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Heterotopic Ossification in Orthopaedic Trauma

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Abstract

Heterotopic ossification (HO) can be defined as the pathological formation of bone in extra-skeletal tissues. There has been a substantial amount of recent research on the pathophysiology, prophylaxis and treatment of HO and traumatic conditions associated with the development of HO. This research has advanced our understanding of this disease and helped to clarify evidence-based approaches to both the prophylaxis and treatment of HO. This article reviews the literature on these topics with a focus on their application in orthopaedic trauma.

Introduction

Heterotopic ossification (HO) can be defined as “the pathological formation of bone in extraskeletal tissues”.¹ Three subtypes of HO have been described: traumatic, neurogenic, and genetic. Traumatic HO occurs in response to injuries such as acetabular fractures, fractures and fracture-dislocations of the elbow, knee and shoulder, blast injuries and burns. Neurogenic HO occurs in response to injury to the central nervous system (CNS) including traumatic brain injury (TBI) and spinal cord injury (SCI). Genetic HO occurs in patients with the rare inherited conditions Fibrodysplasia Ossificans Progressiva (FOP) and Progressive Osseous Heteroplasia (POH) the study of which have helped to advance our understanding of the mechanisms underlying HO formation. This article reviews the recent literature on the pathophysiology, prophylaxis and treatment of HO in orthopaedic trauma

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patients, as well as several select conditions associated with HO formation in trauma patients.

The Pathophysiology of Heterotopic Ossification

The pathophysiology of HO closely resembles the physiologic process of fracture healing. Three prerequisite components have been described regarding the pathophysiology of HO: osteogenic precursor cells, inductive stimuli, and a permissive environment.¹ Although differences exist, these components closely mirror the described critical components of fracture healing: osteogenesis, osteoinduction, and osteoconduction.

Osteogenesis refers to an appropriate population of osteoprogenitor cells that participate in the formation of bone as part of the normal fracture healing response. In the case of HO formation, the process is thought to arise from the disordered differentiation and proliferation of similar cell types. The evidence supporting this concept comes from several sources. Recent investigation on the genetic disorder FOP has demonstrated that this condition arises from a mutation in the BMP type-I receptor, activin receptor IA/activin-like kinase-2 (ACVR1/ALK2), which results in dysregulation of BMP signaling.² It is well-known that osteoprogenitor cell populations such as mesenchymal stem cells (MSCs) migrate, differentiate and proliferate in response to BMP signaling, providing indirect evidence of the role of these cells in HO formation. Further, radiation therapy is a well described treatment for HO prophylaxis that is thought to work by targeting rapidly proliferating and differentiating cells if administered early enough in the time course of HO formation (within 72 hrs of the inciting event).³ It is hypothesized that the osteoprogenitor cell population is targeted by this therapy. In addition, recent investigation of progenitor cell populations obtained from war-traumatized muscle tissue (prone to HO formation) has demonstrated several similarities to bone marrow-derived MSCs including similar morphology, cell surface markers, osteogenic potential, multipotency, and osteogenic gene expression.⁴ Taken together, these findings suggest that HO formation arises from a cell population that is at least very similar to the osteoprogenitor cell population responsible for fracture healing.

Osteoinduction refers to signaling by proteins, most notably the BMPs, which initiate the bone formation process. In the process of HO formation this is thought to be due to a combination of inflammatory signals and BMP signaling. This is supported by the evidence of a genetic mutation in BMP signaling in the most common form of genetic HO, FOP, and by evidence of upregulated BMP expression in the lesional tissue and progenitor cells from these patients.⁵ In addition, BMP antagonists such as Noggin have been shown to be effective in preventing HO formation in animal models.⁶ Potter et al reported on the osteoinductive signaling potential of wound effluent obtained from blast-injured patients who developed HO by culturing MSCs in the wound effluent and demonstrating enhanced osteogenic differentiation in vitro.⁷ Systemic inflammation is also thought to play a significant role in HO formation in trauma patients as these patients demonstrate a profound systemic inflammatory response with elevated levels of cytokines IL-6 and MCP-1 having been demonstrated.⁸ In addition, another commonly used prophylaxis against HO formation is non-steroidal anti-inflammatory (NSAID) administration, which targets inflammation via cyclooxygenase inhibition, thus limiting expression of Prostaglandin E2 and other chemokines, supporting the importance of inflammation in HO formation.⁹

Osteoconduction refers to an appropriate scaffold to support the growth of bone and vasculature in bone formation. In the context of HO formation, this osteoconductive environment is provided by muscle tissue (which is often traumatized) and serves as an ideal environment for the development of the fibroproliferative lesions which precede mature HO

formation.⁷ Similar to fracture healing, these traumatized tissue environments ostensibly have decreased oxygen tension, a prerequisite for enchondral bone formation.

The emerging evidence on the pathophysiology of HO formation, which has arisen from several different sources, highlights two important concepts. First, the pathophysiology of HO closely mirrors the normal physiology of fracture healing in many respects; this presents a further problem in orthopaedic trauma patients where there are often competing priorities of achieving fracture union and preventing HO formation. Second, our enhanced understanding of the pathophysiology of HO formation will likely lead to novel therapies in the future.

Heterotopic Ossification Prophylaxis in Orthopaedic Trauma

The two most commonly used approaches to HO prophylaxis in orthopaedic trauma are NSAIDs and single-dose radiation therapy. NSAIDs are thought to interfere with HO formation by their inhibition of inflammatory prostaglandins, which are known potent co-stimulatory molecules with BMPs in the induction of heterotopic bone.¹ The most well-studied of the different NSAIDs in orthopaedic trauma is indomethacin, which is typically administered for a treatment duration of six weeks. Single dose radiation therapy is proposed to work via targeting rapidly proliferating and differentiating osteoprogenitor cells and thus needs to be administered within 72 hours of the inciting event, and ideally even earlier.

The two most common clinical situations in which HO prophylaxis has been studied in orthopaedic trauma are acetabular fractures and fracture-dislocations about the elbow. The rate of HO formation associated with acetabular fracture surgery has been reported to be as high as 90%, with the incidence of Brooker Class III and IV HO ranging from 19-38%.^{9,10} There is a known increased risk of HO formation with extensile or posterior approaches to the acetabulum.¹¹ The use of indomethacin as prophylaxis is well documented in the literature and is reported to decrease the rate of clinically significant HO formation to 8.9-18%.^{10,12} There is evidence from the literature on HO formation following total hip arthroplasty that a short duration (20 days) of prophylaxis with selective cyclooxygenase-2 (COX-2) inhibition is equally effective to six weeks of indomethacin therapy, but evidence for this in acetabular fracture surgery is lacking.⁹ There are several caveats to indomethacin use for HO prophylaxis in acetabular fractures. First, there is a significant rate of gastrointestinal side effects and patient compliance is poor. Second, there are two randomized trials which have failed to show a significant benefit of indomethacin prophylaxis versus no treatment for the prevention of HO formation in acetabular fracture surgery.^{13,14} Finally, Burd et al reported an increased rate of concomitant long bone nonunion in patients receiving indomethacin versus radiation or no prophylaxis against HO formation following acetabular fracture surgery (26% vs 7%; $p=0.004$), once again highlighting the difficulties of HO prophylaxis in trauma patients.¹⁵ Radiation therapy delivered as a single dose of 700-800 cGy within 72 hours of surgery has demonstrated similar efficacy to indomethacin for HO prophylaxis following operatively treated acetabular fractures in several randomized trials.^{10,16} Radiation therapy appears to decrease the incidence of clinically significant HO formation to 4-9%. While there is a decreased risk of long-bone nonunion with radiation therapy relative to indomethacin treatment, the cost is significantly higher and radiation carries a theoretical risk of radiation-induced sarcoma (although no clinical cases have been reported),^{3,16} as well as potentially inhibited surgical wound healing. Blokhuis et al conducted a systematic review of prospective studies comparing radiation to indomethacin prophylaxis and found an overall HO rate of 8.9% with indomethacin versus 8.3% with radiation.¹² The difference was statistically significant ($p=0.034$), but this small difference is unlikely to represent a clinically relevant difference. Based on the available evidence, we use indomethacin as our primary prophylaxis against

HO formation following acetabular surgery via a posterior or extended approach. We consider the use of radiation therapy, if feasible, in patients who can't tolerate NSAIDs or have a long-bone fracture considered at-risk for nonunion. Further research is needed to evaluate the use of selective COX-2 inhibition in this setting.

The rates of clinically significant HO formation following open reduction and internal fixation (ORIF) of distal humerus fractures ranges from 0-21% in modern series, with pooled analysis (n=239 patients) demonstrating an overall rate of 8.6%.¹⁷ Reported rates in fracture dislocations of the elbow treated with ORIF range from 5.5-18.8%. These rates are significantly increased with associated CNS injuries, delays in surgical intervention, and repeat surgical procedures.^{17,18} The use of NSAIDs for prophylaxis in this setting is controversial and there is a lack of prospective studies in the literature. In the only randomized controlled trial to date in this area, Hamid et al randomized 48 patients with either a distal humerus fracture or elbow fracture-dislocation treated with ORIF to post-operative radiation or no prophylaxis.¹⁹ Their study was terminated early due to an unacceptably high rate of nonunion in the treatment group (38%, 8/21 patients) versus the control group (4%, 1/24 patients). With the numbers studied, there were no significant differences in the rate of HO formation between the groups. There is a lack of high level evidence to guide management with regard to HO prophylaxis in these patients; however, several conclusions can be drawn from the available literature. First, the use of radiation is contraindicated due to the increased risk of non-union. Second, there is no strong evidence to support routine prophylaxis and we recommend the selective use of NSAIDs for prophylaxis in high risk patients, such as those with an associated CNS injury, significant delay to surgery, or repeat surgical procedures.

Treating Heterotopic Ossification in Orthopaedic Trauma Patients

There are several indications for the treatment of HO in orthopaedic trauma patients including: restricted range of motion (primary or secondary athrofibrosis or ankylosis), pain, nerve entrapment, skin ulceration, and difficulties with prosthesis fitting/use. The initial treatment consists of work-up for other sources of pain such as infection, nonunion, post-traumatic arthritis, neuroma, complex regional pain syndrome, and internal derangement, followed by physiotherapy and NSAID use. Of note, the use of NSAIDs in this setting is directed at reducing inflammation and pain for symptom mitigation, not for prevention or regression of bone formation. Ultimately, persistently symptomatic HO in trauma patients requires surgical excision, generally followed by secondary prophylaxis for recurrence prevention.

Traditional approaches to the surgical treatment of HO have recommended delaying surgical intervention until alkaline phosphatase levels normalize and the heterotopic bone is mature on radiographs and quiescent on bone scan. However, this was largely based on anecdotal evidence and more recent evidence from a number of studies suggests that early surgical excision of HO with secondary prophylaxis is safe and confers several advantages such as easier surgery, more effective rehabilitation, and improved health of articular cartilage and surrounding bone.^{20,21} Pre-operative computed tomography (CT) scanning with 3D reconstructions is helpful for operative planning and identifying the entrapment of or proximity to neurovascular structures (Figure 1). The majority of authors have reported on the use of post-operative single-dose radiation for secondary prophylaxis against HO recurrence following surgical excision of HO from the hip, knee, or elbow, although the use of NSAIDs has also been reported.²⁰⁻²³ Fortunately, in the setting of secondary HO prophylaxis following surgical excision, fracture nonunion is not a concern and both radiation and NSAIDs are ostensibly safe. The literature on the surgical excision of HO in the hip, knee, and elbow with secondary prophylaxis demonstrates significant improvements

in pain and ROM with low rates of recurrence (0-19%) and acceptable rates of peri-operative complications (0-25%).²⁰⁻²³

On the basis of the available evidence, we only delay surgical intervention until patients have adequately rehabilitated from their injuries and their fractures have healed. We routinely obtain pre-operative CT scans with 3D reconstructions and surgical principles include adequate exposure, careful identification of neurovascular structures, and meticulous hemostasis. Secondary prophylaxis typically involves single-dose post-operative radiation, although occasionally NSAIDs are used. Adherence to this protocol can provide dramatic improvements in patient function (Figure 2) with a low rate of recurrence.

Blast Injury and Heterotopic Ossification

A significant amount of research on HO in blast injuries has arisen from the U.S. involvement in the conflicts in Iraq and Afghanistan, advancing our understanding of HO formation in this context. Trends in modern warfare have resulted in an increased prevalence of HO due to high energy extremity injuries. Potter et al reported an incidence of clinically detectable HO of 63% in traumatic and combat-related amputations, with blast mechanism of injury and amputation through the zone of injury being identified as important risk factors.²⁴ Forsberg et al identified a 64.6% rate of HO in a war wounded cohort of patients, demonstrating significantly higher rates of HO formation than civilian trauma populations.²⁵ They identified risk factors for HO formation in this population including TBI, age less than 30, amputation, multiple extremity injuries, and an Injury Severity Score (ISS) 16.

Research on this population of war-injured patients has also helped to advance our understanding of the basic science of HO formation. Several biomarkers predictive of HO formation have been identified including increased levels of IL-6, IL-10, and MCP-1 in the serum and MIP-1 α in the wound effluent.⁸ It has been demonstrated that war-traumatized tissue contains an increased number of connective tissue progenitors relative to normal muscle tissue.²⁶ In addition, war-traumatized tissue samples from patients who later developed HO showed elevated levels of osteogenic progenitor cells and up-regulation of multiple osteogenic genes relative to injured tissue that did not go on to develop HO.²⁶ The ultimate goals of this research are both to identify tissues and patients at greatest risk of developing HO early in the treatment process and identify novel biomolecular targets and treatments for the prevention of HO.

CNS Injury and Heterotopic Ossification

The pathophysiology of HO formation secondary to CNS injury (neurogenic HO) remains poorly understood. HO formation can, and often does, occur following TBI or SCI without direct tissue damage or trauma to affected joints, although it is more likely to occur when CNS injury occurs in combination with limb trauma.¹⁸ Factors such as prolonged mechanical ventilation/coma, muscle spasticity, male sex, and age less than 30 appear to contribute to an increased risk of HO formation.²⁷ It is hypothesized that neurogenic HO results from neuro-osseous signals that have a direct effect on bone metabolism. Candidate molecules include leptin, glutamate, calcitonin gene related protein, substance P, vasoactive intestinal peptide, and catecholamines.²⁸ It is further hypothesized that these neuro-osseous signals have a direct effect on the differentiation of progenitor cells. It has been suggested that neurogenic HO occurs in response to systemic factors in conjunction with local tissue stimuli that promote the osteogenic differentiation of progenitor cells (such as MSCs) when not suppressed by CNS signals.

Clinically, Neurogenic HO appears to behave differently in SCI patients versus TBI patients. First, there is different occurrence rate of HO formation between the two patient groups,

with a reported rate in SCI patients of 40-50% versus a rate of 10-20% in TBI patients.²⁹ Second, the distribution of affected joints appears to differ between the two conditions. The hip is the dominant site of involvement in SCI. The hip is also the most commonly affected joint in TBI; however, it is more common for TBI patients to present with HO in other joints such as the elbow and shoulder, and multi-site involvement is more common than in SCI patients.²⁷ Finally, there is evidence to suggest that neurogenic HO secondary to SCI responds better to pharmacologic prophylaxis/treatment with NSAIDs or bisphosphonates, whereas HO secondary to TBI is more likely to require surgical treatment.²⁹ These data suggest that neurogenic HO secondary to SCI and TBI have significant differences, with implications for both prophylaxis and treatment.

Conclusions

The prophylaxis and management of HO in orthopaedic trauma patients is often complicated by competing priorities of HO prevention and fracture healing. The literature presented in this article has arisen from several different sources of investigation, including the study of genetic conditions of HO formation. This literature has helped to advance our understanding of the pathophysiology of HO formation, as well as prophylaxis and treatment strategies in different patient populations. With continued research we will likely identify novel prophylactic agents and treatment strategies, as well as be able to identify patients early in the treatment course whom are likely to develop HO. These advances will allow us to improve the care and outcomes of orthopaedic trauma patients in the future.

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Figures 1A and 1B.

Three dimensional computed tomography scan reconstructions of the right hip of a 29 year-old male patient who sustained an isolated head injury and required surgical treatment of an epidural hematoma with prolonged coma and intensive care unit stay post-operatively. The patient developed heterotopic ossification in his hip that significantly limited his ability to sit and ambulate. The images demonstrate Brooker Class IV HO formation in the anterior aspect of his hip.

Figures 2 A, B, and C.

The same patient from Figure 1 underwent surgical excision of his HO via a modified Smith-Petersen approach followed by single dose radiation therapy 24 hours post-operatively. Images A and B demonstrate pre and post-operative maximum hip flexion. Image C shows the amount of bone removed from the hip.