

The effectiveness of Narrow Band Ultraviolet B Phototherapy in Treatment-Resistant Hemodialysis-Associated Pruritus in Iraqi Patients

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Abstract

Background: Hemodialysis-associated pruritus is a common disabling symptom affecting approximately 22-90% of patients undergoing maintenance hemodialysis. For patients who do not respond to conventional treatments, narrow band ultraviolet B phototherapy (NB-UVB) has demonstrated favorable therapeutic effects.

Aim: To evaluate the effectiveness of NB-UVB phototherapy in treatment-resistant hemodialysis-associated pruritus.

Patients and Methods: Eighteen patients who were unresponsive to conventional treatments including emollient zinc castor oil or antihistamines received NB-UVB phototherapy three times a week for 6 weeks. Pruritus intensity was assessed using the Visual Analogue Scale (VAS) and the 5D-itch scale at baseline, 3 weeks and 6 weeks of treatment, and 6 weeks after treatment cessation.

Results: The VAS improved from 7.1 ± 0.31 at baseline to 3.7 ± 0.52 , $p < 0.001$ and the 5-D itch score improved from 17.6 ± 0.65 before to 9.5 ± 1.24 , $p < 0.001$, 6 weeks after NB-UVB treatment. Relief from pruritus was maintained for 6-weeks after treatment cessation in 77.8% of patients. Side effects were tolerable and did not lead to treatment modification.

Conclusions: NB-UVB is an effective treatment in patients with hemodialysis-associated pruritus with no significant side effects. A larger randomized blinded trial is needed to establish it as a treatment option.

Keywords: Pruritus, phototherapy, Narrow band UVB, hemodialysis.

Introduction

Hemodialysis-associated pruritus is one of the most common and distressing cutaneous symptoms of chronic kidney disease (CKD). It is defined as a localized or generalized, paroxysmal symptom occurring in a patient with end-stage renal disease (ESRD). (1) ESRD is defined as "renal insufficiency requiring dialysis or kidney transplantation for survival. (2)

The prevalence and incidence of CKD has increased dramatically worldwide, making it a major public health issue. (3) The prevalence of CKD-associated pruritus varies substantially, ranging from 22% to 90%. (4) With a few exceptions, the majority of reports have shown that CKD-associated pruritus is independent of sex, age, ethnicity, type of dialysis and the etiology of renal disease. (4) The clinical characteristics of patients with CKD-associated pruritus varies over time, location and severity.

Common exacerbating factors include rest, dry skin, heat, sweat and stress. Major alleviating factors include activity, cold ambient temperatures and cold showers. (4) In patients with CKD, primary skin lesions are rare. Secondary skin lesions occur and include excoriations, impetigo, linear crusts, papules and ulcerations. The pathophysiology of CKD-associated pruritus remains poorly understood. (5) Proposed mechanisms include activation of the immune and opioidergic systems, divalent ions, disturbed epidermal barrier, neuropathic mechanisms, alterations in skin mast cells and histamine levels, parathyroid hormone excess, vitamin A and retinol-binding protein. Because of multiple pathways that could be responsible for pruritus in CKD, its treatment has proven to be particularly difficult. Numerous current therapies in use include emollients, topical calcineurin inhibitors, topical steroids, topical capsaicin, oral antihistamines, gabapentin and others.

However, no definitive therapy has been established. (6)

Several studies have proposed use of phototherapy for CKD-induced pruritus. Controlled studies using UVA (320-400) have not shown benefit, (7) whereas broadband UVB phototherapy has been generally but not uniformly shown to be effective. Narrowband UVB (NB-UVB), that has a narrow spectrum of emission (310-315nm wavelength, peak 311 nm)(8) has been shown in several studies to be safe and effective although its mechanism of action remains to be defined. Its therapeutic action may involve effects on cell cycle kinetics involving urocanic acid, inhibition of DNA synthesis, alterations in cytokine expression, effects on mast cells resulting in apoptosis and suppression of histamine release, immunomodulation via its actions on lymphocytes, natural killer cells and antigen presenting cells,(9) reduction of skin divalent ions and alteration of the cutaneous nerve.(10,11,12) Herein, we aimed to evaluate the effectiveness of NB-UVB phototherapy in treatment-resistant hemodialysis-associated pruritus.

Methods

An unblinded, non-randomized study of NB-UVB therapy was performed in patients with hemodialysis-associated pruritus in the Department of Dermatology and Venereology at Al-Sader Teaching Hospital and the Laser Research Unit at the College of Medicine, University of Kufa, Iraq between October 2015 and October 2016. Ethical approval was obtained from the Scientific Council of Dermatology and Venereology- Iraqi Board of Medical Specializations.

Patients:

Eighteen patients with hemodialysis-associated pruritus with skin type III-V. Type III sometimes mild burn, tans uniformly; type IV burns minimally, always tans well, moderate brown and Type V very rarely burns, tans very easily, dark brown (1) were enrolled after providing written informed consent.

Inclusion Criteria:

1. Aged 18 years or older
2. ESRD on maintenance hemodialysis for more than 3 months. All patients were on thrice weekly outpatient maintenance hemodialysis schedule with regular monitoring of blood urea, serum creatinine, complete blood count, serum ferritin, serum calcium, and phosphorus.
3. Onset of pruritus after ESRD diagnosis.
4. Unresponsive to the conventional treatments including emollients (zinc castor oil) twice daily and antihistamines (diphenhydramine 25 mg PO BID) for a total period of 6 weeks.

Exclusion criteria:

1. Pruritus due to other dermatological causes.
2. Systemic disorders that can cause pruritus including hepatic disorders, malignancies, myeloproliferative disorders, uncontrolled diabetes and hematologic disorders including anemia with a hemoglobin level <10 g/dL.
3. Parathormone level >520 pg/mL, serum calcium > 10.2 mg/dL.
4. Pregnancy; lactation.
5. History of cutaneous photosensitivity, eye cataract or skin cancers.

A complete history was obtained including age, gender, history of present illness, duration of haemodialysis, the onset of pruritus and its duration, generalized or localized, periodicity (constant, paroxysmal), severity, ameliorating and exacerbating factors, personal history, family history, and response to previous therapy. A complete dermatological examination included description of excoriations, linear crust, lichenifications, scaly or crusted nodules, abrasions and keratotic papules. The Fitzpatrick's skin phenotype was assessed.

Treatment protocol:

Forty-two patients with hemodialysis-associated pruritus received conventional treatment with emollients (zinc castor oil) twice daily and antihistamines in the form of diphenhydramine 25 mg PO BID for a total period of 6 weeks. Thirteen patients responded to the conventional treatment and 29 patients who were unresponsive were included in the study and received NB-UVB phototherapy which was administered 3-times a week and was scheduled on the hemodialysis days while being maintained on their prior antipruritic treatment for a total period of 6 weeks.

NB-UVB Phototherapy:

A full explanation about the nature, course, duration and potential complications of the treatment was provided. The genital area was protected and the eyes were protected with UVB-blocking goggles. Because topical agents may block NB-UVB effects, patients were requested to apply topical emollients after UVB treatment. The NB-UVB treatments were administered using a special cabinet (Waldmann-Germany). The initial dose was (0.2j/cm²) and further doses were adjusted according to the maximum erythema occurring at the previous session, determined by patient report and by physical examination. If there was no erythema after starting dose, a 20% increment was used for the next dose. If minimal erythema occurred, a 20% increment was used after every other treatment. If persistent asymptomatic erythema occurred, no further increase

in dose occurred. If erythema occurred with pain and blistering, sessions were discontinued until erythema faded and symptoms subsided. The dose was reduced by 50% from the last dose and if tolerated, was further increased by 10% in the subsequent sessions.

Assessments:

Pruritus severity was assessed using the VAS and 5D itch scales. Subjects were asked to rate their pruritus on a scale of 0 to 10, where a score of 0 corresponded to no pruritus and a score of 10 to severe pruritus. The 5D itch scale included five dimensions of the degree, duration, direction, disability and distribution of pruritus. The scores of each of the five domains were summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus). Single-item domain scores (duration, degree and direction) are equal to the value indicated below the response choice (range 1–5). The disability domain includes four items that assess the impact of itching on daily activities: sleep, leisure/social activities, housework and work/school. The score for the disability domain is computed as the highest score on any of the four items. Taking an average score of all the four items was not used as this may underestimate the impact of itching on daily activities. For the distribution domain, the number of affected body parts was tallied (potential sum 0–16) and the sum was sorted into five scoring bins: sum of 0–2 = score of 1, sum of 3–5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5. The pruritus intensity was measured at baseline, at 3 weeks, at the end of treatment (6 weeks) and after another 6 weeks of follow-up. The patient was considered a responder if there was a reduction in the 5D score of 50% or more or if the minimum score of 5 was recorded (corresponding to no pruritus). Recurrence was considered if there was a return of the 5D score to/above the baseline value. Adverse effects were assessed as immediate or delayed complications and recorded at each visit, including erythema, burning of skin, hyperpigmentation and blistering.

Statistical analysis:

Statistical analysis was performed using the SPSS (statistical package for social sciences) version 20. Paired T-testing was used to compare numerical variables before and after treatment. A P value of ≤0.05 was considered significant. ANOVA test was used to compare the means of different groups

Results

Twenty-nine patients were enrolled in the study and 18 completed all sessions of treatment. Eleven patients defaulted from the study for a variety of reasons. Two patients died, one patient developed deep vein thrombosis of the right leg, three patients transferred to another dialysis center and others were non-compliant with the treatment schedule. Of the subjects completing the treatment schedule, 12 (66.7%) were male, median age was 55 years (range 41–66) and the median duration of dialysis was 16 months (Table 1).

Table 1: Demographic characteristics

Variable	Patients		
	No.	%	
Age (years)	≤ 40	4	22.2
	41 – 50	4	22.2
	51 – 60	3	16.7
	> 60	7	38.9
	<i>Median (IQR)</i>	55 (41 – 66)	
Gender	Male	12	66.7
	Female	6	33.3
Duration of dialysis (Month)	≤ 12	7	38.9
	13 - 24	5	27.8
	> 24	6	33.3
	<i>Median</i>	16 (8 – 30)	

Type of skin was III-V. Pruritus was moderate or severe in severity based on the VAS score (Table 2).

Table 2: Severity of pruritus according to VAS of both studied groups

Baseline	Patients	
	No.	%
Mild	0	0
Moderate	6	33.3
Severe	12	66.7
Total	18	100

The VAS score reduced significantly by $47.9 \pm 7.2\%$ from 7.1 ± 0.31 before NB-UVB to 3.7 ± 0.52 , $p < 0.001$ after 6 weeks of treatment. The 5-D itch score was similarly reduced by $46.1 \pm 6.5\%$, from 17.6 ± 0.65 before to 9.5 ± 1.24 , $p < 0.001$ after therapy. Six weeks after treatment cessation, 14 patients (77.8%) remained free of pruritus, whereas 5 (35.7%) patients relapsed.

Approximately half of the subjects developed sedation, 1 patient developed mild erythema that settled spontaneously and 5 patients developed transient hyperpigmentation that improved at the end of the follow-up period. No one terminated treatment as a result of adverse effects.

Discussion

Pruritus is one of the most common and distressing cutaneous symptoms of CKD. Herein we show that NB-UVB is effective in reducing treatment-resistant hemodialysis-associated pruritus. Both the VAS and 5D itch scores significantly improved with a 77.8% response rate. Relapse of itching 6 weeks after stopping treatment occurred in approximately a third of our subjects.

Phototherapy has been tested in many studies as a treatment option for renal pruritus. Ada et al. tested efficacy of NB-UVB in 20 Turkish patients with renal pruritus with a 6-week treatment period using NB-UVB given three times a week as in our study. Among the 10 patients who completed the study, 8 responded and reported a 70.8% reduction in the VAS score, (13) findings that are comparable to our study. Seckin et al. found that 8-weeks of NB-UVB phototherapy given three times a week significantly relieved pruritus in 17 ESRD patients with a response rate of 60% and relapse rate of 66.7%. (14) In a randomized study of 42 patients with renal pruritus from Taiwan, the intervention group received NB-UVB phototherapy 3-times a week for 2 weeks while the control participants were maintained on prior antipruritic treatment. Renal pruritus was reduced by 68.4% in the treated compared to no significant change in the control group. (15) Ko et al. conducted a randomized controlled trial where 11 patients with refractory uremic pruritus received NB-UVB and the 10 controls received time-matched exposures to long-wave UVA. There was no difference between groups in the VAS score at the end of therapy with both groups reporting significant reductions in pruritus intensity. The authors concluded that the benefits of NB-UVB phototherapy may be due to a placebo effect in unblinded studies. However, it is possible that the UVA (6–18 J/cm² each time) used in the controls may have also had a therapeutic effect on pruritus. (16)

Narrowband UVB can be beneficial in various forms of pruritus, particularly in cases of idiopathic etiology and in those associated with diabetes and hepatic disorders. (17) Availability of full body NB-UVB cabinets in many Iraqi cities provides the potential for this new mode of treatment for hemodialysis-associated and other types of pruritus.

The limitation of this study include the limited sample size, single site investigation, significant incompleteness rate, and importantly the lack of a control group. However, the assessment of the responses and adverse effects was obtained by written questionnaires before, during and after treatment sessions. A larger randomized double-

blinded study will need to be performed to confirm the findings of this investigation.

Conclusions:

NB-UVB may be an effective treatment in patients with treatment-resistant hemodialysis-associated pruritus with minimal rate of adverse effects. A larger randomized blinded study is required to establish its role in this population.

Sources of Funding: None.

Disclosures: None.

References

1. Weisshaar, E., Fleischer Jr, A. B., Bernhard, J. D., & Cropley, T. G. (2012). Pruritus and dysesthesia. In: Bologna JL, Jorizzo JL, Schaffer JV (eds). *Dermatology*, 3rd ed. Mosby Elsevier, USA, 2012; 1, 6: 111-124.
2. Levey AS, Coresh J. Chronic kidney disease. *The Lancet*. 2012; 379(9811):165-80.
3. Robinson BE. Epidemiology of chronic kidney disease and anemia. *J Am Med Dir Assoc*. 2006; 7(9):S3-6.
4. Mistik S, Utas S, Ferahbas A, et al. An epidemiology study of patients with uremic pruritus. *J Eur Acad Dermatol Venereol*. 2006 20:672-678.
5. Kimmel M, Alschner DM, Dunst R, Braun N, Machleidt C, Kiefer T, Stülten C, van der Kuip H, Pauli-Magnus C, Raub U, Kuhlmann U. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transplant*. 2006; 21(3):749-55.
6. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. *Am J Kidney Dis*. 2007; 50(1):11-20.
7. Berger TG, Steinhoff M. Pruritus and renal failure. In *Semin Cutan Med Surg*. 2011; 30(2):99-100.
8. Nicolaidou E, Antoniou C, Stratigos AJ, Stefanaki C, Katsambas AD. Efficacy, predictors of response, and long-term follow-up in patients with vitiligo treated with narrowband UVB phototherapy. *J Am Acad Dermatol*. 2007; 56(2):274-8.
9. Shintani Y, Yasuda Y, Kobayashi K, Maeda A, Morita A. Narrowband ultraviolet B radiation suppresses contact hypersensitivity. *Photodermatol Photoimmunol Photomed*. 2008; 24(1):32-7.
10. Lugin JR. Uremic pruritus: a review. *Hemodial Int*. 2005; 9(2):180-8.
11. Gill DS, Fonseca VA, Barradas MA, Balliod R, Moorhead JF, Dandona P. Plasma histamine in patients with chronic renal failure and nephrotic syndrome. *J Clin Pathol*. 1991; 44(3):243-5.
12. Wallengren J, Sundler F. Phototherapy reduces the number of epidermal and CGRP-positive dermal nerve fibres. *Acta Derm Venereol*. 2004; 84(2):111-5.
13. Ada S, Seçkin D, Budakoğlu İ, Özdemir FN. Treatment of uremic pruritus with narrowband ultraviolet B phototherapy: an open pilot study. *J Am Acad Dermatol*. 2005; 53(1):149-51.

14. Seckin D, Demircay Z, Akin O. Generalized pruritus treated with narrowband UVB. *Inter J dermatol.* 2007; 46(4):367-70.
15. Wang TJ, Lan LC, Lu CS, Lin KC, Tung HH, Wu SF, Liang SY. Efficacy of narrowband ultraviolet phototherapy on renal pruritus. *J Clin Nurs.* 2014; 23(11-12):1593-602.
16. Hindson C, Taylor A, Martin A, Downey A. UVA light for relief of uraemic pruritus. *The Lancet.* 1981; 317(8213):215.
17. Weisshaar, E., Fleischer Jr, A. B., Bernhard, J. D., & Cropley, T. G. (2012). Ultraviolet Therapy. In: Bologna JL, Jorizzo JL, Schaffer JV (eds). *Dermatology*, 3rd ed. Mosby Elsevier, USA, 2012; 1, 134: 2219-35.