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REVIEW

Treatments and Preventative Measures for Trauma-Induced Heterotopic Ossification: A Review

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INTRODUCTION

Heterotopic ossification (HO) is derived from the Greek terms "heteros" ("other"), topos ("place"), and "ossification," a Latin-derived term for "to turn to bone." HO references lamellar bone ossifying in aberrant locations, such as in joints and muscle. It has been cited through medical history, dating to 1,000 C.E. when Al-Zahrawi described a complication of fracture as a "callus often occurs after the healing of a fracture …and sometimes there is limitation of the natural function of the limb …".[1] Outside of rare genetic forms of HO, any state that causes local soft tissue damage, such as high-energy trauma injuries and surgical approaches, can cause HO.[2] Because of its correlation with trauma, HO is among the postinjury and iatrogenic complications that can cause pain and impact a patient's recovery and rehabilitation efforts.[3]

INJURIES AND SURGERIES

HO manifests following certain surgical approaches especially approaches to the pelvis and acetabulum. Following total hip arthroplasty (THA), HO frequency has been reported to be between 2% and 90%.[2] Posterior approaches for acetabular surgery, such as the Kocher-Langenbeck approach, increase the risk of HO formation in the gluteus minimus muscle. This has been demonstrated by a decreased incidence of HO when necrotic gluteus minimus tissue is debrided after acetabular fracture fixation.[4,5] The upper extremity is also affected, especially following surgical approaches about the elbow. Dual approaches to the proximal radius, commonly utilized for bicep tendon repair and reconstruction, result in proximal forearm synostosis. Traumatic injury is also associated with HO formation from isolated limb fractures and fracture dislocations of the joints due to polytrauma.[6–10]

TRAUMA STATES

The frequency of HO in civilian patients with spinal cord injury is reported to range between 20% and 30%, of which up to one-third will eventually experience limited mobility in their affected joints. Additionally, a reported 10–20% of patients with closed-head injuries will likely develop HO. Of those, 1 in 10 will experience joint mobility limitations.[7] HO has been reported in at least 50% of patients who have incurred major burn injuries, suggesting that severity and size of injury significantly contribute to the production of HO. Additionally, the ectopic bone can be found distant to the actual burn injury.[11] Recent military combat operations have heightened attention to war-related wounds, 80% of which are caused by high-energy explosive mechanisms. Combat injuries tend to result in a higher Injury Severity Score and also higher likelihood of HO development.[12,13] The formation of HO is reported in more than 63% of blast-injury patients requiring amputation.[14–17] HO occurring as a result of high-energy blast injury is most commonly reported in men between 20 and 40 years of age.[18]

Due to the complexity of blast-injury etiology, understanding the pathogenesis of HO resulting from multiple injury types, which simultaneously affect several bodily systems, is still under investigation.[12] Furthermore, although medical technology has improved the number of lives that can be saved after high-energy trauma injuries, this has also brought with it the opportunity for long-term complications, including HO, following life-saving surgery.[15] Much of the research thus far largely focuses on the lower limbs; however, there is a critical need for further research on upper-limb amputations and complications.

ABERRANT BONE GROWTH

The formation of bone during skeletal development, fracture healing, and heterotopic bone formation, requires a highly organized cascade of molecular, cellular, and tissue events. The inciting pathophysiology of HO as opposed to normal skeletal development or fracture healing is not entirely understood. Multiple biological systems related to acute phase reactants that are activated during trauma likely play some role, whether activated in an attempt to maintain survival or to begin healing injured sites. Recent research has elucidated several candidate components to the pathogenesis of HO in traumatic states.

Immune response

New findings suggest that both the innate and adaptive immune responses contribute to bone repair and remodeling following injury. The interaction between immune cells and the inflammatory response that drives normal fracture healing also contributes to ectopic bone formation. Both adaptive and innate immune cells, such as neutrophils

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and TH17 cells, are involved in the release of inflammatory cytokines, which stimulate cell differentiation, including osteoblastogenesis. Osteoblasts release inflammatory cytokines, which then stimulate osteoclastogenesis. The balance between osteoclastogenesis and osteoblastogenesis must be maintained for normal fracture healing. However, an imbalance in these processes conducted away from the site of the fracture may be implicated in ectopic bone formation.[19]

Acute phase response

The acute phase response (APR) signals the liver to modulate several genes that contribute to cytokine secretion and are involved in coagulation, inflammation, and tissue repair. The APR is critical to survival after large traumatic injury and disease states, such as sepsis. However, elevated or dysregulated levels of inflammatory cytokines may influence the proliferation of HO in trauma and surgical patients. Reports demonstrate that total knee arthroplasty (TKA) and THA patients exhibit different responses potentially due, in part, to the use of a tourniquet and involvement of another long bone in total knee arthroplasty.[20] An elevated APR may contribute to a prolonged inflammatory state that supports ectopic bone formation. This is further supported by the association of HO with systemic inflammatory insults, such as burn and neurological injury, suggesting that a combination of injuries permits an environment conducive to the release of prolonged inflammatory cytokines.[21] Prolonged inflammation and APR dysregulation may also be the cause of recurrence following HO excision. Early excision patients, within 3 months of injury, have a higher incidence of return to the operating room for complications that are not associated with re-excision as compared with those with excisions after 3 months or more from the time of injury.[22]

Trauma "stem cells"

Normal fracture healing requires an initial inflammatory phase and interactions between bone, overlying muscle, and surrounding vasculature.[23] As a result, the progenitor cells that are primarily responsible for aberrant bone growth could come from osseous, periosteal, muscle, or vasculature origin. Recent examination of progenitors cells from war-traumatized (i.e., high energy trauma) muscle tissues present with similarities to mesenchymal stem cells derived from marrow surrounding soft tissue.[6] Additionally, hematopoietic stem cells have the potential to differentiate into many tissue types, including bone.[24] Furthermore, histological features of osteogenic, adipogenic, and chondrogenic differentiation in the traumatized muscle-derived multiprogenitor cells were similar to those in bone-marrow-derived mesenchymal stem cells, and were consistent in all 10 multiprogenitor cell populations sampled.[2]

UNDERSTANDING THE HO ENVIRONMENT

Several animal models have been developed to facilitate a better understanding of the pathogenesis and outcomes of various types of trauma and the occurrence of HO.[25,26] They are used to elucidate several aspects of HO formation, including severity at specific locations, mechanism of injury, and timing of HO formation after injury and have been of great importance to furthering HO research efforts (see **Table 1**[11,26–36]). Outside of specific models aimed directly at studying war-time injuries, such as the Walter-Reed polytrauma and amputation models, few animal models focus directly on the contribution of blunt-force trauma to the formation of HO.[14,15,17,18,27] Although small animal models cannot directly mimic the formation of clinically relevant HO, each type of animal study provides the opportunity to better understand the pathophysiology and pathogenesis under unique circumstances. A comprehensive evaluation of the mechanistic pathways of bone growth, healing, and complications that may contribute to HO is beyond the scope of this review but some of the discussions are provided for further investigation.[28–37] With improved understanding, better physical and pharmacological therapeutic protocols can be developed for use in human patients.

PREVENTION AND TREATMENT

In certain surgical settings, such as immediately following an at-risk surgical approach to the pelvis, primary prevention strategies may be attempted. Currently, the prevention approaches available to clinicians include systemic nonsteroidal anti-inflammatory drugs (NSAIDs) and radiotherapy (RT) to the surgical field within a short time-period post-surgery. However, in trauma patients, the use of prevention strategies is challenging as practicality, safety, and efficacy of systemic NSAID therapy or RT is debatable and contingent upon several factors, including severity of trauma and ectopic bone formation potential.[18,38–40] Additionally, patients with polytrauma derived HO often present with concomitant injuries that may be adversely affected by the systemic NSAID or RT.[12,14,17] NSAID delivery following acute trauma can complicate bleeding, exacerbate gastritis, and potentially impede fracture healing.[41,42] Radiation can compromise soft tissue healing, including surgical incisions, and affect beneficial immunologic functions. As a result, few practical options for prevention are available under traumatic-injury circumstances.

TREATMENT: EXCISION

When HO is symptomatic, such that standard prophylactic regimens are not effective, ectopic bone excision or re-excision is often necessary, especially in high-energy trauma patients. Excision of ectopic bone is required in approximately 20–41% of combat-related amputees who have developed HO.[22] This can be done as early as 6–8 months post-injury without risk of recurrence in some cases.[12] Excision of ectopic bone is not without complications, however, and may include severe blood loss, infection, post-operative pain management, rehabilitation obstacles, and recurrence.[22] Unfortunately, the risk of infection increases after resection as ectopic bone excised from a patient with HO has been found to be highly vascularized despite its nontraditional placement and origin.[43]

Timing of excision is also controversial. As surgery intervention itself may reintroduce an inflammatory state and increase the risk for recurrence, surgical removal of HO may not be advisable until it has fully matured.[22] In a recent

Table 1 Current heterotopic ossification animal models

	Anatomic location of trauma	Animal	Purpose	Advantage(s)	Disadvantage(s)
Achilles tenotomy model[44,45]	Achilles tendon	Mice	Preventative strategies to reduce the occurrence of HO formation	Simplicity and predictability	Unclear relevance to clinical setting
Immobilization-manipulation model[46]	Quadriceps muscles	Rabbits	Investigation of the role of inflammation in HO formation	Supports role of inflammation as basis for HO formation	Unclear relevance to clinical setting
Implantation/injection model[47,48]	Rectus femoris muscle; subcutaneous	Rabbits Rats Other	Therapy and prevention strategies; HO induction	Straightforward, reliable, mechanistically relevant to humans	Artificial increase in osteogenic factors and implantation is local and does not mimic systemic effects
Direct trauma model(s)[26,49,50]	Hind and forelimbs	Rabbits Dogs	Attempting to induce HO formation	Ability to produce HO as a result of mechanism of injury	Not sufficiently reliable
Irritant injection model[51]	Muscle tissue	Rabbits	Attempting to induce HO formation	Some success with alcohol injection	Insufficient repeatability and unclear relevance to clinical setting
Burn model[11]	Partial-thickness dorsum dermal burn	Mice	Demonstrate pro-osteogenic contribution of burn to HO development	Reproducible in singular mouse strain, corroborates the contribution of inflammation due to burn in HO production	Amount of HO variation among species, supra-physiological levels of osteogenic factors
Hip arthroplasty[52]	Hip	Rats	Replicate response due to arthroplasty	Reportedly reproducible	Small sample size, unclear reproducibility
Blast model(s)[26,53]	Hind limbs	Rats	Replicate wartime injuries	Reproducible	Relevant to specific population

HO, heterotopic ossification

retrospective study examining the symptomatic or radiographic recurrence rate of both partially and fully excised HO before or after 180 days post-injury, a higher risk of recurrence was reported if HO was removed prior to 180 days. Likewise, partial excision was correlated with a higher likelihood of radiographic recurrence and higher potential for re-excision as compared with full excision patients.[22] Additionally, several studies have also documented the rate of recurrence after HO excision at the joints following traumatic brain injury (TBI) but the results have been inconsistent in magnitude and timing.[54–62] The unpredictability of recurrence in a surgical setting is exponentially confounded in polytrauma patients, thus necessitating further research in recurrence prevention strategies.

Prevention: NSAIDs

Because patients with HO tend to present with severe systemic and local inflammation, NSAIDs have long been used as part of HO prophylaxis protocol.[63] In some cases, NSAIDs are feasible to administer within the optimal 24–48-hour time frame to aid in HO prophylaxis. However, priority in theater is placed on life-saving practices.[15] Several NSAIDs are commonly used, including ketorolac, ibuprofen, celecoxib, and indomethacin; however, these are not without complications, including hemorrhage, gastritis, and patient noncompliance.[22,27] Although the use of systemic NSAIDs has been shown to reduce inflammation and the risk for HO manifestation and proliferation, they have garnered notoriety for their propensity to impede fracture healing, especially with the use of indomethacin.[64–67] Because indomethacin is a COX2 nonselective inhibitor, it works by inhibiting prostaglandin-mediated bone remodeling and also by directly inhibiting the differentiation of osteoprogenitor cells.[63,66] Local administration of NSAIDs for the prevention of HO is currently under investigation. Small studies suggest that locally administered NSAIDs may not hinder wound healing.[64] This finding has now generated further interest in continuing research with the goal of becoming a clinically

translatable treatment for current patients as it may be better tolerated.

PREVENTION: RADIATION

Localized RT in 7-Gy doses administered within 4 days of operation has succeeded in diminishing the effects of HO proliferation as long as no other factors obstructed drug administration. It does so by interfering with and suppressing mesenchymal-cell progression to osteogenic cells.[15,22,68] Preoperatively, RT delivery has shown varied reports of effectiveness.[2] Some animal studies suggest that the inhibiting effect on bone healing after the use RT is more pronounced if it is administered closer to the time of the actual injury.[63] However, high and frequent doses have the potential to cause cell death and be carcinogenic.[63,69] As there may not be enough data to support RT's long-term effects, especially on young individuals, it may be worth reconsidering it as an option when deciding to use it on patients.[63] To date, there is no standard time frame, whether pre-operatively or postoperatively, that is universally accepted by all surgeons opting to initiate RT.[18,63]

COMPLICATIONS AND COSTS

From a patient's perspective, frustration undoubtedly correlates with wait-time to excision of mature bone.[18] The financial and social cost of treating complications due to trauma-induced HO can be substantial. For example, when comparing two of the most common treatments, RT or the use of NSAIDs on patients with HO after THA, the cost of NSAIDs is considerably more cost-effective at face value. Postoperatively, the management of HO can be financially costly as well. As NSAIDs are delivered systemically, other complications to be considered include treatment failure or complications due to the drug side-effects. In this regard, the cost of NSAID usage approaches that of RT.[70]

When comparing high-risk patients with HO of THA receiving RT and low-risk patients with HO of THA receiving multiple oral doses of indomethacin (NSAID), the efficacy of each after a 2-year follow-up was effectively the same when defined by failure rates. However, the cost of indomethacin-treated patients was $>$10 times less than those treated with RT. In this case, it is seems that the risk-level of the patient is a factor to consider when deciding the best plan of action for postoperative treatment.[71] Additionally, one study suggests that some critical patients with specific injuries may be more likely to produce HO after long-term care from extended limited mobility after a head injury.[72] The long-term costs of this complication may have considerable implications for the patients both financially and socially.

FUTURE CONSIDERATIONS

Recent reports of acute treatment provide encouraging potential for prevention of primary HO. Successful decreased inflammation, osteogenic and chondrogenic gene expression, and connective tissue progenitor cell proliferation with an oral-gavage delivered retinoic acid receptor-γ, palovarotene, in an established HO blast-injury model has demonstrated promise in future studies.[73] Additionally, orally delivered palovarotene demonstrated at least 50% decrease in polytrauma, infection-induced HO.[74] Intraperitoneal delivery of rapamycin on an established blast-injury model has been reported to successfully inhibit HO formation with no reported wound-healing complications.[75] Finally, local delivery of vancomycin powder in a trauma-induced HO rat model reports suppressed HO formation by 86% when delivered at the time of injury.[76]

Current treatment and prophylactic practices are not always appropriate or effective for polytrauma patients due to their complicated and unplanned nature. Novel combinations of treatment, vehicle, and delivery time in established animal models suggest high success rates and potentially fewer complications when delivered early. These results provide promise for clinical implementation in other trauma-induced patients with HO in the future. Further investigation into timing and modes of prevention and treatment is warranted and should include trauma-relevant animal models. To address recurrence rates, following excision of established HO, timing seems to be a confounding factor as studies suggest that later excision is preferable to earlier excision. Local delivery of novel treatment options, such as NSAIDs, following excision may help decrease recurrence rates and wound healing complications. Additionally, reduced or eliminated delivery of RT may be a viable consideration for patients with HO.

CONCLUSION

The multifaceted complexity of the mechanisms that drive HO in trauma patients is poorly understood. As such, there is no universal treatment without some level of adverse effects to the patient. To mitigate the proliferation and recurrence of this pathological, aberrant bone growth, studies in prevention strategies for trauma patients warrant further investigation into the pathways involved in its development.

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