

Laser Doppler Perfusion Imaging (LDPI) and Transepidermal Water Loss (TEWL) Values in Psoriatic Lesions Treated with Narrow Band UVB Phototherapy. Dermal Vasculature may be useful Indicator of Psoriatic Activity

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Abstract

Objective: This study attempts to objectively measure physiological changes in transepidermal water loss (TEWL), an indicator of skin barrier function and laser Doppler perfusion index (LDPI) an indicator of skin vascularity, of psoriatic skin lesions following treatment to narrow-band ultraviolet B (UVB) phototherapy using the psoriasis severity (PS) score as a measurement of clinical phototherapy response. **Materials and Methods:** Fourteen patients with established diagnosis of plaque type psoriasis were studied. The patients received narrow band UVB phototherapy 3 times a week until clearance of their psoriasis and the frequencies are reduced as clearance is observed. Two psoriasis plaques (“lesional skin”) were used to measure treatment response and another 2 areas of uninvolved (“non-lesional skin”) on the corresponding opposite limbs were identified for comparison. PS score, TEWL and LDPI were carried out at baseline (0 week), 2 weeks and 8 weeks during treatment. Measurements were carried out just before each phototherapy session and repeated 1 hour after phototherapy treatment. **Results:** The mean PS score decreased by almost 40% after 2 months phototherapy ($t = 2.44, P = 0.028$). There was no significant difference in PS score between week 0 and week 2, or between week 2 and week 8. After phototherapy, there was no significant difference in LDPI values on the psoriatic lesional skin between week 0 and week 8 or between week 2 and week 8. It appears that phototherapy does not induce inflammation on non-lesional skin to provoke measurable LDPI changes. The mean TEWL values of psoriatic lesional skin were significantly higher than normal skin throughout the study period before and during phototherapy (week 0, $t = 5.71, P = 0.000$, week 2, $t = 9.29, P = 0.00$, week 8, $t = 6.93, P = 0.000$). It appears that the skin barrier function of psoriatic skin improves only minimally as psoriatic lesions improve clinically (as evidenced by the reduction in PS scores) with narrow-band UVB phototherapy, but the dermal vascularity and blood flow and barrier function of the psoriatic skin remained abnormal. **Conclusion:** It appears that LDPI and TEWL measurement may not be a good surrogate marker of clinical response to narrow-band UVB phototherapy.

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Key words: Psoriasis, Skin physiology, Skin vascularity, Treatment response

Introduction

Non-invasive techniques have become useful procedures in measuring skin physiology and skin response to treatment. This study attempts to objectively measure physiological changes in transepidermal water loss (TEWL), an indicator of skin barrier function, and laser Doppler perfusion imaging (LDPI), an indicator of dermal vascularity, of psoriatic skin lesions following treatment to narrow-band ultraviolet B (UVB) phototherapy using the psoriasis severity (PS) score as a measurement of clinical phototherapy response. It is known that in psoriasis lesions there are perturbation in the epidermal

characteristics including its skin barrier, stratum corneum and ceramide contents^{1,2} that may result in abnormal TEWL. Similarly, it is known that dermal vascularity and capillary blood flow are increased in psoriatic lesions.^{3,4} Treatment of psoriasis leads to reduction in scaliness and infiltration of the skin lesions and reported to lead to a reduction in erythema and dermal capillary blood flows.⁵ The effects of the dermal vascularity appear to play an important role in the manifestation of psoriasis skin lesions. Psoriasis is an immunological disorder with dysfunction Th1 T-lymphocytes. Cytokines derived from these T-lymphocytes are known to affect keratinocytes

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proliferations and angiogenesis that leads to morphologic skin changes in psoriasis.^{6,7}

This study attempts to objectively measure physiological changes in TEWL and LDPI following treatment response to narrow-band UVB treatment of psoriatic lesions using the PS score as clinical response to treatment. The findings will assist us in understanding the patho-mechanism in the evolution of psoriasis skin lesion in response to treatment.

Materials and Methods

Fourteen patients with established diagnosis of plaque type psoriasis were recruited into the study. Only patients receiving phototherapy for the first time and patients who last had phototherapy more than 6 months ago were included in this study. The treatment regimen for the narrow-band UVB (Philips TLO1, Netherlands) phototherapy was based on a standard protocol described elsewhere⁸⁻¹⁰ where treatment was started after determination of minimal erythema dose (MED). Patients received phototherapy 3 times a week until clearance of their psoriasis following which treatment frequencies were reduced. Patients continued to receive emollients while under phototherapy. This was applied at night and was washed off when the patient return for phototherapy the next morning or afternoon.

During the study, 2 psoriasis plaques (“lesional skin” – each about 4 square cm) on the limbs were identified and used to measure treatment response and another 2 areas of uninvolved normal-looking skin (“non-lesional skin”) on the corresponding opposite limbs were identified for treatment response on “non-lesional” skin for comparison.

The following measurements were carried out at baseline (0 week), 2 weeks and 8 weeks during treatment, *viz.* (a) PS score (11); (b) TEWL and (c) LDPI. Measurements were carried out before each phototherapy session (“before phototherapy”) and repeated 1 hour after phototherapy treatment (“post-phototherapy”) on “lesional” and “non-lesional” skin. Measurements were carried out on the 2 psoriatic “lesional” skin and 2 patches of “non-lesional” skin and the average values of the 2 recordings were considered the actual value for the “lesional” and “non-lesional” skin respectively. The lesional and non-lesional skin to be studied are marked by anatomical points and the same areas of the skin are measured during each review visit.

PS score¹¹

Each study plaque was assessed based on the degree of erythema, induration and desquamation of the lesion. Each of these 3 parameters was given a score of 0 (for absence of sign) to 4 (for very marked sign). Therefore, each plaque may have a maximum score of 12 and the average value from the 2 target plaques was used in analysis of the study.

LDPI^{12,13}

The principle of laser Doppler perfusion imager is based on the Doppler effect on monochromatic radiation caused by

erythrocytes in motion in the microvascular network. A Helium-Neon laser is moved over the surface to be examined. When the laser beam is reflected by the erythrocytes, the returning signal is recorded in the head of the scanner and translated into an electrical impulse; a scale of 6 colours demonstrates increasing degrees of perfusion in colours of blue, green, yellow and red. In our study the perfusion was measured using the LISCA LDPI (LISCA, Sweden), which rapidly measures blood flux over a large area without contact with the skin surface.^{12,13} All measurements were conducted at a scanning distance of 15 cm. The mean perfusion was calculated from 264 pixels the borders of the measured areas were marked before measurement.

TEWL¹⁴

Transepidermal water loss was measured with Tewameter (Dermalab, Pennsylvania USA). TEWL values were registered in g/m²/h after equilibration of the probe on the skin 120 seconds. TEWL values are a reflection of skin barrier function. It generally reflects integrity of the stratum corneum.¹⁴

The phototherapy treatment response of the psoriasis plaques and non-lesional skin were assessed using PS score. The LDPI and TEWL values were also measured during the course of phototherapy and compared to the corresponding PS scores. Patients were follow-up and studied over 8 weeks.

Paired Student’s *t*-tests were used for statistical analysis. *P* values of less than 0.05 were considered statistically significant. Paired *t*-test was used to compare mean LDPI measurements taken from different areas (ie. lesional and non-lesional skin), at different time during the study (at 0 week, 2 weeks and 8 weeks) just before and 1 hour after phototherapy.

Results

Fourteen psoriasis patients participated in the study. Their mean age was 40.1 (range, 30 to 62) years. There were 13 males and 2 females. There were 10 Chinese, 4 Indians and 1 Malay.

Table I shows the corresponding mean LDPI, TEWL and PS scores of the 14 patients before and after 8 weeks of narrow-band UVB phototherapy. The mean PS scores were compared with the mean LDPI and TEWL values taken from psoriatic lesional skin and non-lesional skin at baseline (0 week), 2 weeks and 8 weeks after starting phototherapy.

It can be seen that the mean PS score for psoriatic lesional skin improves progressively following phototherapy. The mean PS score decreased by almost 40% following 8 weeks phototherapy ($t = 2.44$, $P = 0.03$). However, there was no significant difference in PS score between week 2 and week 8. There was a corresponding decline in mean LDPI value at 2 weeks after phototherapy on the psoriatic lesional skin, but the LDPI score did not continue to decline further after the second week although mean PS score continued to decline. The mean LDPI value of psoriatic lesional skin declined at 2 weeks following phototherapy ($t = 2.233$, $P = 0.044$), but rebounded and increased to baseline value at 8 weeks, indicating a “dermal revascularisation” and increased blood flow had occurred although clinically the psoriatic lesions have improved.

There was no significant difference in LDPI values on psoriatic lesional skin between week 0 and week 8 and week 2 and week 8.

There was no significant difference in LDPI values of non-lesional skin throughout the study period, indicating that phototherapy did not induce any significant change in dermal vascularity and blood flow on normal skin. The mean LDPI values of psoriatic lesional skin were consistently and significantly higher than non-lesional skin throughout the 8-week study period, indicating increased dermal vascularity and blood flow in psoriatic lesions (week 0, $t = 5.63$, $P = 0.00$; week 2, $t = 4.62$, $P = 0.00$; and week 8, $t = 4.12$, $P = 0.001$). The findings indicated that the dermal vascularity and blood flow of non-lesional skin in psoriatic patients are different from psoriatic lesional skin. As expected, there was no difference in LDPI score before and after phototherapy on non-lesional skin.

The mean TEWL values of psoriatic lesional skin were significantly higher than non-lesional skin throughout the study period before and during phototherapy (week 0, $t = 5.71$, $P = 0.000$; week 2, $t = 9.29$, $P = 0.00$; week 8, $t = 6.93$, $P = 0.000$). Similar to the LDPI value there was only a slight decrease in mean TEWL values corresponding to the reduction in PS scores (but the differences were not statistically significant) over the 8-week study period. It appears that the skin barrier function of psoriatic skin improved only minimally as psoriatic lesions improved clinically with phototherapy, whereas the dermal vascularity and blood flow and barrier function of the psoriatic skin remained abnormal compared to non-lesional skin. As expected, there was no significant change in the TEWL values of non-lesional skin throughout the study period, indicating that the barrier function of non-lesional skin is different from psoriatic lesional skin.

During the study period, comparisons were made between the PS scores and TEWL values of lesional and non-lesional skin just before phototherapy and immediately after phototherapy during each visit and these showed no statistical differences.

Discussion

The patho-mechanism of psoriasis skin lesions is not clearly understood. The local and systemic triggering factors of psoriatic lesions are unknown, but T-lymphocytes derangement and cytokines are believed to play an important part in the appearance of psoriasis lesions.^{7,15-18}

Psoriasis is a chronic inflammatory skin disease in which epidermal proliferation is closely associated with excessive microvascular expansion within the papillary dermis. Studies have shown that there is a derangement of vasculatures in the upper subpapillary dermal capillaries in psoriasis lesions.¹⁹ Cytokines play an important role in inducing endothelial cells growth and proliferation.¹⁹⁻²³ For example, angiotensin 1 induces Tie2 signalling as a receptor activator and maintains blood vessel formation, whereas angiotensin 2 destabilises vessels by blocking Tie2 signalling as an antagonist of angiotensin 1 and acts with vascular endothelial growth factor to initiate angiogenesis. In an earlier study, the role of angiotensins and the Tie2 receptor in vascular changes of psoriasis showed that angiotensin 1, angiotensin 2, and Tie2 were upregulated in involved psoriatic lesional skin compared to non-lesional psoriatic skin, suggesting that upregulation of angiotensin 1, angiotensin 2, and Tie2 was closely associated with the development of microvascular proliferation in psoriasis, and that the angiotensin-Tie2 system may act coordinately with vascular endothelial growth factor and basic fibroblast growth factor to promote neovascularisation in

Table 1. Corresponding Mean LDPI, TEWL and PS Scores of the 15 Patients Before and After 2 Months of Phototherapy

	Lesional skin (Before phototherapy)*		Lesional skin (After phototherapy)*		Normal skin (Before phototherapy)	Normal skin (After phototherapy)
	LDPI (SD)	PS (SD)	LDPI (SD)	PS (SD)	LDPI (SD)	LDPI (SD)
LDPI (n = 14)						
0 week	2.53 (1.43)	3.71 (3.08)	1.96 (1.34)	3.66 (3.21)	0.91 (0.45)	0.92 (0.61)
2 week	1.87 (1.05)	2.75 (1.97)	1.48 (0.43)	2.97 (2.28)	0.78 (0.40)	0.72 (0.22)
8 week	2.04 (0.84)	2.17 (1.73)	2.04 (0.95)	2.06 (1.56)	1.07 (0.87)	1.13 (0.97)
	(ns)	($P < 0.03$)	(ns)	($P < 0.03$)	(ns)	(ns)
TEWL (n = 14)	TEWL (SD)	PS (SD)	TEWL (SD)	PS (SD)	TEWL (SD)	TEWL (SD)
0 week	21.09 (7.18)	3.71 (3.08)	21.59 (6.24)	3.66 (3.21)	10.25 (3.73)	11.71 (5.02)
2 week	19.06 (1.00)	2.75 (1.97)	20.13 (6.82)	2.97 (2.28)	8.61 (3.45)	11.59 (5.81)
8 week	19.05 (3.72)	2.17 (1.73)	22.69 (6.57)	2.06 (1.56)	9.76 (3.51)	11.12 (6.29)
	(ns)	($P < 0.03$)	(ns)	($P < 0.03$)	(ns)	(ns)

*LDPI and TEWL of psoriatic lesional skin were significantly higher than that of non-lesional skin.

LDPI: laser Doppler perfusion imaging, PS: psoriasis severity, TEWL: transepidermal water loss

psoriasis. The study also indicated that successful antipsoriatic treatment was accompanied by noticeable reduction of angiopoietin 2 expression, suggesting that alteration of angiopoietin 2 expression may be particularly important in controlling vascular proliferation in the treatment of psoriasis.²³

Our study confirmed that there was a significant increase in the dermal vascularity and blood flow and derangement in barrier functions of psoriatic lesions compared to non-lesional skin. Our findings are similar to those reported by Suh et al⁵ where the authors reported significant higher capillary blood flows and erythema of psoriatic than non-psoriatic lesions.

Our study indicated that after 8 weeks of phototherapy, when significant clinical improvement in PS score of psoriasis plaques was observed, the LDPI and TEWL values did not improve significantly. Our study showed that there were significant differences in dermal vascularity and blood flow and barrier functions of psoriatic lesions compared to non-lesional skin, and these differences were maintained over time as the patients underwent phototherapy. Our findings concur with an earlier finding where dermal vascularity and blood flow on psoriatic lesional skin continued to persist despite clinical improvement following phototherapy;²⁴ the authors had suggested that the persistence of increased vascularity despite clinical improvement was due to the effects of inflammation following phototherapy.²³ However contrary to our findings, Suh et al⁵ reported that dermal vascularity and blood flow continued to decline with phototherapy. The difference could be due to (a) the different methods of measuring dermal vascularity and blood flow. They had used the laser Doppler flowmetry using the Periflux 4001 Master which measured capillary blood flow and arteriolar regulatory tone, whereas our LDPI measurement using the Lisca computerised imaging system appears to be more sensitive in measuring superficial dermal capillary blood flow, (b) duration and mode of phototherapy where their patients were treated with PUVA and (c) their shorter duration of treatment (5 weeks).

There are 3 possibilities to account for the rebound in higher dermal vascularity and blood flow following phototherapy of psoriatic lesions *viz.* (a) inflammation following phototherapy, (b) following the clearance of thick scales which mask measurements, and (c) effects of cytokines on angiogenesis and vascular proliferation due to persistent presence of deranged T-cells and cytokines secretion on psoriatic skin.^{3,19-21}

The role of deranged T-cells and cytokines in psoriatic lesions in causing increased vascularity is further supported by its response to pulsed dye laser (PDL) treatment. Psoriatic lesions improve with pulsed dye laser treatment where the psoriatic lesions are cleared transiently with treatment when the vascularity is destroyed. However, the remission in PDL treated lesions is usually transient.^{21,24} Studies have shown that the persistent secretion of cytokines on treated psoriatic lesions were responsible for endothelial re-proliferation causing a rebound in vascularity and return of psoriasis.²¹ In the study, the effect of the PDL was limited to the superficial capillary bed, with no changes in the microvessels (including venules

and arterioles) of the upper reticular dermis. Although there was significant clinical improvement in plaques after PDL treatment, complete clearance of lesions was not achieved. Thermolysis of psoriatic capillaries caused a significant reduction in both endothelial surface area and endothelial cell proliferation in the superficial dermis. Endothelial expression of surface adhesion molecules (integrins and E-selectin) important in angiogenesis was not, however, altered by treatment. The CD4+ and CD8+ T-cell infiltrate was significantly reduced in the superficial papillary dermis, but not in the epidermis or upper reticular dermis. Laser treatment significantly reduced epidermal thickness, but did not alter epidermal keratinocyte proliferation. Their results demonstrated that dermal capillary changes alone are unlikely to be causal in psoriasis. They indicated that the expanded psoriatic capillaries may be important in facilitating the access of activated T cells to the skin and in maintaining the psoriatic plaque. These results supported the consensus view that plaque formation may be mediated by the release of growth factors/cytokines from activated epidermal T cells/keratinocytes.²¹

Our findings appear to indicate that LDPI and TEWL measurements may not be useful objective indicator to treatment response in psoriasis. One limitation to our study is the short follow-up period. Perhaps further phototherapy in our patients could lead to further clinical improvements in psoriatic lesions and improvements in barrier skin function and dermal vascular changes.

However of significance in our study, is the persistent increased in dermal vascularity and blood flow and abnormal barrier function deficiency in treated psoriatic skin lesions even when the clinical response is observed (based on PS score). It would appear that activated T-cells and cytokines and other mediator of psoriasis had continued to exert its effects on psoriasis skin even with phototherapy. Novel treatment using monoclonal antibodies against activated T-cells and the relevant cytokines are now being studied.^{3,17-20} Its effects on dermal vascularity and skin barrier functions may offer an answer as to its role in the pathogenesis of psoriasis.

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