Hypertrophic Scar Severity at Autograft Sites Is Associated With Increased Pain and Itch After Major Thermal Burn Injury

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Approximately three quarters of major thermal burn injury (MThBI) survivors suffer from hypertrophic scarring (HTS) and over half experience chronic pain or itch. In survivors of MThBI, HTS and chronic pain or itch are considered one of the greatest unmet challenges of postburn injury care and psychosocial reintegration. Although scarring, itch, and pain have been clinically associated, there are no prospective, multisite studies examining tissue autograft site pain or itch and scar outcomes. The authors collected a representative cohort ($n = 56$) of MThBI survivors who received autografting within 14 days of injury and evaluated graft-site pain or itch severity (0–10 Numeric Rating Scale) and HTS using a validated scar photograph assessment scale 6 months following MThBI. Given that stress is known to influence wound healing, the authors also assessed the relationship between previous trauma exposure, peritraumatic stress, preburn overall health (SF-12), scarring, and chronic pain or itch severity using Spearman's correlation. Association between HTS and chronic pain or itch was significant in a linear regression model adjusted for age, sex, and ethnicity ($\beta = 0.2$, $P = .033$ for pain, $\beta = 0.2$, $P = .019$ for itch). Results indicate that prior trauma exposure is inversely correlated ($r = -.363$, $P = .030$) with scar severity, but not pain or itch severity 6 months after MThBI. Study results suggest that preburn chronic pain or itch is associated with pathological scarring 6 months following MThBI. Results also indicate that stress may improve scarring after MThBI. Further work to understand the mechanisms that underlie both HTS and chronic pain or itch and their relationship to chronic stress is critical to the development of novel therapies to assist burn survivors recover. (J Burn Care Res 2018;39:536–544)

Over 700 000 patients seek care for burn injuries in the United States each year, and more than 50 000 experience major thermal burn injury (MThBI) requiring hospitalization (1, 2). Most hospitalized

burn patients receive an autologous skin graft (autograft), in which skin is removed from a healthy “donor” site and transplanted to a burn site (3–7). Among MThBI survivors, chronic pain, itch, and hypertrophic scarring (HTS) at the tissue autograft site are the major causes of suffering and disability (8, 9). Despite the frequency of these outcomes (8–15), to the best of our knowledge, no prospective studies of MThBI survivors have evaluated the relationship between pain or itch and HTS.

In this multisite prospective study, our aim of this study was to evaluate the relationship between pain or itch and HTS outcomes 6 months after MThBI. To the best of our knowledge, there has been no prospective study that has evaluated pain or itch severity and scar outcome in survivors of burn injury who required tissue autografting. For our primary measure of pathological scarring, we used a validated

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photographic scar assessment scale, which carries the advantage of monitoring scar outcomes remotely by a standardized panel of examiners (16). Based on clinical experience, we hypothesized that abnormal scarring would be associated with increased chronic graft site pain and itch in the aftermath of MThBI. Based on the previous work demonstrating a link between acute stress and wound healing (17, 18), we hypothesized that these two outcomes (stress and pathological scarring) would be associated in the aftermath of MThBI. Therefore, in secondary analyses, we evaluated the relationship between peritraumatic stress exposure and pathologic scar severity.

METHODS

Design, Setting, Participant Eligibility Criteria

Patients undergoing tissue autograft after MThBI between February 2012 through June 2015 at one of the three burn centers (University of North Carolina, Chapel Hill, NC, MedStar Washington Hospital Center, Washington, DC, and University of South Florida, Tampa, FL) were enrolled. Exclusion criteria included age <18 or >65, admission >72 hours after MThBI, estimated total body surface area (TBSA) burn >30%, intentional, electrical or a chemical mechanism, autograft performed >14 days after admission to burn center or autograft decision made >7 days after admission, Childs-Pugh liver failure stage B or C, end stage renal disease, chronic opioid use >20 morphine equivalents per day before burn, preburn skin disorder causing pruritus, substantial co-morbid injury (eg, blast injury resulting in major trauma in addition to burn), pregnancy or breastfeeding, residing greater than 100 miles from site, and burn that required escharotomy. In addition, individuals unwilling to provide a blood sample and prisoners, suicidal, homicidal, psychotic individuals, and individuals who did not read and speak English were excluded. Individuals with <30% TBSA burn were enrolled because such individuals constitute the great majority of burns that present to a burn center (19) and are able to provide pain scores (eg, are not intubated). Other exclusion criteria were chosen to remove heterogeneous populations (eg, children, electrical burns, individuals presenting long after injury). Participants were compensated \$70, \$50, and \$70 for completion of the initial, 6-week, and 1-year assessments, respectively. Participants were provided \$60 for a scar and wound assessment and photographs and \$30 for completion of the 6-month survey.

Study Procedures

The Institutional Review Board at each burn center approved the study protocol and each participant provided written informed consent. Study flow chart is shown in Figure 1. Structured, in-person interviews were conducted by research assistants at the time of enrollment. Follow-up telephone interviews were conducted daily through day 7, weekly through day 21, at 6 weeks, and monthly thereafter. Data regarding burn injury characteristics, including estimated burn TBSA and mechanism, were extracted from the medical record.

Pain/Itch Assessments

Verbal rating scales are strongly correlated with visual analogue scales (20–22) and are ideal for use among patients with burn injuries that may impair dexterity. A 0–10 verbal Numeric Rating Scale (NRS) was used to evaluate graft and donor site pain and itch severity at the time of enrollment and at each follow-up time point. An NRS score of ≥ 4 was used to define moderate or severe pain (23). NRS scores were assessed daily in the 7 days following injury, weekly for the 3 weeks after burn, at 6 weeks, 3 months, and monthly thereafter until 1 year after burn. Itch at the graft site was also assessed with a 0–10 NRS.

Scar Photograph Acquisition

Digital photographs were taken 6 months following burn injury either in clinic or at home via a digital camera. Multiple options to obtain photos were given to participants including 1) personal smartphone, 2) personal digital camera, and 3) mailed digital camera. No standard digital camera was used to increase access for participants. Detailed instructions were sent to each participant and/or clinic to ensure compliance with image acquisition procedures. Participants and clinic staff were instructed to acquire approximately five digital photographs of the skin graft site after removing any dressings or garments overlying the scar. Once garments were removed, participants were asked to wait 5 minutes before acquiring photographs. The flash and autofocus features of the digital camera were enabled, and when possible a white linen backdrop was used. The photos captured a close-up image of the scar and the peri-scar region by obtaining a 4–6 inch margin around the wound when possible considering the extent of the injury.

Scar Photo Assessment

The most representative photo of the scar (one that included the boundaries between the scar and

Figure 1. Study flow chart.

normal skin) was selected from available images and placed in a Microsoft PowerPoint presentation for viewing by observers. One physician and one research assistant performed independent assessments using a previously validated scar photo assessment scale described by Mecott et al (16). In brief, this composite photographic scar scale is a sum of three subscales in which observers rated scar surface appearance, scar height, and

color mismatch between the scar and normal skin each on a 1–4 Likert scale. Written descriptions and published reference scar photos were provided to each observer as a resource while photos were scored. The color mismatch subscale was previously validated using scanning reflectance spectrophotometry and digital image analysis (16). The height subscale was previously validated by measuring actual scar height (16).

Vancouver Scar Scale

During clinic follow-up, a wound assessment was performed using the VSS (24). The VSS assessed scarring by measuring four features of the scar: pliability, height, vascularity, and pigmentation. Pliability was rated on a scale of 0–5, where 0 is normal skin and 5 represents a contracture that produces a deformity. Height of the scar above normal skin was measured on a scale of 0–3, where 0 represents a flat wound and 3 represents a wound with a height of >5 mm. Vascularity was assessed on a scale of 0–3, where 0 is normal and 3 represents a purple appearance. Pigmentation was rated as a 0 for normal skin color, 1 was given for hypopigmentation, and 2 was given for hyperpigmentation. As reported previously, it is not known whether hypopigmentation or hyperpigmentation indicates a poor scar outcome; therefore, pigmentation was not included in the modified VSS reported here (16, 25). The summed score from pliability, height, and vascularity subscales was used to form the modified VSS score.

Posttraumatic Stress Disorder Symptom Severity Assessment

Posttraumatic stress disorder (PTSD) symptom severity was assessed in the immediate aftermath of burn injury (enrollment of the study) and at 6 months following burn injury with the PTSD Symptom Scale–Interview (PSSI) at study enrollment (26). The PSSI is a validated 17-item scale administered at the time of study enrollment to assess initial PTSD symptom severity.

Depression and Anxiety Assessment

Depression and anxiety severity 1 week before burn injury was assessed with the Depression, Anxiety, and Stress Scale (DASS)-21 (27,28) which has been previously used to assess depression and anxiety symptoms (29). The DASS-short form is a 21-item scale comprised of 3- and 7-item subscales to assess the severity of anxiety, depression, and stress. Severity for each item is assessed with a patient-reported Likert scale (“Never,” “Sometimes,” “Often,” and “Almost Always”).

Life Events Checklist

The life events checklist was used to assess participants’ exposure to potentially stressful, traumatic events before burn injury (30). The life experiences checklist is a validated, self-reported 17-item questionnaire that determines the extent to which an individual has been exposed to traumatic events.

Michigan Critical Events Perception Scale

The Michigan Critical Events Perception Scale (MCEPS) is a validated (31) 5-item questionnaire that evaluates dissociative symptoms after traumatic life events. The MCEPS is a composite score of five

items that evaluate dissociation and depersonalization after stressful events using a 1–5 Likert scale. A score of >3.0 indicates a significant peritraumatic dissociation (31).

Statistical Analysis

Sample characteristics and outcomes were summarized using standard descriptive statistics (SPSS Statistics version 24; IBM Corporation, Armonk, NY). Linear regression analysis was performed to examine association between pain and impaired wound healing after correcting for age, sex, and ethnicity. Both wound height and composite wound photo score were used to assess wound healing and were regressed on pain or itch outcomes 6 months following burn injury. Interclass correlation coefficients were calculated to demonstrate agreement in composite wound photo scale and modified VSS score. Spearman’s correlation coefficients were calculated to demonstrate strength of the relationship between preburn health characteristic and both photographic scar score and pain. *P*-values of <.05 were considered statistically significant.

RESULTS

Participants

Demographic Characteristics of the Sample

The majority of patients enrolled in the study were African-American males under the age of 40 (Table 1). Over half of the participants (55%) earned an income that was greater than \$40 000 per year and were educated beyond high school (52%). Patients were enrolled an average of 3 ± 1.5 days after burn injury.

Sample Burn Injury Characteristics

The majority of participants had a burn that was <10% of their TBSA. The most common thermal burn injury mechanisms were scald (25/56, 46%)

Table 1. Characteristics of patient sample (*n* = 56)

Age, mean (<i>SD</i>), yr	39 (13)
Males, <i>n</i> (%)	39 (70)
Ethnicity, <i>n</i> (%)	
African-American	29 (52)
European-American	27 (48)
Type of thermal burn <i>n</i> (%)	
Contact	4 (7)
Flame	23 (43)
Scald	25 (46)
Burn total body surface area (% <i>SD</i>)	5 (3)
Length of hospital stay in days (<i>SD</i>)	11 (3)

n: number of participants; *SD*: standard deviation; yr: year.

and flame (23/56, 43%). Approximately three quarters of patients sustained a burn in only one anatomical region (40/56, 71%). The most common locations of burn injury were the upper extremity (41/56, 73%) and lower extremity (21/56, 38%).

Scar, Pain, and Itch Outcomes at 6 Months

As described in Methods, photographic scar assessments of autograft site photographs taken 6 months after MThBI were performed. A previous study validated this photographic method against objective scar assessments (16), and in secondary analysis of our data (Supplementary Table 1), this scale which measures surface appearance, height, and color mismatch demonstrated high intraclass correlation with the widely used VSS. Based on the height subscale of the photographic scar scale averaged between the two observers, 55% (31/56) of MThBI survivors had a raised, hypertrophic scar.

Pain outcomes were assessed on enrollment and 86% (48/56) of MThBI survivors had moderate-to-severe pain at the site of burn injury. Six weeks following MThBI, 31% (16/52) had moderate-to-severe graft site pain (0–10 NRS ≥ 4) and 25% (14/56) had moderate-to-severe pain 6 months following MThBI.

Itch outcomes were also assessed on enrollment and 23% (13/56) of MThBI survivors had moderate-to-severe pain at the site of burn injury. Six weeks following MThBI, 35% (18 of 52) had moderate-to-severe graft site itch (0–10 NRS ≥ 4) and 25% (23/56) had moderate-to-severe itch 6 months following MThBI.

Association Between Pathological Scarring and Pain/Itch Severity 6 Months Following Burn Injury

Figure 2 shows scatter plots of pain and itch severity vs photographic scar scale score determined 6

months following MThBI using previously validated scar photo assessment (16). After adjustment for age, sex, and ethnicity, a significant linear relationship between pain or itch and severity of scarring 6 months after MThBI was observed (Table 2). To better identify the wound characteristics most strongly associated with pain or itch outcomes, we separated the overall scar scale into components and calculated correlation coefficients between pain or itch severity (0–10 NRS) and each scar subscale (Table 3). Scar surface appearance and scar height were significantly correlated with pain severity; however, color mismatch was not. For itch, the strongest correlation was with color mismatch followed by scar height (Table 3). There was not a significant correlation between scar surface appearance and itch severity. After adjustment for age, gender, and ethnicity, abnormal (hypertrophic) scarring 6 months after burn injury (judged by a raised height on the VSS assessment) was also significantly associated with increased pain severity 6 months after burn injury ($\beta = 0.15$ $P \leq .001$, adjusted means shown in Supplementary Table 2) but not itch ($\beta = 0.05$ $P = .161$).

Correlation Between Wound Healing, Pain, Itch, and Important PeriTraumatic Health Characteristics

Mental health measures, such as PTSD severity, and DASS measure did not correlate with the degree of pathologic scarring or graft site pain at 6 months (Table 4). The life events checklist score, which evaluated participant's exposure to prior traumatic events, was inversely correlated ($r = -.363$, $P = .030$) with scar score, but not pain or itch 6 months after MThBI. A significant correlation was shown between PTSD severity and graft site pain or itch

Figure 2. Relationships between pain or itch severity and degree of scarring assessed with a validated scar photo assessment. A. It shows pain severity (0–10 Numeric Rating Scale, NRS) vs photographic scar severity score. B. It shows itch severity (0–10 NRS) vs photographic scar severity score. The best-fit line was drawn (solid line) along with the 95% confidence interval (gray band).

Table 2. Multivariate linear regression demonstrating association between degree of scarring and pain and itch severity 6 months after MThBI

Variable	Graft site pain			Graft site itch		
	β	SE	P	β	SE	P
Pain at 6 mo	0.2	0.09	.033	0.2	0.08	.019
Sex (ref. male)	-0.3	0.53	.571	-0.2	0.52	.658
Race (ref. EA)	1.4	0.47	.004	1.4	0.47	.005
Age	-0.02	0.02	.397	-0.01	0.02	.484

EA: European-American; MThBI: major thermal burn injury; SE: standard error; β : beta coefficient from linear regression model.
Dependent variable: Scar assessment score (sum of three 1–4 subscales rating scarring at the tissue autograft site).

Table 3. Correlation of pain or itch severity (0–10 NRS) with scar photograph subscale score

Photo scar assessment subscale	Graft site pain		Graft site itch	
	Correlation coefficient	P	Correlation coefficient	P
Scar surface appearance	0.294	.028	0.256	.057
Scar height	0.277	.039	0.271	.044
Color mismatch	0.226	.094	0.336	.011

NRS: Numeric Rating Scale.

Spearman's correlation with graft site pain or itch severity was calculated for each photographic subscale and reported along with P-value.

Table 4. Correlation between survivor characteristics and photographic scar assessment score, and graft site pain and itch 6 months following MThBI

Stress-related symptoms	Graft site itch at 6 mo		Graft site pain at 6 mo		Photographic scar assessment score	
	r	P	r	P	r	P
<i>Reported preburn symptoms[‡]</i>						
Depression (DASS)	.134	.084	.072	.527	-.175	.198
Anxiety (DASS)	.161	.155	.031	.784	-.082	.548
Prior trauma exposure (LEC)	.076	.593	.028	.844	-.363*	.030
<i>Reported peritraumatic Symptoms[‡]</i>						
Peritraumatic dissociative symptoms (MCEPS)	.144	.173	-.204	.075	-.111	.429
Posttraumatic stress severity (PSSI-I)	.239	.032*	.068	.545	-.019	.887
<i>Reported symptoms 6 mo after MThBI</i>						
Posttraumatic stress severity (PSSI-I)	.557	<.001*	.448	<.001*	.163	.229

MThBI: major thermal burn injury.

Spearman's correlation was used to derive r values.

*P-value of < .05 was considered significant.

[‡]DASS, Depression Anxiety Stress Scale assessed mental health symptoms 1 week before burn.

[‡]LEC, Life Experiences Checklist assessed life trauma before burn injury; MCEPS, Michigan Critical Events Perception Scale measures dissociative symptoms around the time of burn injury. The photographic scar assessment scale is a validated measure of scarring used 6 months following MThBI.

severity 6 months following MThBI; however, there was no significant correlation between PTSD severity and scarring 6 months following injury (Table 4). We also found that increased peritraumatic stress symptoms were associated with itch in the graft site 6 months following MThBI (Table 4).

DISCUSSION

The results of this study support our hypothesis that scarring and pain or itch are associated with MThBI survivors who receive an autograft. At 6 months, both our composite assessment of HTS and individual scar characteristics of HTS (wound

height and color mismatch) were strongly correlated with pain or itch severity. These results suggest that interventions reducing HTS may also improve pain outcomes. Further studies are needed to better understand mechanisms mediating HTS and chronic pain or itch, and the pathogenic interplay between these morbid outcomes, to inform better preventive or treatment interventions.

In addition, study results also supported our hypothesis that previous life stress or peritraumatic stress would be associated with scar severity. However, the direction of the effect was opposite to that expected and previous life stress was associated with reduced scarring. Consistent with our hypothesis and previous studies (14, 32, 33), the present study shows that greater peritraumatic stress was associated with increased pain and itch following MThBI. One mechanism that may contribute to this finding is evidence that greater stress across the life span can result in enduring changes to the hypothalamic–pituitary–adrenal axis (34), which may result in reduced negative feedback inhibition and increased cortisol levels. Such changes may in part transduce the influence of emotional and psychosocial factors on wound and pain or itch outcomes. Specifically, the inverse effect that psychological stress has on scar development and pain observed in this study may be explained by a differential effect of stress hormones (eg, cortisol) on inhibiting hypertrophic scar formation (35, 36) while promoting stress-induced hyperalgesia (32, 37–40).

To the best of our knowledge, a single previous study found histological correlates between pain and HTS, in a small sample ($n = 38$) of individuals experiencing MThBI after skin grafting (41). Our findings are consistent with these results. Historically, scarring has been thought to potentially increase pain via the increased expression of nociceptors due to dysregulated healing. However, more recent evidence suggests that the association between increased nociceptor density and scarring may be bidirectional, as evidence suggests that nociceptors may play a key role in wound healing by releasing inflammatory mediators (eg, substance P, CGRP) at peripheral nerve terminals (42–44).

In our sample, previous exposure to life stress was associated with improved wound healing outcomes. This finding is in contrast to previous studies, which found a significant impairment in wound healing due to stress. However, these studies differed greatly from the present study as follows: they 1) assessed the acute phase of wound healing (epithelialization and closure) (45), 2) evaluated current rather than aggregate life stress (18), and 3) did not examine

later outcomes in the maturation phase of wound healing, namely, HTS. The results presented here suggest the alternative hypothesis that chronic stress leads to improved scar outcomes. Future studies are needed to confirm this alternative hypothesis.

Mechanisms responsible for the association between stress and wound healing remain poorly understood. Interestingly, accumulating evidence suggests that the skin is an extra-adrenal site of cortisol production in response to stress which may be important in wound healing (46, 47). Given that corticosteroids (cortisol) are known to reduce collagen production (48, 49) and that glucocorticoids clinically reduce HTS (10), it is possible that in chronically stressed individuals, local and systemic cortisol production impedes the development of hypertrophic scarring.

Our study results are consistent prior studies that identified an association among pain, itch, and PTSD (2, 14). For example, in burn-injured soldiers, early pain scores predict the development of later PTSD (2), and in pediatric burn survivors, reducing acute pain has been shown to result in improved PTSD outcomes (50, 51). In addition, several studies of burn patients have found an association between itch and PTSD outcomes (14, 15). Future studies are needed to establish whether better treatment of acute stress, pain, and itch reduces the development of PTSD and chronic pain or itch.

Finally, our results support the validity of using digital photos to assess wound or scar outcomes in follow-up studies. This study used a previously validated, robust scar photo assessment to evaluate scarring in the maturation phase of wound healing. The use of digital photography has the advantage of reducing interinstitutional and interobserver variability.

LIMITATIONS

Several limitations of this prospective cohort study should be considered. First, the study sample was relatively small. However, no previous studies examining chronic pain and scar outcomes have been performed using a photographic scar scale. A larger prospective study would be valuable to confirm our findings. Second, scar photographs were collected by a combination of study participants, research assistants, and clinical personnel using various lighting conditions, backgrounds, and cameras. This approach could increase noise into scar characteristics; however, our interobserver reliability was excellent and this ecological approach is valuable in assessing wound outcomes

in cohort studies of MThBI survivors who present to burn centers from a broad catchment area and may have difficulty returning for follow-up. Additionally, this prospective, observational cohort study was designed to examine associations between pain and scar outcomes, but cannot determine causal relationships. Finally, our study only included one common population of burn patients. Other studies are needed which evaluate pain and itch outcome disparities in other burn populations (eg, pediatric populations, those with electrical or chemical burns). Future preclinical and clinical studies are needed to elucidate the likely complex relationships between stress, HTS, and chronic pain in MThBI survivors.

CONCLUSIONS

Study results show that chronic pain or itch and pathological scarring (assessed by scar photography) are associated 6 months following injury. These results suggest that interventions that reduce HTS may also improve pain outcomes. Further studies are needed to better understand mechanisms mediating HTS and chronic pain or itch, and the pathogenic interplay between these morbid outcomes, to inform better preventive or treatment interventions.

SUPPLEMENTARY MATERIAL

Supplementary data is available at *Journal of Burn Care & Research* online.

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