overall, treatment reduced swelling (p<0.01). 3. No significant differences noted between the IV and orally treated groups in effect on HO.
Subbarao et al. 1987 USA Case Series N=5	Population: Age range: 29-41yr; Injury etiology: SCI; Time since injury range: 18-197 mo. Treatment: Didronel given 10 days-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	Population: Age: >16 yr; Injury etiology: Acute SCI. Intervention: 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 and 1yr 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.
Garland et al. 1983 USA Case Series	Population: Mean age=25 yr; Gender: males=9, females=5; Injury etiology: SCI; Level of injury: cervical=6, thoracic=5;	1. 8/9 pretreatment patients had HO in 10 hips. 2. Post-treatment all patients

N=14	Severity of injury: complete=7, incomplete=2. Treatment: Bisphosphonate treatment was administered for 2wk at 20 mg/kg/day and then for 2yr at 10 mg/kg/day. Outcome Measures: Effectiveness of treatment and adverse effects.	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.
Pamidronate		
Schuetz et al. 2005 Switzerland Case Series N=7	Population: Age range: 47-68 yr; Gender: males=7, females=0; Injury etiology: SCI=7; Level of injury: thoracic=1, tetraplegia=2. Treatment: All patients underwent excision surgery for removal of HO. Pamidronate was administered IV peri-op 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. Outcome Measures: Prevalence of HO.	No statistical results reported 1. None of the patients treated with pamidronate showed clinical, x-ray or lab signs of HO recurrence or new forming HO at 5-54 mo follow-up.

Discussion

Alendronate

Ploumis et al. (2015) prescribed 70 mg per week of Alendronate to 125 SCI patients over a mean of 267 days. Development of HO was compared with 174 SCI patients who did not receive Alendronate. No direct correlation was found between prevention of HO and Alendronate intake; however, there appeared to be an indirect link between the two as abnormal ALP serum levels were significantly correlated with patients with HO whilst normal ALP serum levels were significantly correlated with Alendronate intake. Therefore, Alendronate may be effective in reducing one of the risk factors of developing HO rather than a direct prophylactic advantage. A potential drawback for the use of Alendronate was the finding that patients were more likely to develop contractures whilst taking the drug compared to patients who were not (Ploumis et al. 2015).

Etidronate

Several studies aimed to determine the effect of Etidronate on HO and the regimen of administration. 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 (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.

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.

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.

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). 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.

Pamidronate

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 one prospective controlled trial; Ploumis et al. 2015) that Alendronate does not inhibit the development of heterotopic ossification and in fact may contribute to the development of contractures.

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

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

Alendronate does not prevent the development of heterotopic ossification and may cause contractures.

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).

Table 5 Pulse Low Intensity for Treatment of Heterotopic Ossification

Author Year Country Research Design Score Total Sample Size	Methods	Results
Durovic et al. 2009 Italy RCT PEDro=6 N=29	<p>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.</p>	<ol style="list-style-type: none"> 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 ($p < 0.04$).

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

There is Level 1b evidence (from one 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 6 Radiation Therapy for Treatment of Heterotopic Ossification

Author Year Country Research Design Score Total Sample Size	Methods	Results
Sautter-Bihl et al. 2001 Germany Case Series N=52	Population: Mean age: 33 yr; Gender: males=44, females=8; Treatment: Patients received a single dose of radiotherapy 2-10Gy through a linear accelerator at 6-8 MV photons. Outcome Measures: Efficacy, Brooker classification, adverse effects.	<ol style="list-style-type: none"> 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.
Sautter-Bihl et al. 2000 Germany Case Series N=36	Population: Age range: 17-59 yr; Gender: males=32, females=4; Follow-up range: 4-98mo. Treatment: 25/36 subjects received 10 Gy radiotherapy in fraction of 2-2.5 Gy, 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.	<ol style="list-style-type: none"> 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.

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 three 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.

A case study by Cramarossa et al. (2013) reported on the use of radiation therapy on a patient who had previously experienced an SCI at the C5-C6 level and had been diagnosed with dysphagia due to HO-induced osteophytes. One day after surgical intervention which involved anterior cervical decompression and drilling of the osteophytes, the patient received a single treatment of radiation at 8 Gy. At follow-up, the patient reported that they were not experiencing any recurrence of dysphagic symptoms. The authors add that radiation should only be considered for patients at high risk of HO due to the risk of creating a radiotherapy-induced malignancy and that an expansion of the literature is required to better assist treatment decisions.

Conclusion

There is limited Level 4 evidence (from two 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 is still somewhat controversial.

Table 7 Surgical Resection for Treatment of Heterotopic Ossification

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Genet et al. 2011 France Case Series N=86	Population: Mean age: 27.1yr; Gender: males=70, females=16; Mean time since injury: 13.1 mo. Treatment: Charts of patients who underwent surgical resection for HO were examined. Outcome Measures: Recurrence of HO.	<ol style="list-style-type: none"> 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). 5. A significant association was found between recurrence and delay until first surgery for SCI (p<0.01).
Schuetz et al. 2005 Switzerland Case Series N=7	Population: Age range: 47-68 yr; Gender: males=7; Injury etiology: SCI=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 1 st 12 hr and gradually increasing for a total of 6-14 days. Outcome Measures: Prevalence of HO.	<ol style="list-style-type: none"> 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).
Meiners et al. 1997	Population: Mean age: 37.87 yr; Gender: males=28, females=1; Level of injury:	<ol style="list-style-type: none"> 1. Mean range of motion improved from 21.95° pre-

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Germany Case Series N _{Initial} =31 (43 hips); N _{Final} =29 (41 hips)	paraplegia=19, tetraplegia=10; Severity of injury: complete 22, incomplete 7; Time since injury range: 17-298 mo; Hip side: L=16, R=23. Intervention: Resection of HO of the hip via ventral approach. Post-operation: wk 1-irradiation of hip with a linear accelerator; Day 15–passive movement exercises implemented. Outcome Measures: Range of motion (flexion and extension) pre-, post-, intra-operatively and at follow-up.	operatively to 94.51° intra-operatively, to 82.68° post-operatively (mean=4.2 yr).
Garland & Orwin 1989 USA Case Series N=19	Population: Mean age=22.5yr; Level of injury: paraplegia=8, tetraplegia=11; Severity of injury: complete=12, incomplete=7. Intervention: Records of those who underwent hip resection for HO between 1970 and 1985 were reviewed. Outcome Measures: Range of motion, recurrence rate, and adverse effects.	<ol style="list-style-type: none"> Of 24 hips operated on, three had similar or less motion when compared with preoperative motion, 15 had 10-39° improvement, and 6 had >40° improvement. Total recurrence rate was 92% (22 of 24 hips). A high number of complications, infections and blood loss occurred.
Subbarao et al. 1987 USA Case Series N=5	Population: Age range: 29-41 yr; Time since injury range: 18-197 mo. Treatment: Etidronate given 10 days-2 wk preoperatively, medication withheld for immediate postop period (72 hr) and continued for minimum of 3 mo. All patients underwent wedge resection at hip to permit free movement of hip in flexion. Outcome Measures: Function, range of motion.	<ol style="list-style-type: none"> All patients at last follow-up could function independently in their wheelchairs except one (was able to function independently in a semi-reclining wheelchair). Patients had severe restriction of range of motion in involved joints.

Discussion

The timing for surgical resection continues to split consensus with surgery being conducted once the ectopic bone has completely matured being considered the usual course of action. Despite that, there are growing calls for surgery to be delayed until the patient has fully recovered from their SCI (Gurcan et al. 2013). However, a delay in excision has been found to lead to a series of negative events such as increased risk of fracture, ankylosis, bone loss, and intra-articular lesions (Genêt et al. 2015).

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 four year (mean) follow-up. Garland and Orwin (1989) also reported that HO excision improves 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 (six years post-surgery), three 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.

Some studies stress that surgical resection must be followed up by prophylaxis, either radiation therapy, NSAID or bisphosphonates due to high recurrence rates after surgery alone. A case study by Gurcan et al. (2013) investigated the use of surgical resection in a patient with total ankylosis of the right hip following a T8-T9 fracture. Upon excision of the cephalad mass, the patient's hip could be flexed to 100° and abducted to 30° on the operating table, indicating a successful operation. At post-surgery, the patient completed passive movements of the hip, and was treated with a single dose of radiation (eight Gy) and a prescription for indomethacin with a dosage of 150mg a day. At 12-month follow-up post-surgery, the range of motion in the hip remained preserved with no recurrence of HO or ankylosis.

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).

Genêt et al. (2015) conducted a review of the literature regarding recurrence rates of HO after surgical excision. A finding of concern was the lack of consensus towards the classification of HO and risk of recurrence and whilst some studies have attempted, the authors point out that these are based on observations and are merely descriptive. Moreover, the review was not able to clarify ideal timing for surgical resection, in part due to disparate rates of recurrence post-surgery. A prominent issue of HO recurrence is the definition of recurrence. Genêt et al. (2015) highlight that some patients are not deemed to have had recurring HO post-surgery if the patient's functioning is not impaired, and adds that pre- and post-surgical care are not standardized with early rehabilitation such as limb mobilization often being delayed due to inflammation and treated with NSAIDs instead.

Conclusion

There is level 4 evidence (from three case series; 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; however, post-surgical recurrence and complications are a concern for this treatment.

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

There is level 4 evidence (from one case series; Subbarao et al. 1987) that surgical resection combined with etidronate treatment improves independence with wheelchair use but contributes to reduced range of motion.

Surgical resection of heterotopic ossification can improve hip range of motion but it may reoccur in a large number of individuals.

Surgical resection and pamidronate treatment halts secondary heterotopic ossification progression.

6.0 Summary

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

There is Level 2 evidence (from two 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 one prospective controlled trial; Ploumis et al. 2015) that Alendronate does not inhibit the development of heterotopic ossification and in fact may contribute to the development of contractures.

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

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

There is Level 1b evidence (from one 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 two 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 three case series; 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; however, post-surgical recurrence and complications are a concern for this treatment.

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

There is level 4 evidence (from one case series; Subbarao et al. 1987) that surgical resection combined with etidronate treatment improves independence with wheelchair use but contributes to reduced range of motion.

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