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CLINICAL REPORT

Itch in Burn Areas After Skin Transplantation: Patient Characteristics, Influencing Factors and Therapy

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Pruritus is a frequently encountered symptom following burns. Higher intensity of itching has been associated with depth of the wounds and specific body locations but these differences are not well understood. Our aim was to investigate the intensity of post burn pruritus in grafted and non-grafted burns across anatomic areas and to report on itch-inducing factors and applied treatments. The study included 226 patients prospectively followed for 18 months. Results showed that grafted patients and non-grafted patients reported similar overall itch intensity in-hospital. At 3 months post burn, grafted patients had higher overall itch scores, a difference that was found robust across the study period. Grafted wounds were found to produce higher mean itch intensity at 3 months post burn but this difference disappeared at 12 months post burn. Differences in itch prevalence rates were found across anatomic areas, but only in non-grafted burns. The differences in itch intensity on patient level versus wound level suggest that on the longer run, peripheral mechanism do not explain the higher itch scores in grafted patients. ***Key words: itch; pruritus; burns; scars; skin grafting.***

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A substantial proportion of the patients with burns suffer from pruritus and this has been shown to interfere with sleep and daily activities (1, 2). The symptom often presents when re-epithelialisation takes place and may persist for years (3–6). The prevalence is as high as 93% at discharge and subsequently declines to 67–73% 24 months after the burn event (3, 5). Within the first years post burn, a significant reduction in the intensity of pruritus was found (3, 5, 7). Of those reporting itch at 24 months, 2 out of 3 patients had only mild complaints, 29% and 6% suffered from moderate to severe itching, respectively (5). In one study, however, 62% of patients who had paresthetic sensations, including itching, reported an equal or even increased intensity of their sensations over a one-year period, illustrating the persistency of the complaints in this sample (4).

Burn severity has been found to play an important role in burn-related itching. The number of surgeries and total burned surface area were identified as risk factors of pruritus at 3 months post injury (3, 5, 8) as well as on the long term (3, 4, 6, 9). In particular grafted wound sites seem to cause higher itch intensity, painful and paresthetic sensations (4), and elevated sensory thresholds or absent responses to various physical stimuli (10, 11). Related to depth of the wound, patients with dry skin and hypertrophic scars were more likely to report itch, up to 24 months post burn (3). Furthermore, some studies found pruritus to be related to the anatomic location. The legs (8, 9) and the trunk (9) showing to be the most predisposed locations to the development of itch, whereas the face was the least susceptible location to high itching (8). These findings suggest peripheral differences across wounds in the generation of pruritic impulses.

Histamine is the best known mediator for the induction of itch. It is present in mast cells, which release their content upon activation. Histamine has been shown to increase collagen production by fibroblasts (12) and may explain why itchy scars are more hypertrophic. Besides an increase in collagen content, hypertrophic scars are also characterised by prolonged inflammation and associated with an adverse environment for sensory structures to recover. The subsequent reduction in skin fibre density may account for the aforementioned elevated sensory thresholds (10, 11). Higher itch intensity across different body parts may also suggest a role of nerve density in itch. Previous research has shown that the density of epidermal free nerve endings differs across the body (13) and that nerve fibre density may be correlated to pruritic sensations (14). Thus, it is now assumed that both an increase of mediators and neuronal damage caused by deep dermal burns, contribute to the pruritic symptoms (15). Although the evidence for involvement of the central nervous system in itch

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perception can not be ignored (16), all these studies suggest that processes at the skin level may have a role in itching but few studies investigated itch at body location level and investigated more thoroughly the role of skin grafting.

Along with the lack of understanding of underlying mechanisms, the management of post burn pruritus has been shown to be extremely challenging (15, 17). Currently, emollients and systemic antihistamines are the leading therapy. These treatment modalities provide relief in a substantial group of patients but mostly no complete resolution of symptoms can be accomplished. Several treatment options are now available with varying efficacy. Centrally acting pharmacological agents include opioid agonists and antagonists (18), and antidepressants (19). Emerging clinical evidence appears to tentatively support gabapentin (20) and pregabalin (21). Non-pharmacological treatment consists of pressure garments, silicone gel treatments, laser therapy (22), massage therapy (23) and transcutaneous electrical nerve stimulation (24). However, a clear consensus on the care of patients with post burn itch is lacking. Little evidence is available on a potential correlation between successful therapy and depth of the wounds. Studies shedding light on characteristics of itch and inducing factors may identify subgroups of patients with different needs and thus help clinicians to tailor interventions.

The objective of this prospective cohort study is to focus on differences between grafted and non-grafted areas and to examine possible differences across anatomic locations. We hypothesise that grafted wounds produce higher itch intensity and that the itch intensity is depending on the affected body location. Furthermore, a description of itch-inducing factors and pharmacological and non-pharmacological interventions is provided.

MATERIAL AND METHODS

Patients and procedure

The study was approved by the ethics committee of the Martini Hospital, Groningen, The Netherlands, and featured a prospective longitudinal cohort design using a self-report questionnaire. As part of a larger study, participants were consecutive admissions from 5 regional burn centres in the Netherlands and Belgium between January 2005 and January 2009. Sample selection included all burn survivors from 18 years or older with external burns of at least 1% total body surface area (TBSA), admitted to the burn centre for 48 h or longer, and with a sufficient command of the Dutch language. Patients were excluded from the survey if the injury was the result of a suicide attempt, or if they suffered from cognitive disorders that prevented reliable data collection. All patients who gave their written informed consent completed the questionnaire in the week before discharge, and at 3, 12, and 18 months following their injury. Patients who did not return the questionnaire within 2 weeks were contacted with the request to return the questionnaires. No further efforts were taken to increase the response rate.

Measurement instruments

The Burn Itch Questionnaire (BIQ). The BIQ is a 22-item scale that was developed with the aim to gather information on itch intensity, itch occurrence, impact on daily functioning and treatment (25). For the purpose of this study we used the information on overall itch intensity and itch intensity across anatomic locations rated on a 10-point scale. Patients were asked to rate the itch intensity in the several anatomic areas affected by the burns which were marked on a drawing adjusted to the patient's situation. The distinction between grafted and non-grafted areas was recorded from the medical files before discharge from the hospital. Besides itch intensity, the questionnaire inquires about aggravating factors of itch and treatment related questions such as 'Are you taking medication against itching' and 'Do you use other means and/or ways of combating itch' and 'what is the result of this' indicated by 'no improvement', 'minimal improvement' or '(practically) complete reduction of itching'.

Demographic, injury characteristics and treatment

Sex, age, burns percentage total body surface area (TBSA) and percentage body surface area full thickness skin loss (FT), total number of initial skin grafting procedures and length of hospital stay were obtained from medical records. In the burn centres partial thickness (PT) wounds are treated conservatively with topical antiseptics or a membranous dressing such as hydrofibre dressing. Mixed PT and FT wounds < 15% are usually treated conservatively for 10–14 days, followed by tangential excision or excision to the fascia and split skin autografting. FT wounds <15% TBSA and mixed PT and FT wounds > 15% are generally treated with early tangential excision or excision (up) to the fascia and split skin autografting.

Statistical analysis

Mann-Whitney *U* tests were used to compare grafted vs. non-grafted on continuous data: Kruskal-Wallis tests were used to compare itch prevalence in the different body areas. Pearson χ^2 or Fisher's exact tests (2×2 tables) were used to identify dependency between nominal data. Wilcoxon Signed Ranks Tests were executed to test within-subject differences of itch intensity over time. Effects were reported as significant at $p < 0.05$. Spearman's rho was used for the correlation between itch scores and patient's total number of itching areas. The analyses were executed using the commercial statistical package (IBM© SPSS© Statistics version 20, release 20.0.0).

RESULTS

Patient characteristics

A total of 226 patients gave informed consent and completed at least one of the 4 measurements of which 137 (60.6%) completed 3 or more measurements. The in-hospital measurement was completed by 208 patients (92.0%), 3 months follow-up itch data were obtained for 179 (79.2%), 12 months follow-up for 143 (63.3%), and 18 months follow-up for 99 patients (43.8%). Table I presents the sample characteristics.

Itch prevalence and intensity

Itch prevalence rates during hospitalisation, at 3, 12 and 18 months were 70%, 54%, 37% and 35%, re-

Table I. *Sample characteristics of patients with post burn itch*

Subjects	*n* (%)	Mean (SD)	Min–Max
Male (*n*/total *n*)	177/226 (78)		
Age, years		40.4 (13.7)	18–76
Total body surface area burns, %		12.7 (12.1)	1–65
Full thickness, %		4.3 (8.1)	0–60
Number of skin grafting procedures		1.2 (1.7)	0–8
No skin grafting procedure	92 (41)		
One skin grafting procedure	90 (40)		
≥ 2 skin grafting procedures	44 (19)		
Hospital stay, days		24.0 (30.0)	2–337

spectively. More females had itch complaints during hospitalisation (84.1% versus 66.5%; χ^2 (1) = 5.15, $p = 0.026$), but the gender difference disappeared with the course of time.

On average, itch intensity in the total sample decreased with time; the highest decrease was observed between 3 and 12 months follow-up. Excluding patients who had no itch complaints, the mean itch intensity measured at 3 month follow-up showed an increase compared to hospitalisation, but this was not statistically significantly different ($Z = –1.158$, $p = 0.097$). Itch intensity scores measured at 12-month follow-up were significantly lower compared to the 3-month follow-up ($Z = –2.968$, $p = 0.003$). No further decrease could be observed in the following 6 months ($Z = –1.788$, $p = 0.074$). Mean itch scores were significantly correlated with patient's total number of itching areas i.e. the more separate body areas produced itch, the higher the overall itch intensity (during hospitalisation: $\rho = 0.639$, $p < 0.001$; 3 months: $\rho = 0.707$, $p < 0.001$).

Itch intensity in grafted versus non-grafted burn wounds

Fig. 1 summarises the results. The intensity and prevalence of wound itching during hospitalisation was similar in grafted and non-grafted patients. A steep decrease in itch intensity was noticed in the non-grafted group between hospitalisation and 3 months. The itch intensity also decreased during follow-up. In contrast, mean itch scores of the grafted patients increased at 3 months post burn, but then slowly decreased up to 18 months post burn. Table S1[1] supports Fig. 1.

Itch prevalence and itch intensity in different body locations

At 3 months post burn, 672 locations were scored of which 289 (43%) received a score of 1 or higher. At 12 months post burn 510 body locations were scored of which 147 (29%) locations received a score of 1 or higher. Most patients had head, arm or hand burns and they had either grafted or non-grafted wounds, although some patients had both type of wounds. Comparing the prevalence of itch (itch score = 0 versus itch score ≥1) across the 5 body areas (head/neck, arm/hands, thorax/abdomen, back/buttocks, leg/feet), statistically significant differences across body areas were found for non-grafted areas ($\chi^2 = 27.59$, df = 4, $p < 0.001$) but not for grafted areas ($\chi^2 = 1.41$, df = 4, $p = 0.842$). At 3 months post burn the lowest itch prevalence was found in the face/neck area, significantly lower than in arm/hands, back/buttocks, and legs/feet. At 12 months post burn, similar findings although not statistically significant, were found for non-grafted areas ($\chi^2 = 8.63$, df = 4, $p = 0.071$) in which face/neck prevalence was lower than arm/hands and thorax/abdomen prevalence. The prevalence in grafted areas did not differ across body areas ($\chi^2 = 2.30$, df = 4, $p = 0.680$).

Looking at itch intensity in more detail excluding 0-scores (number of locations = 289), Fig. S1a[1] shows that at 3 months post burn, on average, grafted wounds produced higher itch intensities than non-grafted wounds. This effect was statistically significant in 2 body locations, i.e., arm/hand (Mann-Whitney $U = 1{,}369$, $p = 0.002$) and legs/feet ($U = 174$, $p = 0.022$). No statistically significant differences in itch intensity were

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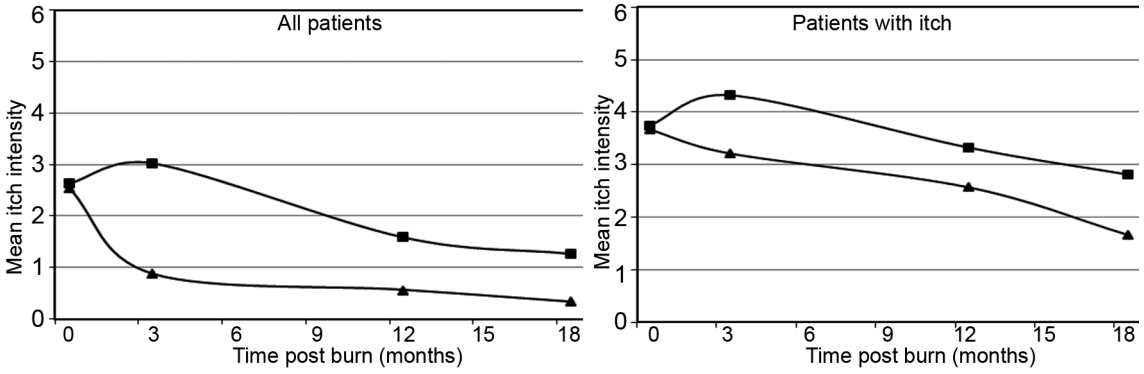

Fig. 1. Course of itch. Patients with grafted wounds (squared marker) have significantly higher itch intensity than patients with non-grafted wounds (triangle marker). In patients with grafted wounds, the itch intensity increases between hospitalisation and 3 months post burn. The subsequent follow-up moments show a decrease in itch intensity. In contrast, the itch intensity of patients with non-grafted wounds show a decrease from the first measurement onwards.

Table II. *Factors that provoke or aggravate the itch*

		Post burn		
	In-hospital *n* = 146 *n* (%)	3 months *n* = 97 *n* (%)	12 months *n* = 54 *n* (%)	18 months *n* = 35 *n* (%)
Psychogenic factors				
Sleep, rest, sitting, lying down	11 (7.5)	6 (6.2)	4 (7.4)	0 (0)
Activity	5 (3.4)	4 (4.1)	5 (9.3)	1 (2.9)
Stress, fatigue	7 (4.8)	7 (7.2)	6 (11.1)	3 (8.6)
Dermatologic factors				
Dry skin	3 (2.1)	1 (1.0)	0 (0)	0 (0)
Sweat	20 (13.7)	14 (14.4)	10 (18.5)	5 (14.3)
Neurologic factors				
Cold, cold water	17 (11.6)	23 (23.7)	10 (18.5)	13 (37.1)
Warmth, warm water	28 (19.2)	31 (32)	17 (31.5)	14 (40)
Special fabric, touch	5 (3.4)	8 (8.2)	2 (3.7)	0 (0)
Other				
Food	1 (0.7)	3 (3.1)	3 (5.6)	2 (5.7)
Letting limb hang down	0 (0)	3 (3.1)	1 (1.9)	2 (5.7)

found across body areas in both grafted and non-grafted areas. At 12 months post burn (number of locations = 147), on average, grafted areas did not produce higher itch intensity. In one area, i.e. back/buttocks, the non-grafted wounds had a higher intensity. Itch intensity in grafted wounds was similar across body locations whereas itch intensity in non-grafted wounds significantly differed from each other ($p = 0.001$) (Fig. S1b[1]).

Factors that provoked or aggravated the itch

Table II shows the diverse factors that were self-reported to provoke or aggravate the itch of patients with burns. For most, these triggers remained stable over time. The 2 most commonly reported factors exacerbating pruritus were thermal stimuli and sweating. No differences between grafted and non-grafted wound sites were found (data not shown).

Treatment of itch

The majority of the patients did not use any therapy for their itch complaints. During hospitalisation 11.6% of the patients used medication against itching (Table III). The use of antihistamines (promethazine, dimetindene, cetirizine, levocetirizine or clemastine) gradually decreased from 11.1% in-hospital to 2.0% at 18 months post burn. Most of the patients experienced a moderate improvement (Table III). Adjunct therapies were used by 29.3% of the patients during hospital stay, which remained quite stable over time, to 24.2% at 18 months post burn. The majority of the patients applied some kind of moisturiser on the burn scars. For a large proportion of these patients this was perceived as beneficial, which is also reflected by the high use of these moisturisers even at 18 months post burn. The use of pressure garments was found helpful against itch at 3 months post burn but this effect disappeared later on.

Table III. *Antipruritic strategies (patients with and without itch)* n *(%total)*

		Post burn		
	In-hospital *n* = 208	3 months *n* = 179 *n* (%)	12 months *n* = 143 *n* (%)	18 months *n* = 99 *n* (%)
One or more therapies	83 (39.9)	74 (41.3)	40 (28.0)	25 (25.3)
Medication				
Antihistamine	23 (11.1)	16 (8.9)	4 (2.8)	2 (2.0)
No improvement	2	0	0	0
Minimal improvement	15	11	1	1
(Practically) complete reduction	6	5	3	1
Analgetics	1 (0.5)	2 (1.1)	1 (0.7)	0 (0.0)
Adjunct therapies				
Moisturiser	57 (27.4)[a]	53 (29.6)	36 (25.3)[a]	20 (20.2)[a]
No improvement	1	4	0	0
Minimal improvement	23	26	15	7
(Practically) complete reduction	29	23	16	10
Pressure garments	4 (1.9)[a]	28 (15.6)	5 (3.5)	4 (4.0)[a]
No improvement	0	2	0	0
Minimal improvement	1	19	3	1
(Practically) complete reduction	1	7	2	2
Alternatives				
Rubbing, scratching	9 (4.3)	7 (3.9)	4 (2.8)	2 (2.0)
Bathing, showering	10 (4.8)	10 (5.6)	7 (4.9)	2 (2.0)
Distraction	2 (1.0)	2 (1.1)	0 (0.0)	0 (0.0)

[a]A strategy has been reported, but not all patients reported the effect.

DISCUSSION

Our results confirm that pruritus is a frequently experienced symptom for the majority of burn survivors during hospitalisation (70%) and at 3 months post burn (54%), whereas the prevalence rate of 35% at 18 months post burn was substantially lower than in previous studies varying between 67% and 83% (3–5). Possibly, the lower mean TBSA in patients included in the current study may explain the lower long-term prevalence rate of itch. Differences compared with an earlier study from our group (5) may be partly explained by the fact that patients with mild itch might have evaluated their itch complaints as insignificant in view of the effort of completing a 22-item questionnaire.

This study revealed notable differences between grafted and non-grafted wounds when comparing itch intensity at patient level. During hospital stay itch intensity appeared not dependent on depth of the burn, suggesting that in the acute phase pruritus emerges regardless of the depth of the injury. This finding may be explained by the pathophysiological processes involved in the wound healing phase; as part of the intrinsic wound healing process several pruritogenic mediators are released (26).

At 3 months post burn, patients who had undergone skin grafting showed an overall increase in itch intensity whereas those who

did not need skin grafting showed a decrease in itch intensity. Both groups of patients showed, however, a decrease in itch intensity between 3 and 18 months post burn. This progress is likely to be related to the scar maturation process. Most of the clinical relevant scar features become more apparent in the first 6 months post burn, followed by a general improvement of these scar features in the next 6 months (7).

On wound level, grafted wounds produced higher itch intensity relative to non-grafted wounds at the 3-months measurement. However, the overall difference disappeared at 12 months post burn. On patient level, grafted patients still reported a higher overall itch intensity at 12 months post burn. Thus our data shows a discrepancy between itch intensity on patient level versus wound level on the longer term. This finding may indicate that in an early phase, the itch intensity differences between deep and superficial wounds may stem from differences in peripheral processes (e.g. histamine mediated processes). Although speculative, on the longer term, the differences in itch intensity may rather stem from adaptations in the central nervous system. In accordance with chronic pain, central and peripheral sensitisation may play a role in the pathophysiology of chronic itch; continued nociceptive input can cause neuronal pathways to change in a way they exhibit increased excitation and reduced inhibition. On the long term, increased responsiveness to stimuli may result (27). More research using a different study design is required to confirm this explanation. An alternative explanation may be that grafted patients may have, on average, more affected locations and as a consequence, the overall itch score represents the sum of these, resulting in a higher overall score. A psychophysical study showed that an increase in patient's itching body areas was accompanied by significantly higher itch intensity. The authors proposed that spatial summation may follow as more nerve fibres are stimulated (28).

This study also supports prior studies regarding differences in itch prevalence rates across anatomical locations, be it only in non-grafted areas; both at the 3- and 12-month measurement, the face/neck had the lowest itch prevalence, significantly different from limbs and trunk. Casaer et al. (9), investigating itch in a sample of small mainly non-grafted burns, reported a higher itch prevalence on the trunk. Vitale et al. (8), making no distinction in grafted and non-grafted wounds, reported higher itch prevalence rates in limbs and no itch in facial scars. At 12 months, the current study did not reveal significant differences in mean itch intensity scores excluding the back/buttocks area. Natural regional variability in nerve fibre density seems a plausible explanation for the higher itch prevalence in some areas for non-grafted wounds. In grafted wounds, however, a well-innervated graft bed for optimal reinnervation of skin grafts may be lacking (10). This idea is supported by the observation of an incomplete or abnormal regeneration of nerve fibres in grafted wounds (10, 29). Therefore, due to distorted nerve regeneration in grafted wounds, the diversity in nerve density across anatomical location may no longer play a role in itch induction. Further research is warranted to elucidate this proposed nerve density explanation in non-grafted and grafted wounds at different body locations.

Almost half of the patients experienced factors that worsen their pruritic sensations. Thermal stimuli have been shown to influence itch sensation in other pruritic conditions as well (30, 31). The role of psychological stress in relation to itch following burns has been earlier identified (5) and warrants further clinical and research attention.

Despite the high prevalence of itch complaints in burn populations, only about 40% received one or more therapies in the first 3 months post burn which decreased to about 25% in the following year (Table III). These results suggest that a substantial proportion of the patients may experience itch not severe enough to use medication or that the problem is overlooked in clinical practice. Of those applying therapies, the majority used moisturisers and antihistamines during hospitalisation and at 3 months post burn. When time passes, the use of medication declined, most likely due to the natural decrease in itch intensity. Although antihistamines are the most frequently used pharmacological therapy against itch, it only produced complete relief in a small number of patients. This finding supports the need for other medications to reduce the itch problem. Moisturisers are the mainstay of scar treatment, providing itch relief to some extent. In contrast to antihistamines, the use of moisturisers did not decrease over time. Dry skin is a frequently observed problem during burn rehabilitation and particularly related to grafted wound sites (3), possibly resulting from e.g., an increased transepidermal water loss or destroyed sebaceous glands. Alterations in the barrier function of dry skin, such as stratum corneum abnormalities in keratinisation, surface lipid content, and water content may contribute to the sensation of itch. Emollients help restore this altered barrier function and therefore may contribute to symptomatic relief (32).

Limitations of the present study: Firstly, the rate of patients lost-to-follow up was substantial. Although this study is relatively large, the sample size may still be too small to find statistically significant findings on body location level, especially in body parts that were less frequently affected. Furthermore, the question about provoking and aggravating factors was accompanied by a list of examples. This may have guided the respondents' answer and therefore, other factors may have been overlooked.

In conclusion, this study emphasises the influence of skin grafting on itch intensity. Starting at the 3

months measurement, consistently higher itch intensity in patients with grafted areas was found across time. The variation in triggers and the responses to available therapeutic modalities could not be linked to the depth of the burn. More research is needed to further elucidate the itch processes in grafted areas that may induce long-term central mechanisms.

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