Heterotopic Ossification after Trauma

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KEYWORDS

• Trauma • NSAIDs • Heterotopic ossification • Orthopedics • Hip arthroplasty
• Myositis ossificans

KEY POINTS

- Heterotopic ossification (HO) is most common after trauma, specifically traumatic brain injuries, spinal cord injuries, and thermal burns.
- HO may be treated prophylactically with nonsteroidal anti-inflammatory drugs and in some cases, radiation may be suitable.
- Recommendations regarding the timing of surgical intervention are variable, with some studies recommending against waiting for lesion maturation of the heterotopically ossified bone, whereas other studies support waiting for HO bone maturation before surgical intervention.
- Preoperative computed tomography scans can show entrapped Neurovascular structures as channels through the heterotopic bone that can be safely freed with Kerrison Rongeurs. First, identify normal anatomy and bone then resect from normal to abnormal to avoid injury to normal tissue.

INTRODUCTION

Heterotopic ossification (HO) refers to benign ectopic bone formation in soft tissue and is common following trauma surgery. Early symptom presentations include nonspecific findings such as erythema, swelling, loss of motion, occasional joint tenderness, and pain appearing 3 to 12 weeks post-trauma.[1] HO bone can restrict movement and progress into ankylosis that may necessitate surgical intervention. Forsberg and colleagues[2] reported an observed HO rate of 64.5% with extremity trauma necessitating orthopedic intervention in combat wounded patients. Most of the patients reported in the study are males under the age of thirty with high impact trauma involving blast injuries and gunshot wounds. No effective treatments for HO have been identified to date as the underlying cellular and molecular mechanisms have not been completely elucidated.[3] The current literature suggests that the pathogenesis of HO involves inductive signaling pathways in inducible osteoprogenitor cells, yet attempts to locate systemic and local factors have not been successful.[3] Recent studies have uncovered the involvement of inflammatory signals and both the innate and adaptive immune system involvement in HO bone formation in response to soft-tissue damage.[4] The development of HO is likely complex and multifactorial. Although HO is not exclusive to trauma and orthopedic surgery, this article will discuss the current literature on the pathophysiology, prophylaxis, epidemiology, and treatment of postoperative HO following orthopedic trauma.

PATHOPHYSIOLOGY

Most of the studies on the pathophysiology of HO used animal models with the heredity version of HO, known as Fibrodysplasia

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Ossificans Progressiva (FOP) providing mechanistic insights. Soft tissue prone to HO has an altered response to inflammation and injury-mediated cytokines. Mesenchymal stem cells are thought to be the major cell population involved in the formation of HO.[5] Beta morphogenic protein (BMP) and transforming growth factor-β are two cellular components responsible for regulating bone development through SMADs. In particular, BMP4 is of interest in HO as it is expressed in both bone and soft tissue. The levels of BMP4 are expressed in similar amounts in soft tissue and bones before fracture. However, following a femoral fracture in a rat model BMP4 expression increased tenfold in 6 h in soft tissue and BMP4 expression was unaffected in bone before returning to baseline in 72 h.[6] Moreover, BMP2 receptors are also of interest as their overexpression has been reported to induce HO.[7] However, eradicating BMP2 fails to prevent HO but it does delay onset.[8] Other nonspecific osteogenic progenitors including the expression of an angiogenic receptor Tie-2 have been shown to contribute to half of bone-forming cells with HO lesions.[8] These cells respond by differentiating through endochondral ossification and respond to BMP signaling.[9] Lin and colleagues[10] reported that the formation of HO appears to show intracellular homeostatic dependence by using Metformin to down-regulate AMP-activated protein kinase (AMPKA) inhibiting BMP and preventing trauma-induced HO in mice. Another study used pyrase locally at a burn site to prevent HO through the same mechanism by decreasing phosphorylated SMAD 1/5/8 in mesenchymal cells in vitro.[11] Moreover, nuclear retinoic acid receptor-g (RAR-g) agonists are also significant in the pathophysiology of HO due to their role in chondrogenesis.[12] Local micro-environment factors such as ischemic time, oxygen saturation, and mechanical stimulation also impact HO formation.[13,14] Therefore, the pathophysiology for HO induced following trauma surgery is likely multifactorial, with complex signaling pathways.

RISK FACTORS

Risk factors such as a prior history of HO, hypertrophic osteoarthritis, ankylosing spondylitis, and male gender have been linked to the development of HO in both THA and Open Reduction/Internal Fixation (ORIF) patients,[15] but many of these factors have also shown no increased HO in other studies. Risk factors that were more consistently found to increase HO prevalence were traumatic brain injury (TBI) and prolonged mechanical ventilation. Patients requiring prolonged mechanical ventilation have an increased risk of developing HO with an odds ratio of 7.[16] One study showed an odds ratio of 8.6 for the development of HO following a TBI.[17] Following a TBI HO commonly affects the hip the most followed by the elbow, and rarely the knee. In contrast, the order of HO following an Spinal cord injury (SCI) more commonly affects the hip, knee, and elbow below the site of injury respectively. Hip flexors and abductors are more commonly affected than extensors or adductors.[18] Different surgical approaches have different rates of postoperative HO development. A meta-analysis comparing anterior and posterior surgical approaches to Pipkin I and II fractures of the femoral head reported a statistically significant 22% risk increase in the postoperative frequency of HO formation with the posterior approach compared with the anterior approach.[19] For acetabular fractures, the surgical approach has been implicated in the incidence of HO with the iliofemoral approach having the greatest risk of HO, followed by the Kocher–Langenbeck approach, and the ilioinguinal approach with the lowest risk of HO.[20–23] Interestingly, in patients with polytrauma with an associated head injury, HO occurred adjacent to the initial fracture zone. Whereas, in cases of polytrauma without an associated head injury, HO occurred in regions without any signs of injury.[24]

LAB FINDINGS

In early stages of HO, serum alkaline phosphatase level is elevated (3.5 × normal) but returns to physiologic levels in later stages of maturation.[25] It is important to note that age-adjusted levels of serum alkaline phosphatase do not increase in children during any stage of HO bone formation. Therefore, serum findings for the purpose of HO are only useful in ruling out bone mineralization disorders. A urinary increase of Prostaglandin E2 (PGE2) levels 24 h following trauma can be suggestive of HO. prophylaxis should be considered for those patients (Fig. 1).[26]

IMAGING

A distinguishing feature of trauma-induced HO bone formation is the appearance of an ectopic bone fragment with a peripheral ossification site. It is important to differentiate early stages of HO from conditions for which it is commonly

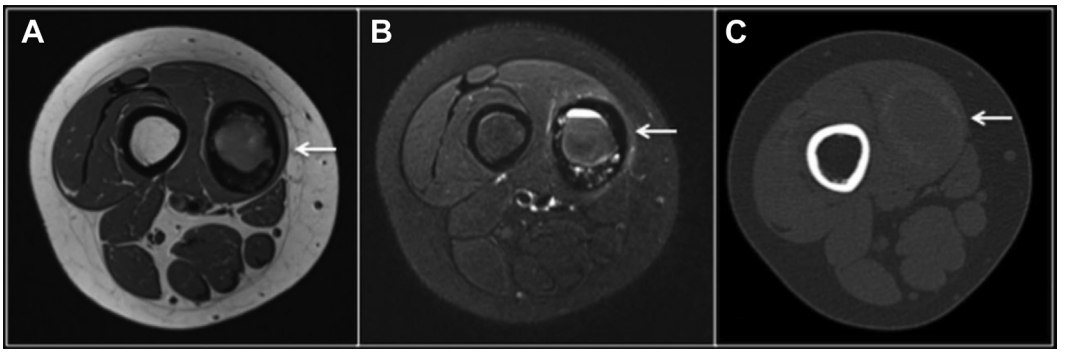

Fig. 1. Axial T1 (*A*), STIR (*B*), and CT (*C*) showing myositis ossificans (*arrow*) in the vastus medialis. (*From* Saad A, Azzopardi C, Patel A, Davies AM, Botchu R. Myositis ossificans revisited - The largest reported case series. J Clin Orthop Trauma. 2021 Mar 13;17:123-127. https://doi.org/10.1016/j.jcot.2021.03.005. PMID: 33816108; PMCID: PMC7995649.)

misdiagnosed including osteosarcoma and osteomyelitis.[27,28] Osteosarcomas have a central ossification site detected on imaging and are commonly seen in the metaphysis of long bones and don't typically occur following trauma.[29] During the early stages of bone mineralization, HO is indistinguishable from dystrophic calcification (DC) in imaging. As the mineralization process progresses, DC will remain as a nonossified amorphous calcification with a hazy ill-defined appearance that increases in density over time, whereas HO will develop into laminar bone.[28,30] Radiography and CT scans remain the most commonly used imaging modality for staging HO due to their cost-effectiveness and practicality. However, they are only sensitive to HO 6 weeks post-traumatic incident.[28] MRI can be used to confidently diagnose HO bone during the maturation stage only, presenting as a cancellous fat bone hyperintense of T1- and T2-weighted images with a hypointense rim of cortical bone.[31] Triple phase bone scans are the most sensitive imaging modality providing detections as early as 2.5 weeks following traumatic events through an increase in vascularity and radioactivity on potential HO sites.[32] To distinguish HO from osteomyelitis on bone scintigraphy ^{67}Ga uptake in HO is proportional to the uptake of 99mTc-diphosphonates, in contrast to the relatively greater ^{67}Ga uptake characteristic of osteomyelitis.[33] Ultrasonography (US) allows for bedside examination of soft tissues providing a convenient imaging modality for the detection of HO as a hyperechoic mass with an acoustic shadow and irregular muscular surrounding.[34] Furthermore, US grayscale values were shown to indicate a further progression of HO bone maturity.[34]

HIP

There are several events that can precipitate HO of the hip: thermal burns, hip arthroplasty, neurologic injury, and spinal cord injuries.[5] The reported occurrence of HO due to hip arthroplasty occurs in approximately 40% of patients after surgery.[5] The hip is the most common site of HO after a spinal cord injury, with the knee, elbow, and shoulder following.[5] Most of the HO does not necessitate clinical intervention, but severe HO can lead to decreased range of motion of the hip and pain.[35] The formation of HO is divided into classes using the Brooker classification system (I–IV). Class I of HO is small pieces of ossified bone floating within the soft tissue of the hip. Class II of HO is described as the bone spurs originating from the bone with at least 1 cm between bone surfaces. In the case of the hip, this will either be the pelvis or the proximal femur. Class III of HO consists of larger bone spurs that leave less than 1 cm between bony surfaces and Class IV of HO shows complete ankylosing and fusion between the bony surfaces.

There are several risk factors associated with HO of the hip: gender, prior occurrence, and osteoarthritis. Males are twice as likely as females to present with HO, however, women with osteoarthrosis show the same prevalence of HO as their male counterparts. Furthermore, any individual that has had an HO once before is far more likely to present with one later (Fig. 2).[36]

KNEE

Postoperative HO can arise from surgical trauma with the treatment of floating knee injuries.

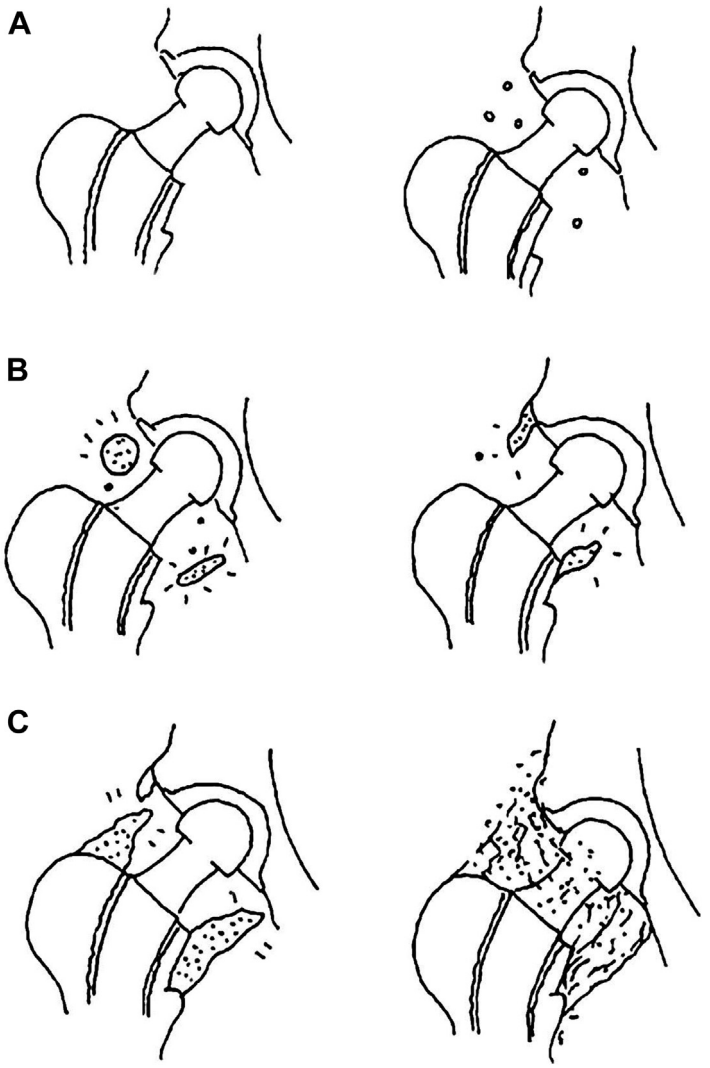

Fig. 2. (*A*) Normal (left); Class 1 of HO: islands of bone start to form within the soft tissue (right). (*B*) Advancement of Class 1 of HO consists of larger islands of bone (left); Grade 2 of HO consists of bone spur formation with a gap of greater than 1 cm between pelvis and femur (right). (*C*) Grade 3 shows the continued growth of bone spurs, now with less than 1 cm gap between pelvis and femur (left); Grade 4 shows ankylosis of the hip joint (right). *From* Della Valle AG, Ruzo PS, Pavone V, Tolo E, Mintz DN, Salvati EA. Heterotopic ossification after total hip arthroplasty: a critical analysis of the Brooker classification and proposal of a simplified rating system. J Arthroplasty. 2002;17(7):870-875.

Floating knee injuries are a flail knee joint that is due to fracturing of the shafts or metaphysis of the femur and tibia. These kinds of fractures are typically caused by a high impact or high-velocity injury and are typically treated with antegrade tibial intramedullary nailing/ipsilateral antegrade or retrograde femoral intramedullary nailing. Between these two treatment modalities, there was a significantly higher development and severity of HO in the retrograde group versus the antegrade group (90% vs 43%).[37] Despite the higher rates of HO formation and severity in the retrograde group, the study concluded that this increased severity is unlikely to affect range of motion.

SHOULDER

Clinically significant HO in the shoulder is rare but can cause severe impairment in daily activities. Fuller and colleagues[38] retrospectively reviewed HO bone excision in 11 shoulders following a TBI. Significant improvements were seen in the Range of Motion (ROM) in all three planes, the HO bone occurred most frequently in motion interfaces, ligaments, and joint capsules, and HO recurrence was reported in 3/11 shoulders. Prophylactic use of nonsteroidal anti-inflammatory drugs (NSAIDs) for primary shoulder arthroplasty did not reduce postoperative HO, it is only indicated in patients with cuff tear arthropathy.[39] In patients with early HO in the shoulder post-SCI, a single-dose radiation 7 Gy and 6–15 MV therapy was used as an alternative treatment, resulting in no HO recurrence or adverse side effects reported during the follow-up period.[40] Male sex and dislocation as the initial injury all increase the risk of HO formation, whereas surgical treatment method, patient age, and fracture pattern were unpredictive.[41]

ELBOW

Direct trauma is the most frequent cause of HO in the elbow, and the incidence is positively correlated with the magnitude of injury.[42] The prevalence of postoperative trauma-induced HO on the proximal radius and ulna is 37%, and 42% on the distal humerus.[43,44] Other causes that can contribute to the development of HO in the elbow include thermal burns and injuries that precipitate general HO development risk below the level of injury (TBI, and spinal cord injury). HO is the most common cause of elbow contracture.[45] Despite variations in different populations, the overall incidence of HO postoperatively in the elbow is 28.7% in the adult population.[46] Floating elbow injuries accounted for the largest prevalence of HO, followed by combined olecranon and radial head fractures.[47] The collateral ligaments are the most common site of HO in the elbow.[47] Elbow ankylosis secondary to HO although rare causes significant disability in flexion and extension in HO bone anterior and posterior to the humeroulnar joint, respectively. Surgical open release of complete ankylosis secondary to HO has shown a significant arc improvement from 0° to 113.4° on average and mean pronation and supination improved from 34° to 52° and 51° to 76° respectively.[48] The excision of HO bone secondary to thermal injury also resulted in a significant improvement in ROM with an average gain of 80° from 0° in flexion and extension.[49] Despite minor variation in ROM improvements in different etiologies, surgical excision of HO bone in the elbow is effective.[50] The average complication rate of HO bone resection in the elbow is 22.6% with an 11.6% HO recurrence, ulnar nerve injury, and infection[50] Patients with brain injury had the most complications (27.5%), and burn patients had the fewest (16.4%).[50] Although HO, in general, does disproportionately affect men, the sex difference is less pronounced in the elbow joint.[47] Risk factors for clinically relevant HO include dislocation and surgery delay.[47] The use of any form of prophylaxis decreased the incidence of HO bone formation in comparison to the group without any prophylaxis with an odds ratio of 0.51, $P < .001$.[46] Therefore, prophylaxis should be considered in high-risk populations.

PEDIATRICS

The incidence of trauma-induced HO in the pediatric population following a TBI is 3% - 20% without variation between sex.[51,52] Clinically significant HO in children develops in 4 months on average.[51] Traumatic events that have been attributed to HO bone formation in children include near drowning, strangulation, cerebral hemorrhage, hydrocephalus, and spinal cord injury.[51] Serum alkaline phosphatase levels do not increase beyond age-normalized values in children under less than 20 during HO maturation.[51] Prophylaxis should be considered for children in a persistent vegetative state (PVS) as approximately 12% of all children in a PVS for 30 days or more developed HO bone.[51] Neurogenic HO rates are lower in children with an incidence rate of 8% compared with 20% in the adult population respectively.[53,54] To the best of our knowledge, no studies have identified an optimal time to excise the HO bone in children. Kluger and colleagues[51] suggested waiting for a minimum of 1 year before excision. Risk factors for HO following trauma surgery in children and adolescents include being older than 11 years and comatose for over 7 days, children with two or more extremity fractures, and spasticity.[52] In children, HO bone forms in the hip and knee most frequently, followed by shoulder, elbow, and nonjoint sites.[52] Following burns HO bone commonly forms on the elbow directly affected by the burn.[55] Gaur and colleagues[55] reported their management of HO bone excision following burn trauma in children. Surgical excision of HO bone in the elbow was done when the arc of motion was less than 50%. HO bone formed in a subset of patients with burns directly on the joint affected by the burn, no HO recurrence was reported during the follow-up period. Interestingly, the authors used pain resolution reported by surgical candidates to gauge HO bone maturity as the basis of excision timing.[55] Surgical recommendations include abandoning the use of a single posterior midline incision on the elbow through burned skin in favor of a multi-incision approach. The postoperative findings support the use of alternating splints to increase the arc of motion as opposed to the series of continuous passive motion. Furthermore, the position of elbow immobilization should be considered as it may impact the location of the HO bone. They reported a 0.25% prevalence of clinically significant HO bone causing a severe restriction ROM in burned children while studies reported an incidence of 0.1% to 3.3% but did not separate statistics from the pediatric population.[55,56] Radiation prophylaxis is not deemed suitable for the pediatric population due to the risks inherent with radiation on premature bone.

PROPHYLAXIS

NSAIDs can be used for HO prophylaxis in individuals at risk if no contraindications are present. Selective COX-2 inhibitors can also be used in place of nonselective NSAIDs if gastrointestinal disturbances are reported. Selective and nonselective NSAIDs are equally effective in prophylaxis.[57,58] Indomethacin has been tested with varying outcomes. Some studies show a decrease in the incidence of HO with indomethacin prophylaxis,[59,60] whereas others show no difference in HO incidence with indomethacin prophylaxis following THA.[61,62] In a prospective randomized trial, Brooker grade III to IV ossification occurred in nine of 59 patients (15.2%) in the Indomethacin group and 12 of 62 (19.4%) in the placebo group 3 months following the stabilization of their acetabular fractures through the posterior Kocher-Langenbeck approach[63] Those studies show no statistical significance between the groups. Indomethacin is commonly prescribed at a dose of 75 mg twice a day or 25 mg three times a day for 10 days to 6 weeks postoperatively.[5]

Other medications that have been used for HO prophylaxis include bisphosphonates with the use of etidronate in particular. Although one meta-analysis pointed to the efficacy of bisphosphonates in halting the progression of HO when administered before HO bone appears radiographically,[64] another meta-analysis reported no significant difference with the use of bisphosphonates on the incidence of HO although the effect size in that study was noted to be inconclusive.[63] More prospective studies need to be done on the use of bisphosphonates for HO prophylaxis following SCI, and TBI. Etidronate can be initiated orally, as intravenous administration provided no additional protection for HO prophylaxis.[64] The literature does not support the use of bisphosphonates for the treatment of HO after it appears radiographically.

Some studies reported local radiation therapy and indomethacin provide equal effectiveness as prophylaxis in preventing HO formation following surgical treatment of acetabular fractures through a posterior or extensile approach.[65] A systematic review compared local radiation therapy with indomethacin prophylaxis performed an underpowered meta-analysis suggesting that radiation therapy is superior to indomethacin with an HO incidence of 3% to 8% in acetabular fractures respectively.[66] Radiation can be administered at a dose of 700 to 800 cGy within a 24-h preoperative to 72-h postoperative period with equal prophylactic potential.[65] However, to the extent of our knowledge, no study has looked at the use of radiation therapy for HO in other joints.

Although radiation can be beneficial for HO prophylaxis, it remains controversial due to the cost, access, and possibility of increasing solid tumor risk. The most concerning potential side effect of radiation therapy for HO prophylaxis is carcinogenesis with no attributable cases documented to date. This may be due to the latency for radiation-induced tumors typically being greater than 10 years. It is possible that the lack of documented secondary malignancies is partially attributable to the relatively small number of patients who are followed up with long enough to develop them and the relatively low radiation dose used for HO prophylaxis.

For ORIF acetabular fractures, one study concluded that a revision of the surgical approach to include the debridement of the gluteus minimus necrotic muscle did not yield benefits in HO incidence, severity, and recurrence rate,[67] whereas another study stated debriding the necrotic gluteus minimus muscle did lower HO formation while treating acetabular fractures through a Kocher–Langenbeck approach.[68]

TREATMENT

If the patient experiences a significant joint mobility impairment, vascular or peripheral nerve entrapment caused by the HO bone, then surgical excision can be considered once the lesion is completely mature.[33] Indications for completely mature HO bone include the appearance of a bony cortex on a radiographic scan, sharp demarcations from surrounding tissue, decreased activity on a three-phase bone scan, formation of trabecular bone, and the normalization of C-reactive protein (CRP) and Alkaline phosphatase (ALP). The typical HO bone is considered mature 6 months after general trauma, 1 year after spinal cord injury, and 1.5 years after TBI. [69] However, the resection timeline following a TBI for HO bone is becoming controversial as some studies find no significant difference in HO recurrence following an early excision.[70–72] Classically, it has been accepted that HO should not be surgically resected until the bone formation is mature. In a systematic review, Chalidis and colleagues[70] compared early versus late surgical resection of HO in patients with TBI and showed no difference between the two groups in recurrence rates or overall gain of range of motion postoperatively. This study did not discreetly define the

early or late time frame, but did recommend against watchful waiting for lesion maturation in the treatment of HO. A retrospective analysis reported a significant improvement in elbow functionality in patients that received HO excision early (<12 months) reflected by improvements in the Mayo Elbow Performance Score.[73]

The two surgical approaches for HO bone excision include the arthroscopic approach and the open approach.

Arthroscopy is suitable for when the HO bone is located peripherally and is easily accessible. This approach is minimally invasive with less blood loss, a lower risk of infection, and a faster recovery time. A radiofrequency ablation device and grasper are used to excise the HO bone while causing minimal damage to the surrounding tissue.[74] A burr can be used to divide the bone into smaller pieces that are more manageable with the arthroscopic approach. It is also important to note that the HO bone can be vascularized and bleed during resection. This approach can also address any concurrent intra-articular pathologies including femoroacetabular impingement syndrome or Labral Tears.[74]

Open approaches are more commonly used for the treatment of HO. Open approaches are also recommended when arthroscopy cannot adequately treat the HO or the location is unsafe to treat through a scope, such as proximity to a neurovascular structure. A preoperative computed tomography (CT) scan with three-dimensional reconstructions can be helpful for operative planning as well as identifying any surrounding structures that may be entrapped by the HO.[75] If there is a neurovascular structure encased in the heterotopic bone, often a channel can be seen running through HO on the CT. In this instance, a Kerrison Rongeur can be helpful in debriding the heterotopic bone and freeing the neurovascular structure without injury. The open approach can many times use the same incision as the index procedure, but it should be extensile enough to expose the whole HO lesion and allow for identification/protection of any neurovascular structures and normal anatomy. The HO can be excised en bloc or it can be excised in a piecemeal fashion through a smaller approach with the use of rongeurs and osteotomes. Identifying normal anatomy/bone and then working from normal to abnormal can prevent accidental injury to native tissue. After excision of the HO, a bleeding bed of healthy tissue remains and meticulous hemostasis is recommended. Intraoperative fluoroscopy can be used as well to aid in identifying HO and the completeness of resection. Scar tissue excision and manipulation may be warranted during the procedure to address any contractures. In general, secondary prophylaxis with radiation and or NSAIDs is recommended to decrease the recurrence of HO after surgical excision.

To the best of our knowledge, the only study that compared the different outcomes of arthroscopic, open, and combined approaches for the excision of ectopic bone is a retrospective review of HO excision in the elbow.[76] The use of either indomethacin or radiation therapy for HO prophylaxis was reported in 84% of individuals in the open group, 92% of individuals in the combined group, and 95% in the arthroscopic group. No significant difference in postoperative complications was noted with the three approaches. However, the arthroscopic approach had the highest rate of HO recurrence or worsening contracture.[76] The study also highlights the importance of switching to multiple incisions medial and lateral as opposed to a single posterior incision with the open approach to minimize raising skin flaps, and the creation of a small posteromedial skin incision for ulnar nerve decompression prophylaxis.[76,77] Altogether, the study reported a decrease in the rate of major complications and reoperation with the open approach from 35% and 34% respectively to approximately 10% from 1997 to 2005 through the preventative measures described.[76]

Contraindications to the arthroscopic HO bone excision include:

1. Bony ankylosis.[76]
2. Radioulnar stenosis.[76]
3. Ossification greater than 50% of the collateral ligament.[76]
4. Extensive hardware.[76]
5. HO bone located near a major nerve comprising a safe excision via arthroscopic excision on CT.[78]

SUMMARY

Many factors have been implicated in predisposing to HO, but the main factors that have consistently been validated are the need for prolonged mechanical ventilation and TBI. There needs to be more research done on the efficacy of NSAIDs and radiation therapy as prophylactic agents because there are conflicting results in the literature, but many studies do advocate for their efficacy and safety and may be used in patients who are at higher risk of HO. Surgical

excision of HO through an open, arthroscopic, or combined approach are all viable options for the treatment of HO but the timing of excision remains debated. In regard to future direction in HO research, the pathophysiology and mechanisms underlying HO are still being elucidated as are the novel therapeutic agents that could potentially target and alter these pathways through pharmacologic intervention.[7,8]

DISCLOSURE

The authors of this article have nothing to disclose.

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