**Risk factors in hospitalised patients with burns injuries for developing
heterotopic ossification - a retrospective analysis**

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Abstract

Aims: Heterotopic ossification (HO) is the formation of bone in locations where it should not occur. Little data is available on the risk factors for HO, a complication in burns patients. The aims of this study are to identify the risk factors for developing HO in patients with burns injuries and secondly to describe appropriateness of local prescribing and the frequency of adverse drug effects associated with disodium etidronate.

Methods: Patients with HO at our tertiary referral burns unit were identified using the unit computer database. The control group were patients that were the next admission post admission of patient that subsequently developed HO. Demographic and clinical data as well as data on disodium etidronate therapy were collected. Univariate and multivariate techniques were used to identify risk factors for HO.

Results: We reviewed 337 patients admitted over a 5-year period and identified 19 patients with HO (5.6%). A further 19 burn injury patients were included as controls. HO developed clinically and radiologically after a median time of 37 days (interquartile range [IQR], 30-40) and 49 days (IQR, 38-118) respectively. In univariate analysis HO development was associated with a greater %TBSA, inhalation injury, need for and length of mechanical ventilation, number of surgical procedures, sepsis, and longer time to active movement. In a multivariate analysis that adjusted for severity of burn injury by means of the Belgian Outcome in Burn Injury (BOBI) score, time to active movement was recognized as an independent risk factor for HO (odds ratio 1.48, 95% confidence interval 1.09-2.01). Disodium etidronate was prescribed to 18 of 19 patients at a median initiation dose of 18mg/kg (IQR, 16-21). Elevations in serum calcium concentrations were the only observed adverse effect.

Conclusion: This study has demonstrated that delays in physical rehabilitation are predictive of the development of HO. Logically, a longer period of immobilization is linked with an overall higher severity of burn injury as evidenced by %TBSA, inhalation injury and need for ventilatory support and multiple surgical procedures.

Key words: Heterotopic ossification; burn injury; disodium etidronate; adverse drug reaction; intensive care unit

Introduction

Burns are a serious trauma that not only have a profound effect on patient's health and outcomes but also require enormous health care system resources for patient management and rehabilitation with a single admission costing over AUD\$100,000 for each patient with severe burns¹.

Mortality among patients hospitalized following burn injury ranges 1.4% to 18% and varies according to the presence of major risk factors for death such as older age, flame burns, a greater percentage total burned surface area (% TBSA), and inhalation injury^{2,3}. The mortality rate, however, appears to be decreasing with an Australian study at a tertiary referral burns unit reporting a mortality decrease from 5.3% between 1972 and 1980 to 3.4% between 1993 and 1996⁴. This improvement was attributed to advances in burn care such as improved resuscitation, nutritional support, early surgery, and novel skin replacement techniques⁴. Improved burns management is further reflected by the increased survival rates of those sustaining severe burns with greater % TBSA affected⁵. Similar favourable trends have been observed in European burn centres as well^{6,7}. This increased survival rate of those patients with more severe burns may lead to an increased incidence of morbidity related to the burn rehabilitation process including heterotopic ossification (HO) which has been documented to prolong hospital length of stay and healthcare costs⁸.

HO is the formation of lamellar bone in connective tissue in which it normally should not exist⁹. The distinction here being that it is the formation of lamellar bone as opposed to simply calcification of the tissue, such as that which occurs in metastatic calcification, as with hypercalcaemia. The primary causes of HO most frequently encountered clinically are the central nervous system insults such as traumatic brain injury (TBI) and spinal cord injury (SCI), and traumatic, violent, or surgical insults¹⁰. HO has also occurred as a consequence of a number of other conditions including tetanus¹¹, acute respiratory distress syndrome (ARDS) in conjunction with neuromuscular blockade¹², and of interest for this study, the burns patient.

The reported incidence of HO in non-burn injury populations have varied from 35% to 75%^{13,14}. In burns patients, the reported incidence varies particularly with the study design and the method of diagnosis. Retrospective studies report rather low incidence rates at 0.1% to 3.3%, while incidence rates in prospective studies range 13.6% to 23.0%¹⁵. The development of HO first involves the formation of osteoid, which then calcifies within 4-8 weeks¹⁶.

A number of factors have been identified to be associated with an increased risk of HO in patient groups of non-burn related origin^{8,17-24}. These have been summarised in table 1.

Surgical resection of manifest ossification and or radiation therapy has been successfully used to treat HO in burn patients^{25,26}. This approach however, is resource and time-consuming and includes the risk of complications²⁷. Alternatively pharmacotherapy is commonly used for both prevention and treatment of HO, although there is no consensus on which drug should be used and when treatment should begin²⁸. Whilst non-steroidal anti-inflammatory drugs like indomethacin have been used, bisphosphonates like disodium etidronate remain common therapies in burns patients with HO.

The aims of this study were to identify the risk factors for developing HO in patients with burns injuries and to describe appropriateness of local prescribing of disodium etidronate for HO as well as the frequency of adverse drug effects associated with this treatment.

Methods

Setting

This retrospective study was undertaken at the Stuart Pegg Burns Unit at the Royal Brisbane and Women's Hospital (RBWH) which is the tertiary referral centre for all major burns for Queensland as well as northern New South Wales in Australia, Papua New Guinea and parts of Indonesia. This study was approved by the local Institutional

Review Board (IRB) as Low and Negligible Risk Research as outlined by the National Statement on Ethical Conduct in Human Research (2007).

Study Design, Data Sources, and Participants

Data from the charts of patients admitted to the RBWH Burns Unit over a 5-year period from September 2002 to September 2007 were retrospectively reviewed using a structured data collection tool.

The Stuart Pegg Burns Unit has a hospital-specific burns database with records for all patients admitted with burn injuries which includes basic demographic, clinical and burn severity data including the presence of HO. The charts of the patients studied were obtained from the Medical Records Department at our hospital. Physiotherapist and occupational therapists see all patients in the Burns Unit. Passive mobilisation is considered part of standard rehabilitation with commencement occurring depending on the whether grafted limbs have taken successfully or at the direction of the Surgeon.

Patients identified as suffering from HO were considered the test group of the study. The control group of patients was selected based on time of admission to the burns unit only and were a priori selected as the next admitted burns patient that did not experience HO, following admission of a patient that has developed HO.

Process

Charts of the patients recorded as having HO and controls were reviewed in detail. The following information extracted for each patient were demographics (e.g. age, gender), burn injury details (e.g. type of burn, % TBSA, presence of inhalation injury), treatment outcome (e.g. hospital length of stay (LOS), intensive care unit (ICU) LOS, duration of ventilation, number of surgeries and number of days that serum calcium, phosphate and magnesium concentrations were outside the normal range) and factors relating to HO (e.g. immobility, time to development of HO and changes in range of motion of affect joints). Data related to prescription of disodium etidronate were also collected including dosing, duration of treatment, use of other therapies (e.g. anti-inflammatories) and documentation of any adverse effects caused by disodium etidronate.

Analysis of Data

Data was statistically analysed using SPSS version 15.0 (Chicago, Illinois, USA). The results are described as n (%) or as median [interquartile range (IQR)]. The Mann-Whitney *U*-test was used for comparisons of continuous variables. Categorical data were analysed by Fisher's exact test or Chi-Square where appropriate. Multivariate analysis was also undertaken. A cross-tabs procedure was used initially to estimate maximum likelihood. Factors from the univariate analysis that were associated with a *P*-value <0.05 were entered into a binary logistic regression to detect which factors were independent predictors of the development of HO. Because many variables regarding severity of burn injury are related to each other, the Belgian Outcome in Burn Injury (BOBI) score was used to summarize severity of injury and entered in the regression model. The BOBI model is a validated scale quantifying injury severity and related expected mortality on basis of age, %TBSA, and inhalation injury requiring mechanical ventilation. The logistic regression model is reported with use of odds ratios (OR) and 95% confidence intervals (CI). *P*-values <0.05 were considered significant for all analyses.

Results

Over a 5-year period from September 2002 to September 2007, 337 patients were admitted to the Royal Brisbane and Women's Hospital, Stuart Pegg Burns Unit. Of those, 22 were recorded in the departmental database to have had HO. Further review of these patients revealed that only 19 were eligible for inclusion in this study (Figure 1).

Table 2 describes the comparative demographic and clinical features of the control and HO groups. Notably, there were statistically significant differences between the groups in terms of the requirement for ICU admission and length of admission ($p<0.001$), the requirement for and length of ventilation ($p<0.001$). Further, in the 19 patients who developed HO, the site of ossification was in or around a joint that had sustained a burn and been surgically grafted ($P<0.001$).

Only 16 of the 19 HO group had radiologically proven HO. Three did not have any radiological evidence reported but were all clinically diagnosed with HO on basis of reduced mobility, local swelling and erythema, and palpable mass. The median time to clinical development of HO was 37 days (30-40) and the median time to radiological development was 49 days (38-118). The most common limb affected with HO was the elbow with 89% (n=17) patients affected, 26% (n=5) of these having bilateral HO. HO in knees and shoulders was less common. The mean decrease in range of motion of HO affected joints was 37% (25-67). In not a single patient the HO was surgically removed.

Independent predictors of HO

Univariate analyses demonstrated that many variables referring to injury severity were associated with the development of HO. All these factors contribute to an overall clinical picture of a patient immobilized for a substantial time period. Therefore we choose to summarize severity of injury by the BOBI score, to adjust for this score in the logistic regression model. Subsequently time-dependent co-variables referring to aspects of mechanical ventilation, immobilization, and delayed physiotherapy were evaluated for their relationship with HO. After adjustment for injury severity as summarized by the BOBI score (OR 0.86; 95% CI, 0.36-2.08) the only variable significantly associated with the risk of HO was time to active movement (OR 1.41; 95% CI, 1.03-1.94).

Factors Relating to Treatment with Disodium Etidronate

Of the 19 patients with HO, 95% (n=18) were treated with disodium etidronate (the remaining patient was prescribed indomethacin). One patient was prescribed both disodium etidronate and indomethacin. Disodium etidronate was commenced 43 days (40-59) after the burn injury. This timing corresponds with 4 days (1-25) days after clinical suspicion. As such, in 7 patients etidronate was initiated before radiological diagnosis or in the first 4 days following radiological confirmation. The median dosage initiated was 18mg/kg/day (16-21) with only 44% (n=8) of patients having initial doses later decreased to 10mg/kg/day after a median of 7 days (3-17). Data was insufficient in the medical records to record duration of use of disodium etidronate because it was frequently continued post-discharge from hospital.

Only two patients had disodium etidronate therapy ceased as a result of potential or confirmed drug adverse effects. One of these patients had renal failure requiring dialysis and therapy was pre-emptively ceased to prevent renal tubular damage. The second patient was ceased due to an escalation in serum calcium concentration after initiating disodium etidronate (2.87 mmol/L to 3.14 mmol/L after commencement). Once disodium etidronate was ceased the calcium level decremented. This increase in serum calcium concentration was the only adverse drug reaction documented for disodium etidronate.

Discussion

The precise mechanism of HO in burns patients is unclear and is thought to be multifactorial. The proximity of the involved joint to the burn is not consistently a significant factor, rather it is the unique metabolic environment created by the burn injury²³. The commonest site of HO formation is the elbow, and ulnar nerve entrapment can occasionally occur²⁹.

In regards to prevention in the burns patient, early burn debridement and grafting minimizes the period of metabolic upset and seems to reduce the incidence of HO⁸. A recent study concluded that the time to elbow wound closure significantly impacts the risk of development of HO, and that increased attention is warranted to optimize time to wound closure over joints³⁰.

The comparison of the HO and the non-HO group demonstrated statistically significant differences between most factors tested. Length of hospital admission, ICU admission and length of stay, the requirement of ventilation, length of ventilation, escharotomy requirement, surgery requirement and number of surgeries, grafting to limb/s, sepsis, time from admission to active movement, time from admission to assisted walking, and number of days of derangement of serum calcium, phosphate and magnesium levels were all significant different between the two groups when compared by univariate analysis. After adjustment for severity of burn injury binomial logistic regression, identified delayed time to active movement as independently associated with the risk of HO development. Other factors likely to be of significance

include the position of limbs during immobility and length in that position, period of immobility post grafting, continuous pressure to areas during immobilization, and physical manipulation, as well as metabolic related factors including, nutritional support, biochemical markers such C-reactive protein, and alkaline phosphatase, and conditions of antigen-antibody disorders¹⁷⁻²⁴. These factors have all been suggested in previous studies as potential predictive factors for the development of HO but were unable to be investigated in this study.

Data collection relating to the appropriateness of prescribing and the frequency of adverse drug effects associated with disodium etidronate was affected by the retrospective nature of the study. This was most evident with the duration of administration of disodium etidronate. Once patients were discharged from the hospital there was no more information regarding prescribing of the drug available. The doses of disodium etidronate were initiated at appropriate doses with a mean of 19mg/kg/day. Doses of 20mg/kg/day have been suggested to be used and continued for 6 months¹⁰ and the majority of patients did not have any dosage adjustments. Eight patients, however did have dosage adjustments after a mean duration of 19 days with doses reduced to a mean of 10mg/kg/day. It has been shown that lower dose of 10mg/kg/day did not prevent radiographically evident progression of HO³¹. Lower doses of disodium etidronate are adequate to inhibit crystal resorption, but are less effective at inhibiting crystal growth¹⁰ hence the reason why lower doses are used in the treatment of osteoporosis. This may also explain the adverse effect of an increase in serum calcium level in one patient when disodium etidronate was commenced at 20mg/kg/day. It may be that the higher doses affect of inhibiting crystal growth may have led to a rise in serum calcium levels.

This was the only reported side effect. Given the very high doses of disodium etidronate used for HO, a lack of other side effects (e.g. oesophageal and/or duodenal ulceration, osteonecrosis) thought to be prominent with this class of agent is a valuable finding that endorses the safety of disodium etidronate for therapy of HO in this patient population.

The retrospective method of this data collection presented several limitations of this study that we would like to declare. Firstly the most significant limiting factors regarding this study were the small sample size and the selection of patients in the

control group. As patients were selected based on being the next patient admitted to the burns unit following HO patients, then the severity of the burn injury was varied, but overall the control patients had significantly less severe burns. Future analyses could consider matching patients for %TBSA burn, to normalise both groups for burn severity. It was believed that by matching for time of admission we could still adequately analyse the different indicators and at the same time maintain %TBSA as an independent variable. The time matching would also help eliminate certain biases in reporting and treatments that may vary over time. Additionally, matching on severity of burn injury and length of hospitalization would most likely diminish the odds of detecting clinically relevant risk factors for HO.

In regard to the small sample size, this is difficult to avoid owing to the low number of patients developing HO each year. However the true incidence may actually be somewhat higher than the incidence of 5.6% in our patient population it is possible that other patients had developed HO and were either not detected or were detected but not recorded in the database as such. In addition, the chart of one of the patients indicated as having HO from the database was not available as their record relating to their burn admission had been lost.

The retrospective method of data collection had further implications on the results in relation to the clinical development of HO. It appeared from the notes that it was not always documented when HO was suspected. Although patient notes would describe a reduction in joint range of motion and increasing pain there was no mention of HO in some cases until x-rays had confirmed the diagnosis. Therefore the collected data may have some variance to the true value.

The route of administration was charted as nasojunal/oral for a number of patients so this was therefore recorded in our study as being 'not oral', even though the patient may have been taking the drug by the oral route.

In addition, as the information regarding the continued administration of disodium etidronate was not known following discharge from the RBWH, due to no documentation in the RBWH medical records, it was not possible to record the duration of treatment and the reason for ceasing treatment in the majority of patients.

It is important to mention that this observational study was not appropriate to demonstrate the efficacy of disodium etidronate as no control group of patients with HO was available. However it did demonstrate the safe use of the drug at dosages prescribed in this study.

Conclusion

HO is a significant morbidity associated with burns trauma that can significantly increase a patient's hospital length of stay and elevate healthcare costs. This study has confirmed that a prolonged period of inactivity is a main risk factor for the development of HO in burns patients. Of course, this is closely related to severity of burn injury including need for prolonged mechanical ventilation, escharotomy, several surgical procedures, grating limbs, etc. These data illustrate the importance of early mobilization of patients with severe burn injury. The results of this project also support the safety of disodium etidronate as a therapy for HO in burns patients, although the clinical efficacy remains to be demonstrated for this patient population.

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TABLE 1. Factors associated with HO

- Prolonged immobilisation with limitation of active joint movement¹⁷
- Coma >30 days¹⁷
- Long term pulmonary ventilation¹⁷
- Possibly continuous pressure to an area^{17,18}
- Trauma from aggressive physical manipulation^{19,20}
- Severity and extent of burn (>20% TBSA)⁸
- Increased nutritional support (ie. protein >150g/day) causing calciuretic response^{21,22}
- Alterations of calcium metabolism and osteoporosis²³
- Tissue hypoxia²³
- Local infection²³
- Circulatory stasis²³
- Antigen-antibody disorders²³
- C-reactive protein (as an early marker of HO formation)²⁴
- Alkaline phosphatase (later marker, 2-3 weeks after completion of osteoinduction)²⁴

Table 2: Demographics, comparison of treatment and outcomes between HO and non-HO groups.

Category	HO Group (n=19)	Non-HO Group (n=19)	P-value
Male	16 (84)	16 (84)	1.00
Age (years)	43 (32-48)	35 (23-60)	0.284
%TBSA	46 (37-65)	18 (12-31)	<0.001
Inhalation injury	10 (53)	2 (11)	0.013
BOBI score	4 (2-6)	1 (0-2)	<0.001
Predicted mortality, % (based on BOBI score)	20 (5-50)	1.5 (0.1-5)	<0.001
Hospital LOS (days)	99.8	15 (5-26)	<0.001
ICU Admission	18 (95)	4 (21)	<0.001
ICU LOS (days)	22 (15-34)	7 (3-12)	<0.001
Ventilated	18 (95)	4 (21)	<0.001
Length of Ventilation	24 (13-33)	6 (2-12)	<0.001
Escharotomy required?	10 (53)	2 (12)	0.005
Burn Debridement Surgery Required	19 (100)	11 (58)	0.001
Number of Surgeries	9 (5-11)	1 (0-2)	<0.001
Graft to Limb	19 (100)	11 (58)	0.001
HO to grafted limb	19 (100)	0 (0)	<0.001
Sepsis	19 (100)	1 (5)	<0.001
Admission to active movement (days)	26 (11-32)	0 (0-3)	0.001
Admission to assisted walking (days)	55 (25-59)	0 (0-2)	<0.001

Legend.

Data are described as n (%) or median (1st – 3rd quartile).

TBSA, total burned surface area; LOS – length of stay; HO heterotopic ossification; BOBI, Belgian Outcome in Burn Injury score.

Figure 1: CONSORT diagram for selection of patients with HO

*Of the four patients excluded, on review of their medical charts, three of the patients had no record of having, or suspected of having, HO and one patient's medical chart was not available as the volume related to burns admission was lost.