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Heterotopic ossification following upper extremity injury

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Synopsis

Heterotopic ossification (HO) presents a substantial barrier to rehabilitation for patients with severe burns or trauma. Although surgical excision is a mainstay of management for this condition, this is unable to address the chronic sequelae of HO including chronic pain, joint contractures, nerve dysfunction, and open wounds. Current therapeutic modalities are aimed towards excision and the prevention of recurrence using NSAIDs or radiation therapy. Research is now focused on identifying alternative strategies to prevent the initial occurrence of HO through NSAIDs and novel inhibitors of the bone morphogenetic protein (BMP) signaling pathway.

Keywords

Heterotopic ossification; Burn injury; Elbow; Upper extremity

INTRODUCTION

Heterotopic ossification (HO) is the pathologic formation of extra-skeletal bone within soft tissues or joints. HO occurs in two patient populations – those who have severe trauma and those who have genetic mutations in the bone morphogenetic protein (BMP) signaling pathway. The latter are a minority of patients with an extremely debilitating disease process, representing approximately 500 individuals nationwide. However, patients with trauma including musculoskeletal injury, spinal cord injury (SCI)/traumatic brain injury (TBI), and burns represent a much larger population of patients at risk for HO. Patients with any of these injuries may develop HO in the upper extremities, even if the extremities are uninjured from the initial trauma.

HO presents a substantial barrier to patient recovery after major trauma, burns, and surgical procedures. These patients have often already undergone procedures related to the initial traumatic insult, and may present 6 or more months later with signs indicative of HO including localized pain or discomfort, reduced range-of-motion, and open wounds. However, current therapeutic modalities are limited in their ability to prevent HO, and surgical excision to remove the osseous lesion is unable to address chronic sequelae of HO

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such as pain and joint contractures. Furthermore, even after successful excision, patients are at risk for recurrence due to the local inflammation caused by surgery.

The elbow is the most common anatomic location of HO in burn patients, even in the absence of burns to the upper extremity(1–3). However, diagnosis of HO at this site can be particularly challenging, as the elbow can become stiff after trauma due to prolonged inactivity or direct injury. Cognitive decline caused by prolonged sedation can further compromise successful rehabilitation in these patients(4). Although there are several surgical approaches to remove HO in the upper extremity, none is able to completely restore pre-injury function(5).

EPIDEMIOLOGY AND RISK FACTORS

Heterotopic ossification occurs in patients following musculoskeletal injury and extensive burns. A recent review of nearly 3,000 burn injury patients from six high-volume centers found that 3.5% of patients developed HO(6). Included patients were 18–64 years old with total body surface area (TBSA) greater than 20% in patients, 65+ years old with TBSA 10% or greater, or any patients with burn injury to face/neck, hands or feet(6). They found that patients with the highest odds of developing HO had greater than 30% TBSA burns and patients with upper extremity burns requiring grafting had nearly 100 times higher odds of developing HO. Overall elbow HO has been reported to occur in 0.1–3.3% of burn patients(7–9). A systematic review of reports describing excision of HO in the elbow found that 28% (174/626) of cases were in burn patients, 55% (343/626) of cases were in trauma patients, and 17% (109/626) were in TBI patients(10). Studies of burn patients have found the elbow to be the most commonly involved joint, with formation approximately 3 months after the initial injury(1–3). These findings provide further evidence that HO may form in the elbow after a variety of injuries.

In patients with elbow fractures, those who underwent surgery over 1 week after injury, or had mobilization of the elbow delayed by over 2 weeks were at the highest risk for HO, with 7% (55/786) of patients developing HO(11). Another review of 124 patients with elbow fractures found clinically relevant HO, defined as being Class 2 or greater using the Hastings and Graham classification scheme, in 21% (26/124) of patients(12).

HO is also reported in the lower limbs of patients with polytrauma including blast injuries, as in those sustained by military members. A review of injured military personnel with amputations found that over 60% of the 213 residual limbs had HO(13). A separate study by the same group found that traumatic brain injury (TBI) was associated with HO, as was an increased injury severity score (ISS ≥ 16 , O.R. 2.2, $p < 0.05$)(13, 14). Upwards of 20% of patients with SCI have been reported to develop HO(15, 16). Increased systemic inflammation, local spasticity, and prolonged immobilization all place these patients at higher risk, and both pre-clinical and clinical studies are studying how controlling these sequelae of trauma may reduce or eliminate HO (17).

Finally, patients who have had elective orthopedic operations are also at risk for HO, particularly those who have had total hip arthroplasty (THA). One study cited over 40% of

patients developing some form of ectopic bone after THA(18). More recent studies have reported HO rates ranging from 26% to 58% in THA patients(19–21). The predictably higher rate of HO in these patients has prompted investigators to test prophylactic measures such as non-steroidal anti-inflammatory drugs (NSAIDs) or radiation therapy to prevent HO or its recurrence, as described below(22–33).

DIAGNOSIS

Examination

Due to the central role of the elbow in upper extremity movement, HO at this site can cause substantial disability. Signs include limited range of motion, arthritis, pain, stiffness and swelling. Concomitant symptoms of ulnar nerve compression at the elbow can occur requiring detailed sensory and motor examination of the upper extremity in the ulnar nerve distribution. This should include evaluation of 2-point discrimination, documentation of Wartenberg or Froment signs, examination of the intrinsic muscles for atrophy, and testing for Tinel sign over the cubital tunnel(34). Delayed conduction on nerve conduction studies can provide additional objective data regarding the severity of nerve compression.

Current Imaging Techniques

Currently a conclusive diagnosis of HO is based on radiographic imaging. Patients may present with clinical signs or symptoms prompting x-ray imaging (Fig 1). Ectopic bone on x-ray can aide in determining the appropriate approach for excision. Importantly, radiographic imaging modalities are able to only detect the ossified lesion. These imaging modalities will not identify patients who are developing early cartilage deposits which later undergo ossification, nor are they able to identify patients who are at the highest risk for developing HO prior to even cartilage formation. Therefore, at the time when patients have presented with clinical signs or symptoms prompting radiographic evaluation, the major therapeutic option available to patients is surgical excision which is ablative and does not restore function. Radiotherapy or NSAID therapy, which are currently studied for prophylaxis have not been shown to reduce the size of ossified lesions.

Magnetic resonance imaging (MRI) may provide further information regarding the relationship between the ossified lesion and surrounding soft tissue structures. Proximity to nerves can be instructive in determining the risks of surgical excision, and in surgical planning. MRI also allows for identification of surrounding areas of inflammation based on T2 hyperintensity indicative of edema.

Experimental Imaging Techniques

Alternative techniques for detecting HO lesions prior to ossification are now in pre-clinical and clinical investigation. Identification of HO prior to ossification may allow for prophylactic measures to be instituted such as radiotherapy or NSAIDs, which do not typically affect ossified lesions. One of these modalities is single-photon emission computed tomography (SPECT), which is able to correlate metabolic activity using radioisotope uptake with the presence of osseous lesions (Fig 2). Areas of early HO may be non-ossified but have high metabolic activity, indicated by increased up take of the radioisotope (35, 36).

Studies are now underway to determine whether SPECT can guide extent of surgical excision, or whether evidence of metabolic activity can guide therapeutic intervention. Ideally, imaging to identify highly metabolic foci prior to ossification may provide a prophylactic window. However, this technology requires specialized imaging protocols, is time-consuming, and does not provide real-time information to guide surgery.

Another clinically available imaging modality which may be useful for the identification of HO is ultrasonography. One study reported that ultrasonography was able to identify HO even before the development of clinical signs(37). A recent case report describes the use of ultrasound to identify a heterogeneous, hypervascular lesion which eventually developed into HO. Ultrasound was even able to identify the lesion two weeks before bone scan showed characteristic intense metabolic activity(37). The changes identified by ultrasound may represent cartilage which precedes HO, and which is identifiable by ultrasound in other musculoskeletal conditions (38). Our laboratory is currently studying how ultrasound findings correspond with specific histologic features during HO formation. Ultimately, a non-invasive point-of-care approach to HO diagnosis, as provided by ultrasound, would facilitate in-office evaluation of at-risk patients.

Experimental imaging techniques are also being studied in the laboratory for their ability to elucidate tissue changes prior to ossification. Raman spectroscopy is one such imaging modality which is able to identify spectral changes associated with collagen and early mineral deposition – two critical components of osseous lesions (Fig 3) (39). Using a mouse model of HO, we found that Raman spectroscopy was able to detect changes associated with HO up to two weeks prior to radiographic evidence in a mouse model (39). Raman spectroscopy does not require administration of radiotracers and is not invasive, providing another opportunity for point-of-care diagnosis in the office(40, 41). Furthermore, the development of algorithms which can interpret spectroscopic readings may obviate challenges associated with user expertise as required for ultrasonography.

Finally, despite the numerous imaging modalities which are available clinically, none have been standardized for HO imaging. Some surgeons prefer to rely on physical exam and wait until edema has decreased and scars have optimized prior to intervention(4).

PREVENTION

The approach to patients at risk for HO involves both prevention and surgical excision (Fig 4). Due to the variable frequency of HO after trauma, and the potential adverse effects associated with preventative therapy, routine prophylaxis against HO is not standard practice for trauma patients.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective for both primary prevention of HO and secondary prevention (after excision) of recurrent HO(22–28). NSAIDs are believed to prevent HO by reducing inflammation and simultaneously reducing signaling through the bone morphogenetic protein (BMP) pathway. Recent literature suggests that cellular components of the inflammatory response to trauma including macrophages and neutrophils can induce osteogenic differentiation through their

production and secretion of BMP ligands. Clinical studies have shown that NSAIDs reduce HO after total hip arthroplasty (THA) procedures(33, 42, 43). In a retrospective review of 152 patients who underwent surgical excision for post-traumatic elbow HO, 30.7% (23/75) of untreated patients and 10% (8/77) of Celecoxib-treated patients experienced recurrence within 3 months after surgery. These findings persisted at 9 months after injury, when 57% of untreated patients and 26% of Celecoxib-treated patients had developed recurrence(44). The protocol reported in that study was daily Celecoxib (200 mg) administered for a total of 28 days after surgery(45). However, use of NSAIDs is not without consequence, as they may increase the risk of gastrointestinal bleeding, which is already increased in patients with severe musculoskeletal or neurologic injury; proton pump inhibitors (PPIs) can reduce the risk of GI bleeding. Furthermore, musculoskeletal injury often includes some component of normal bone injury such as fractures; however, NSAIDs and selective COX-2 inhibitors have been shown to reduce fracture healing in patients and animal models(46, 47). The mechanism by which NSAIDs reduce fracture healing remains unclear, although this may be through a mechanism similar to its effect on HO –reduced inflammation and BMP signaling. Overall, studies have shown that NSAIDs are a more cost-effective approach to HO prevention than radiotherapy, and do not have inferior results(28, 48).

Radiation therapy has also been extensively studied as a preventative strategy for patients and can be administered either pre- or post-operatively (9, 28–33, 49–53). With respect to upper extremity HO, radiation has been shown to be effective in the reduction of HO recurrence after initial excision (9, 51, 52). One study found that of 11 cases of elbow HO in burn patients who underwent excision and radiation therapy within 24 hours after excision, only one elbow developed recurrence with no reported wound-healing complications (9). Another study reported recurrence in 10% (n=19) of elbows which underwent initial HO excision with radiation therapy administered within 48 hours after surgery(50). In another report of 20 patients with excised HO and radiation therapy, 2 (10%) developed recurrent lesions(52). A recurrence rate of 8% (3/36) was described in another group of patients that had received post-operative radiation therapy after elbow HO excision(51). These findings suggest that radiation therapy is well-tolerated in the peri-operative period and that the risk of recurrence after excision with radiation prophylaxis is near 10%. These findings compare favorably with rates of 30% described in other studies without prophylaxis.

Finally, bisphosphonates have been studied for the prevention of HO. Initial double-blinded studies showed a significant reduction in HO after trauma with etidronate treatment (54). Interestingly, a retrospective review found that burn patients treated with etidronate actually had a higher incidence of HO when compared with patients who were untreated(55). In another report, no patients (n=5) who underwent surgical excision of HO had recurrence after intravenous infusion with the bisphosphonate pamidronate(56). Treatment was not associated with adverse effects such as osteomalacia or osteoporosis.

SURGICAL MANAGEMENT

Indications

Surgical excision remains a central aspect of HO management, as patients often present after a radiographically identifiable lesion forms. Patients may present with signs or symptoms

concerning for HO including joint arthritis causing pain or restricted motion. Patients may also present with signs sensory or motor disruption consistent with ulnar nerve disruption. The indications for operative intervention vary among surgeons, but include arthritis with loss of motion more than 30-degrees and pain at the end of arc(5). Contraindications to operative intervention include inadequate soft-tissue envelope, loss of motor function at the elbow which would preclude return of function, or inability to perform post-excision rehabilitation(5).

Approach

Both open and arthroscopic procedures have been described for HO excision. In general, an open approach is recommended for patients with prior fractures or in the setting of prior procedures where nerve anatomy can be aberrant. Open procedures are also preferred when a large joint contracture needs to be released and soft tissue coverage will be necessary as is often the case in patients who present late. Nerve involvement is best addressed with an open procedure where decompression of the nerve can be performed.

The surgical approach for open excision has been described through a posterior midline incision to gain access to both the lateral and medial aspects of the elbow and minimize risk to cutaneous nerve branches(4, 57). An incision shifted slightly medially may reduce the risks of wound-healing complications while allowing for ulnar nerve decompression; a lateral approach may also minimize wound-healing complications but does not provide access to the ulnar nerve(58). Others prefer two separate incisions located medially and laterally(5). Patients with burn injury directly involving the elbow should have incisions placed over the most durable skin which allows access to the elbow(57). In all instances, thick skin flaps should be raised to avoid skin necrosis and reduce injury to cutaneous nerves during elevation.

Operative Techniques

Restricted flexion may indicate impingement by anterior osteophytes and a tight posterior capsule, while loss of extension may be due to involvement of posterior osteophytes and anterior capsule tightness. Separation of HO from native bone requires identification of a tissue plane, although this may be difficult to identify in some patients. An osteotome or rongeurs can be used to separate joined structures, although care must be taken to avoid disrupting the normal bone surface(57). When anterior HO is removed, the underlying capsule is usually involved and needs to be released. This is not always the case with posterior HO(57).

Medially, the ulnar nerve is identified, traced proximally and distally freeing it from the scar of the HO and transposed anteriorly into subcutaneous tissues. Ulnar nerve injury has been reported in these patients, although it is difficult to determine whether this is always due to excision, or due to the underlying pathology(45). Identification of the nerve well proximal to the elbow joint decreases risk of ulnar nerve injury(4). The ulnar nerve may be encased in heterotopic bone, requiring careful dissection. The nerve can then be transposed anteriorly into the subcutaneous tissues(57). Laterally, the posterior interosseous branch of the radial nerve is identified and protected. The radial nerve proper is usually well-protected; however,

when anterolateral HO is present, the radial nerve can be identified between the brachialis and brachioradialis(4). The median nerve and brachial artery are usually not encased in HO. However, during dissection of the anterior musculature, the median nerve must be protected.

The anterior or posterior capsule should then be released depending on the patient's primary restriction (extension – anterior, flexion – posterior). Soft tissue coverage may be required for burn patients if a scar contracture is also released at the same time. Coverage of important structures can be performed using brachioradialis or flexor carpi ulnaris muscle flaps followed by skin grafting.

At the end of the procedure, the elbow is gently manipulated to confirm improved passive range of motion. This should be done carefully to avoid further injury in a fresh surgical field. Patients are then placed in a dorsal orthoplast splint overnight with range of motion exercises initiated within 24 hours afterwards. A complete neurovascular exam should be performed post-operatively to confirm preserved function of all three major nerve branches.

Rehabilitation

Rehabilitation protocols vary among published reports. Some advocate early continuous passive motion with additional use of static progressive or dynamic splints after a month post-excision(58, 59). Care must be taken not to perform aggressive range of motion to avoid re-instating the inflammation that was responsible for the heterotopic bone in the first place. Studies are underway to better understand the role of immobilization and range of motion on burn induced HO as well as post-resection HO development.

Outcomes

Pre-injury function is rarely restored with HO excision, although range-of-motion and contractures are generally improved. Most series are single-center case reports and report an improvement of 50 to 110 degrees in arc-of-motion(57, 60–62). Complications include infection, nerve injury, and recurrence. One systematic review included 33 patients with 626 elbows and reported a mean improvement in arc-of-motion of 67- degrees (range 13–131 degrees)(10). They further stratified data by initial injury type including trauma, burn, and traumatic brain injury – patients with trauma had the best mean improvement in motion (109-degrees) while burn patients and TBI patients had reduced improvements 88-degrees and 75-degrees respectively). In their review they found that 14% of patients (41/299) required re-operation due to residual stiffness from recurrent HO (31), infection (5), ulnar fracture (2), ulnar nerve dysfunction (2), and brachial artery rupture (1)(10). Due to the risks of post-excision stiffness and HO recurrence, post-operative management is critical to patient recovery. A systematic review of over 600 elbows which underwent HO excision found a recurrence rate of 20%(10).

BASIC SCIENCE RESEARCH

Animal models

HO occurs in a variety of clinical scenarios, which has led to the development of several animal models for pre-clinical investigation. HO in these models are generally assessed

using radiographic means including x-ray or micro-computed tomography (microCT) scanning. Our laboratory regularly uses the burn/tenotomy model in which a mouse receives hindlimb Achilles' tendon transection and dorsal 30% total body-surface area (TBSA) burn injury(63–65). This model is intended to replicate polytrauma often observed in patients who develop HO. Therapeutic approaches to reduce inflammation caused by the burn injury alone are sufficient to reduce the volume of HO on microCT. In this model, HO forms through endochondral ossification, similar to human HO (Fig 5). Therapeutics such as Cox-2 inhibitors which are in clinical investigation also reduce HO in this model (Fig 6)(65).

Military personnel with blast injuries are also at high risk for HO. A group of researchers at the naval academy have developed a rat model of HO in which the hindlimb is exposed to high-energy blast followed by transfemoral amputation and bacterial inoculation. These extensive injuries are not dissimilar to the conditions experienced by wound military personnel; in this rat model, HO forms at the site of the transfemoral amputation(66, 67).

Patients with traumatic brain injury (TBI) or spinal cord injury (SCI) are also at high for developing HO in the hips. Recently, one group has found that mice with spinal cord transection develop HO in the gluteal musculature after local injection of cardiotoxin, a chemical agent which induces myonecrosis(68). Mice which receive cardiotoxin without spinal cord transection do not develop HO however. Further studies are required to understand how the spinal cord transection mediates HO formation, and whether this effect is due to local versus systemic inflammation caused by the spinal cord injury.

Other models of HO which have been used in the past include local implantation of bone morphogenetic protein (BMP)-impregnated sponges and transgenic mice with hyperactive BMP receptor activity(69). BMP-impregnated sponges do not reproduce the clinical scenario encountered by trauma patients, but may be representative of HO in patients with BMP implants. Finally, transgenic mice with hyperactive BMP receptor activity are used as models of fibrodysplasia ossificans progressiva (FOP). FOP is a genetic condition in which patients develop progressive, painful ectopic osseous lesions after minor trauma. A causative mutation in the type I BMP receptor, *ACVR1* has been identified in these patients; transgenic mice with this mutated *ACVR1* transgene develop HO after local activation of the mutation and injection of cardiotoxin(70).

These models underscore the variety of clinical scenarios in which HO can develop, ranging from burn and trauma patients as in patients who develop upper extremity HO, and those who have genetic mutations. Importantly however, genetic mutations or polymorphisms are not believed to underlie the HO seen in trauma patients.

Therapeutics under laboratory investigation

The animal models described above are being evaluated for experimental treatments against trauma-induced HO. The first series of compounds being evaluated are inhibitors of the BMP signaling pathway. These therapeutics, including LDN-193189, are kinase inhibitors which target the type I BMP receptor ACVR1/ALK2(65, 70). We have demonstrated efficacy in the burn/tenotomy model, and mechanistic studies to improve targeting and

therapy delivery are in progress(65). Drugs with improved specificity for BMP receptors are also being designed using LDN-193189 as structural analogue.

Another series of drugs under investigation are the retinoic acid receptor (RAR) gamma agonists(69). These drugs have been shown to block or reduce HO in models of recombinant BMP2 delivery, and in the transgenic mouse model described above. Retinoid signaling is an inhibitor of chondrogenesis, an essential early histologic phase of HO. Though promising, these therapeutics should be used with caution in burn patients given their detrimental effect on wound healing.

Another group of drugs under investigation are inhibitors of hypoxic signaling. Hypoxia-inducible factor-1 α (HIF-1 α) is a mediator of hypoxic signaling which up-regulates vascular endothelial growth factor (VEGF) to induce angiogenesis. Recently, HIF-1 α has been recognized as a mediator of chondrogenesis as well, possibly through activation of the chondrogenic transcription factor SOX9. We have recently shown that inhibitors of HIF-1 α are able to reduce or block HO after burn/tenotomy and in a transgenic mouse model of hyperactive BMP receptor(63).

One of the challenges associated with prevention of trauma-induced HO is patient selection. Not all patients who have been in major trauma will develop HO, and therefore administering therapeutics indiscriminately risks adverse effects. There is a need to synthesize techniques for early diagnosis with therapies which prevent progression of the lesion. In addition, further studies are required to evaluate the impact of these diseases on overall wound healing. As our clinical appreciation of HO and associated risk factors improves and the laboratory investigations into therapies advances, we anticipate a directed approach to preventing HO in high-risk populations using targeted, effective, and safe drugs.

SUMMARY

Heterotopic ossification (HO) presents a substantial barrier to rehabilitation for patients with severe burns or trauma. Although surgical excision is a mainstay of management for this condition, this is unable to address the chronic sequelae of HO including chronic pain, joint contractures, nerve dysfunction, and open wounds. Current therapeutic modalities are aimed towards excision and the prevention of recurrence using NSAIDs or radiation therapy. Research is now focused on identifying alternative strategies to prevent the initial occurrence of HO through NSAIDs and novel inhibitors of the bone morphogenetic protein (BMP) signaling pathway.

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Collaborate with Boehringer Ingelheim on project not discussed here. We have filed a patent application for the new use of Rapamycin in heterotopic ossification. IP has not yet been licensed.

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KEY POINTS

- Heterotopic ossification (HO) is the formation of ectopic bone within or involving soft tissues including joint spaces, nerve, and/or muscle.
- HO occurs in patients following trauma, and often develops in the elbow of patients with severe burn injuries, even without direct injury to this anatomic site.
- HO causes restricted motion and subsequent joint contractures, chronic pain, and open wounds.
- Diagnostic approaches to HO are limited primarily to clinical presentation and radiography.
- Prophylactic measures against HO include non-steroidal anti-inflammatory drugs (NSAIDs) and radiotherapy, although each of adverse consequences with imperfect outcomes.

Figure 1.
Operative photographs and radiography demonstrating heterotopic ossification present in the soft tissue of the wrist.

Figure 2.
Single-photon emission computed tomography (SPECT) demonstrating areas of uptake in a pre-osseous HO lesion of the right elbow (*red box*).

Figure 3.

Raman spectroscopy identifies distinct peaks for mineral, lipid, and protein in early/developing HO lesions.

Modified from Peterson JR, Okagbare PI, De La Rosa S, et al. Early detection of burn induced heterotopic ossification using transcutaneous Raman spectroscopy. *Bone*. 2013;54(1):30; with permission.

Figure 4.

An approach to surgical and non-surgical management of heterotopic ossification.

Endochondral Ossification

Figure 5. Histologic progression of heterotopic ossification in a mouse model recapitulates the process of endochondral ossification.

Figure 6.
Cox-2 inhibitors decrease the formation of heterotopic ossification in a murine burn-trauma model.