Characterization of Heterotopic Ossification in Burn Patients

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Heterotopic ossification (HO) is a clinical condition of ectopic bone formation in soft tissue. This clinical entity has been associated with genetic disorders, traumatic injuries, and musculoskeletal surgeries. In this regard, functional impairments secondary to scar contractures seen in burn injuries may be exacerbated with underlying HO. The appropriate prevention or management of this complication is crucial to optimize outcome in burn patients. This clinical study reviews the incidence of HO in our burned patients, diagnostic methods, therapeutic approaches including surgical timing and techniques.(J Burn Care Res 2014;35:251–256)

Heterotopic ossification (HO) is a clinical condition where mature lamellar bone is formed in damaged tissues such as muscle, tendon, and fascia.[1] This clinical entity has been associated with genetic disorders (ie, fibrodysplasia ossificans progressive), traumatic injuries (ie, spinal cord injury, brain injury, amputations, burns), and musculoskeletal surgeries (ie, elbow/acetabular fractures, hip arthroplasty).[2,3] HO may cause skin breakdown, significant soft tissue deformity or firmness, and chronic pain that reduce the rehabilitation outcome. For instance, HO can severely limit pressure garment compliance and prosthesis tolerance. Thus, this complication may affect not only the local function such as range of motion (ROM), but also activities of daily living and quality of life of trauma patients and their families.

Several reports have highlighted that the HO incidence in some patient subgroups is considerably higher than previously recognized. Thus, approximately 64% of major combat-related extremity wounds develop HO, and at least 19% of these cases require surgery for clinically relevant symptoms.[4–6] In burn patients, the incidence of HO varies between 0.2 and 4%,[1,7] and is more frequent in patients with burns >20% TBSA.

This clinical study reviews the incidence of HO in our burn patients, the risk factors, clinical features, diagnostic methods, and therapeutic approaches including surgical timing and techniques as well as long-term outcomes.

MATERIALS AND METHODS

We conducted a retrospective study of burn patients admitted to the Firefighters' Burn Treatment Unit at the University of Alberta Hospital during a 30-year period, using the burn registry to identify patients. Approval to perform this study was obtained from the Health Research Ethics Board of the University of Alberta. We collected demographic data such as age, sex, date of injury, TBSA, total full-thickness burns, and length of stay. In addition, comorbidities, postadmission complications, HO location and their radiographic imaging studies, total number of related burn surgeries, and HO treatment modalities were also reviewed. The ROM of joints undergoing surgery were evaluated before and 3 months after surgery. To process data, Microsoft Excel® 2008 (Redmond, WA) and GraphPad InStat 3 (GraphPad Software Inc, La Jolla, CA) for windows were used. Data are presented as mean ± SEM. Statistical analysis was performed by two-tailed paired *t*-test. A P value ≤.05 was considered statistically significant.

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RESULTS

During the study period (1982–2012), 17 burned patients (14 Caucasians, three native North American Indians) were identified to have clinically symptomatic HO. Within this group, 14 patients were men (82.4%) and three patients were women (17.6%). Their mean age was 33.6 ± 3.4 years (range between 10 and 59). Causes of burn were flame burn (88.2%) and high-voltage electrical burn (11.8%). These patients suffered extensive burns (60.1% ± 4.1% TBSA; range between 20 and 90) with a large component of full-thickness skin injuries (46.9% ± 6% total full-thickness; range between 10 and 85; Table 1). They presented frequent postadmission complications including ventilator-dependent respiratory failure (88.2%), graft loss (76.5%), sepsis (64.7%), and wound infection (47.1%) (Table 2). They also required multiple surgical procedures (7.9 ± 3.5 total surgeries) and prolonged hospitalization with a mean length of stay of 128.8 ± 14.5 days (range between 63 and 312).

HO was clinically suspected in burn patients with increasing limitation in the ROM of affected joint associated with locking sensation, swelling, and local pain. No clinical evidence of ulnar nerve compression was found in this group. Plain radiographs confirmed the diagnosis of HO in all cases by the presence of different degrees of calcification from localized increase of soft tissue density to extensive calcified lesions (Figure 1). Other imaging studies were also used, including bone scan (47%), CT scan (12%), and magnetic resonance imaging (12%). Serum levels of calcium, phosphate, and alkaline phosphatase did not increase from the normal range in these patients.

A total of 43 HO lesions were identified in the study group (Table 3). Elbows were the most frequently affected site (62.8%), with 14 of them on the right side (32.6%) and 13 on the left side (30.2%). Eleven patients from our study group (64.7%) developed HO in bilateral elbows. Other HO locations included shoulder (9.3%), forearm (6.9%), and knee (6.9%), among others. Interestingly, some of the HO sites were located distant from the burned area (Table 3).

Table 1. Demographic characteristics of burn patients who develop clinically significant HO

	Mean	SEM
Age, yr	33.6	3.4
TBSA, %	60.1	4.1
TFT, %	46.9	6.0
Total surgery, n	7.9	3.5
LOS, d	128.8	14.5

HO, heterotopic ossification; *LOS*, length of stay; *TFT*, total full-thickness burns.

Values are expressed as mean ± SEM.

Table 2. Common comorbidities and postadmission complications developed by burn patients with heterotopic ossification

	%
Sepsis	64.7
Wound infection	47.1
Graft loss	76.5
Respiratory failure	88.2
Pneumonia	41.2
Pulmonary edema	23.5
Hyperglycemia	23.5
Anemia	17.7
ACS	17.7
DVT	11.8
Pulmonary embolism	5.9

ACS, abdominal compartment syndrome; *DVT*, deep venous thrombosis.

Four patients (23.5%) received etidronate treatment (400–800 mg p.o. daily for 3 months). Three of these patients required surgical excision of HO lesions. A total of 10 HO lesions required surgical excisions (23.3%), which were performed between 1.5 and 16 months after burn injury (Table 4). All surgeries were performed for significant elbow limitations (6 right elbows; 4 left elbows). Surgical procedures included the application of sterile pneumatic tourniquet, posteromedial longitudinal incision, removal of HO lesions with rongeurs and osteotomes, release of adjacent joint and anterior transposition of ulnar nerve in the subcutaneous tissue (Figure 2). No capsulectomies were necessary to reach appropriate ROM. Jackson-Pratt drains were inserted and then wounds were appropriately sutured. Regular dressings and protective splints were applied at the end of these procedures. No postoperative complications (ie, hematoma, skin necrosis, wound dehiscence, wound infection, and neurovascular injury) were documented.

An early ROM program was initiated on the first postoperative day. Physiotherapy was tailored to each patient's tolerance within the pain-free range and included gentle passive, active-assisted, and active ROM exercises. One patient was excluded from the ROM assessment because of lack of postoperative physiotherapy and follow-up. The remaining patients had postoperative follow-up for at least 2 years (mean, 80.1 ± 16.7 months). Their average preoperative ROM was 45.6° ± 10.5°, which reached 110° ± 8.7° 3 months after surgery (Table 4). Therefore, the

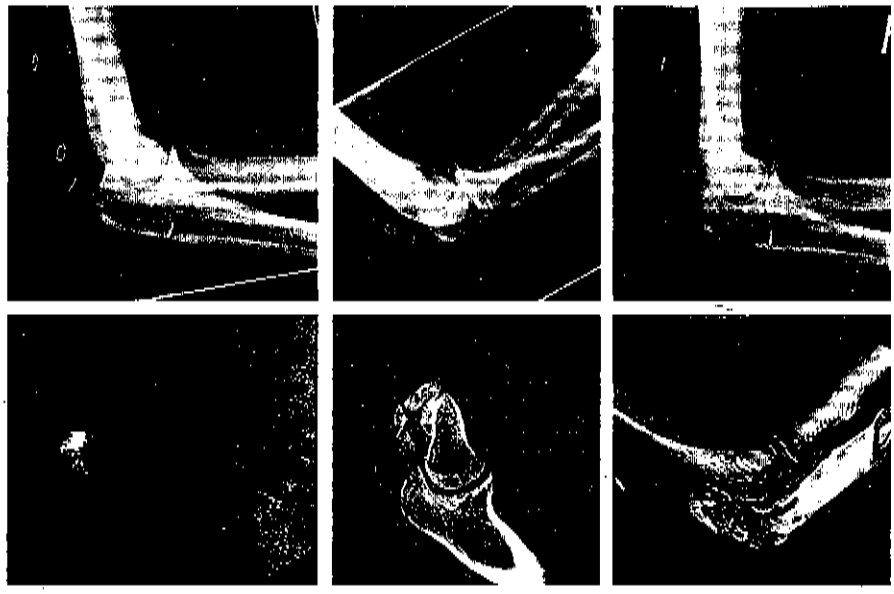

Figure 1. Imaging studies in a burn patient with heterotopic ossification (HO) of the right elbow. Upper left image shows no bony or other joint abnormalities seen 40 days after burn injury. Upper middle image shows the presence of HO lesion on the posterior aspect of the distal humerus and olecranon (51 days after burn injury). Upper right image reveals a significant increase in the HO lesion (5 months after burn injury). Left lower image shows a three-phase bone scan centered on the right elbow showing intense uptake. Middle and right lower images show regular CT scan and 3-D CT reconstruction from the same HO lesion.

surgical intervention added on average of 64.9° ± 6.8°. These results were statistically significant with a P value <.0001. Despite this substantial benefit in ROM, three HO lesions from two patients experienced a clinically significant local recurrence (30%). A second surgical procedure (7.33 ± 2.96 months after primary surgery) successfully removed HO lesions and re-established appropriate ROM in these cases.

DISCUSSION

HO in burn patients is associated with prolonged loss of consciousness (ie, mechanical ventilation), long-term immobilization, burn wound infection or delayed wound closure, loss of skin graft, and recurring local trauma (ie, forceful joint manipulation).[8–10] Even though they may occur in joints unrelated to burn injuries, HO lesions usually develop in those that are underneath full-thickness burns, especially in the elbow.[8,9] As shown in Tables 1, 2, and 3, our patients exhibit similar characteristics to those from previous reports.[1,8,9] Accordingly, HO lesions were located posterior to the medial epicondyle extending into the medial olecranon fossa (Figure 1).

Table 3. Locations of HO in burn patients

Location of HO	N	%
Elbow	27	62.8
Shoulder	4	9.3
Forearm (interosseous membrane)	3	6.9
Knee	3	6.9
Others (hip, axillae, psoas muscle, paralumbar region)	6	13.9
Total	43	100.0

HO, heterotopic ossification.

Along with clinical assessment, the plain radiographs establish the diagnosis of HO. This imaging study defines not only the location, but also the extension and maturity of the HO lesion as well as the associated morbidities of the adjacent joint (ie, malunion, osteophytes, among others).[11] In extensive burns, HO lesions have been detected as early as 20 to 90 days after injury.[12] Although no other imaging studies are routinely required, CT scan and MRI help to define the local architecture and the relationship of the HO lesion to surrounding structures (ie, ulnar nerve) to plan surgical intervention.[11] Three-phase bone scanning is the most sensitive imaging method for early detection of both primary HO lesions and postoperative HO recurrences. Typically, bone scans show evidence of soft tissue uptake several weeks before an HO lesion is detectable in standard radiographs.[13] Serial bone scans are also useful in monitoring the local metabolic activity and maturity of the HO lesion to determine the appropriate timing for the surgical excision.[13]

Table 4. Long-term results of surgical excision of HO lesions in burn patients

Patient	Sex	Delay Surgery, mo	ROM (Degrees)			Follow-Up, mo
			Preop	Postop	Added	
DS-R	M	16	10	100	90	60
OW-R	F	1.5	25	75	50	157
TH-R	F	2	70	146	76	132
TH-L	F	2	105	146	41	132
GW-R	M	4	70	108	38	40
GW-L	M	4	50	125	75	40
PW-L	M	11	18	18	0	*
JV-R	M	5	11	80	69	31
JV-L	M	5	29	122	93	31
DS-R	M	3	40	92	52	98

HO, heterotopic ossification; *R*, right; *L*, left; *M*, male; *F*, female; *ROM*, range of motion from maximal flexion to maximal extension (expressed in degrees). Postoperative ROM was measured 3 months after surgery. Delay of surgery and follow-up are expressed in months.

* Patient excluded from final analysis because of lack of postoperative physiotherapy and follow-up.

Therapeutic strategies for the prevention of HO are still limited and show variable levels of success. For instance, indomethacin has shown inconsistent results when used in HO prophylaxis. Even though indomethacin may prevent osteogenic differentiation of bone marrow mesenchymal stem cells,[14,15] some authors have reported no benefits and have even found increased risk of complications.[16–19] Several other nonsteroidal anti-inflammatory drugs such as naproxen, ibuprofen, and diclofenac have also been used.[20] They prevent ectopic bone formation by inhibiting prostaglandin synthesis and

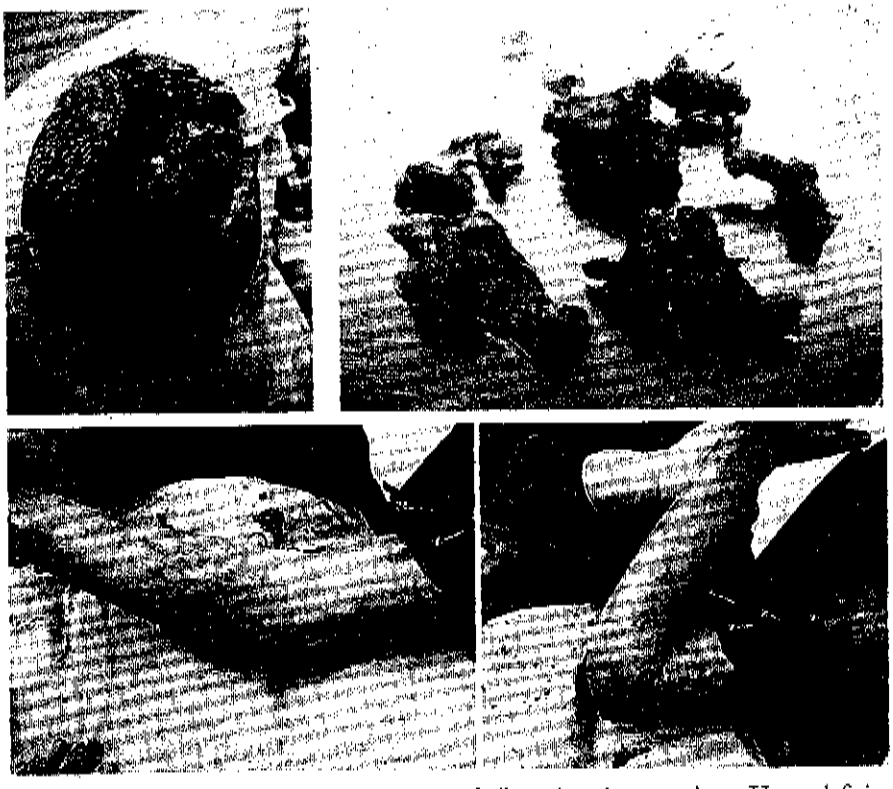

Figure 2. Surgical removal of heterotopic ossification (HO) of elbow in a burn patient. Upper left image shows surgical approach of HO at the right elbow (same patient from Figure 1). After a posteromedial longitudinal incision, removal of the HO lesion, release of the adjacent joint and anterior transposition of the ulnar nerve in the subcutaneous tissue was performed. Upper right image shows the HO specimen. This patient had 11° of preoperative flexion-extension range of motion, which reached 69° during the surgery (lower images).

cyclooxygenase.[21] However, they have potential gastrointestinal side effects and interactions with anticoagulant medications.[22] Biphosphonates are another therapeutic option to prevent the development of HO by blocking the aggregation, growth, and mineralization of calcium hydroxyapatite crystals.[23] Unfortunately, they exert a nonselective suppression of bone matrix mineralization, which can also affect the normal bone. In addition, the mineralization process resumes immediately after the treatment is discontinued.[24] Radiation therapy has been described as one of the most effective prophylactic approaches in preventing HO formation. However, many clinicians have expressed concerns about the long-term side effects of local radiation, especially the development of secondary malignancies.[2] Although no reports of radiation-induced tumors after HO prophylaxis can be found in literature, the concern still persists because the latency period to develop malignancies after radiation therapy is about 15 to 24 years, and most of the HO cases treated with this therapeutic modality correspond to elderly patients who underwent hip surgery.[2] In addition, a meta-analysis of randomized trials showed that prophylactic irradiation is slightly more effective than nonsteroidal anti-inflammatory drugs in preventing clinically significant HO.[25] Furthermore, prophylaxis of HO with radiation therapy acutely after elbow trauma has shown unacceptable high numbers of nonunion.[26] Younger patients with ectopic bone formation, as seen in wartime amputations or burns, have more extensive and severe insults with systemic inflammatory responses where the prophylactic low-dose radiation therapy may not be as effective as in HO secondary to elective hip surgery. In this regard, this subgroup of trauma patients who usually require aggressive initial fluid resuscitation may not be stable when prevention of HO with radiation therapy has demonstrated to be effective in total hip arthroplasty (therapeutic window from 8 hours before to 72 hours after surgery).[27]

As shown in this report and others, HO may develop early manifestations in burn patients, especially in those with extensive full-thickness injuries (Table 4). Therefore, a high level of clinical awareness is crucial to prevent this complication. In this regard, elbows are the predominant joints affected by HO in burn patients.[1,7,8] Other locations are also described (Table 3), but they do not often cause significant functional impairment. Abnormal local conditions such as chronic nonhealing ulcers or wound infection may increase the risk of either unilateral or bilateral elbow compromise. The prompt treatment of these local complications as well as the establishment of an ROM program within the patients' tolerance may produce a profound impact in preventing HO. To detect early HO lesions, we routinely order periodic x-ray of suspected joints (usually elbows) at bedside. In stable patients, we also request three-phase bone scan. We do not use on a regular basis anti-inflammatory medications and biphosphonates because of the lack of specificity and high frequency of side effects and drug interactions.[22,24] In our experience, surgery has been a valid method to treat both primary and recurrent HO in burn patients (Figure 2). Several authors have demonstrated that early excision of HO provides acceptable results.[7,9] As shown in Table 4, we removed HO lesions in early stages in all our more recent cases. This approach not only re-establishes adequate ROM, but also prevents the appearance of associated complications (ie, muscle shortening, capsule contracture, and nerve entrapment) and minimizes the risk of postoperative complications. The use of sterile tourniquet and magnification loupes is recommended to identify adjacent cutaneous nerves and prevent permanent sensory loss or secondary neuromas.[28] In our patients, the early surgical removal of HO lesions (mean, 5.35 ± 1.46 months), in association with postoperative physiotherapy, has established a statistically significant improvement of ROM (110° ± 8.7°) in affected joints necessary to perform activities of daily living.[29,30] In our practice, radiation therapy has not been used because a second surgery alone was enough to establish appropriate ROM in those patients who developed postoperative HO recurrence. However, further multicenter trials with larger number of cases are required to determine the role of prophylactic radiation therapy in burn population.

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