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Treatment of Hemodialysis-associated Pruritus with Narrow Band Ultraviolet B Phototherapy (NB-UVB) alone vs. Combined NB-UVB and Gabapentin

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ABSTRACT

Many of renal failure patients on hemodialysis suffer from itching. Treatment options of such cases are diverse and variable responses are recorded. The most frequently used therapy is UVB phototherapy, eliciting favorable response in most of patients. Promising results have also been obtained by treatment with the anticonvulsant gabapentin. This study aimed to assess the effectiveness of combined treatment of Hemodialysis-associated Pruritus (HAP) with NB-UVB and gabapentin therapy versus NB-UVB alone. Forty eight cases of HAP were enrolled in this study. Cases were randomized into two groups; the 1st group was treated with NB-UVB alone on three sessions' bases /week and included 24 patients and was termed as "the control group". The second group was treated with combined NB-UVB sessions on the same bases (3 sessions/week) with addition of gabapentin 300 mg -as a single dose after each hemodialysis session for a similar period (6 weeks) and included another 24 cases and was termed as "the study group". After treatment, patients were followed up for 6 months for recurrence of pruritus. For every case, the assessment of pruritus was done using the 5-D itch scale, before treatment, at the end of treatment and after 6 months post-treatment for recurrence. A patient was considered as a responder to treatment if he showed 50% or more reduction of his baseline 5-D itch scale at the end of treatment period. Return of the score to/or above the baseline levels after 6 months follow up was used to mark recurrence. Twenty two cases of the control group and twenty one cases of the study group completed the study. In the control group, 14 patients were responders to NB-UVB alone (63.64%) while 8 cases (36.36%) were non-responders. In the study group, 16 cases were responders to combined NB-UVB and gabapentin (76.19%) while 5 patients (23.81%) were non-responders. No statistically significant difference was found between the response rates in both groups ($p > 0.05$). After 6 months follow up, 8 responders in the control group (57.14%) and 2 responders in the study group (12.5%) developed recurrence of pruritus and this was statistically significant ($p < 0.05$). Response to gabapentin and NB-UVB was not significantly superior to NB-UVB alone in treatment of HAP. However, this mode of therapy significantly reduces the rate of recurrence of pruritus.

Key words: Uremic pruritus, hemodialysis, gabapentin, narrow band ultraviolet B phototherapy

INTRODUCTION

Pruritus is an unpleasant sensation that induces a desire to scratch. It is a common symptom of many skin and systemic diseases such as dermatitis, malignancy, endocrine disorders,

myelo-proliferative disease, psychiatric and neurologic diseases (Schwartz and Iana, 1999). In patients with chronic kidney disease, pruritus presents a severe and distressing symptom which affects their sleep and quality of life (Pisoni *et al.*, 2006). Since episodes of uraemic pruritus have been reported to occur more often at night, it is expected that pruritus could have a negative impact upon sleep quality and ultimately affect physical and mental functioning (Yosipovitch *et al.*, 2001). Pruritus is a frequent and troublesome symptom in patients with chronic renal failure receiving hemodialysis. However, it also may occur in patients on conservative uremia treatment or undergoing continuous ambulatory peritoneal dialysis (Urbonas *et al.*, 2001).

Because of the use of biocompatible hemodialysis membranes and the improvement in hemodialysis efficacy, the incidence of uraemic pruritus has declined over years, from an estimated 85% in the 1970s and 50-60% in the 1980s to an estimated incidence of 22% (Mettang *et al.*, 2002). In about 25% of patients with HAP, symptoms are most severe during or immediately after dialysis (Gilchrest *et al.*, 1982).

The mechanism underlying HAP is poorly understood; current theories include secondary hyperparathyroidism, divalent-ion abnormalities, histamine release, allergic sensitization, proliferation of skin mast cells, iron deficiency anemia, hyper-vitaminosis A, xerosis, opioid system involvement, cytokines, serum bile acids, or some combination of these (Urbonas *et al.*, 2001).

There is increasing evidence that HAP is a systemic rather than an isolated skin disease and that derangements of the immune system with a pro-inflammatory pattern may be involved in the pathogenesis of this disorder (Kimmel *et al.*, 2006). This forms the rationale of using phototherapy in treatment of HAP. UVB exposure was shown to be a pronounced modulator of Th1 and Th2 lymphocyte differentiation and to attenuate Th1 expression (Garssen *et al.*, 1999). Also, cutaneous mast cell proliferation and degranulation and resultant histamine release, have a major role in the pathogenesis of HAP (Szepietowski and Schwartz, 1998). Increased release of substance P evokes mast cell degranulation and histamine secretion. NB-UVB was found to induce apoptosis of dermal mast cells (Szepietowski *et al.*, 2002). It also reduces the release of neuropeptides such as substance P by decreasing epidermal nerve fibers (Wallengren and Sundler, 2004). The role of nitric oxide (Yamaoka *et al.*, 2000) and pruritogenic cytokines such as IL-2 (Walters *et al.*, 2003) has also been implicated in HAP. NB-UVB was found to decrease the production of nitric oxide and pruritogenic IL-2 (Walters *et al.*, 2003).

On the other hand "neuropathic hypothesis" was assumed to play a role in pathogenesis of HAP, based on the observation that about 65% of those patients exhibit a dysfunction of the peripheral nervous system (Zakrzewska-Pniewska and Jedras, 2001). Abnormal nerve conduction -in both motor and sensory circuits- is also a common concomitant of the early manifestations of uraemia, such as paraesthesia, burning feet and restless leg syndrome (Zakrzewska-Pniewska and Jedras, 2001). Pruritus in such cases may arise from a diminished threshold of perception and this augmented sensitivity to pruritic stimuli may result from nerve fibre damage. It has been demonstrated that uraemic patients on haemodialysis develop abnormal innervation. In them, but not in controls, nerve terminals and fibres have been found sprouting throughout the layers of the epidermis (Johansson *et al.*, 1989).

The above mentioned observations formed the rationale of applications of gabapentin for treatment of HAP. This was enforced by other reports that showed the efficacy of gabapentin in relieving the symptoms of brachio-radial pruritus which is another form of neuropathic itch

(Bueller *et al.*, 1999; Winhoven *et al.*, 2004). Gunal *et al.* (2004) were the first to evaluate the effectiveness of gabapentin in the renal itch. The authors found that 300 mg of oral gabapentin administered 3 times weekly is safe and effective treatment for reducing the mean pruritus score in such cases.

Gabapentin is structurally related to the gamma-amino-butyric acid "GABA" and was developed for control of neuropathic pain (Rose and Kam, 2002). Itching originating in the skin, like pain, is induced by the stimulation of the free nerve endings and conducted to the sensory cortex by C-fibers (Naini *et al.*, 2007). The effectiveness of gabapentin is best explained with the combination of neuropathic and altered divalent ion metabolism hypotheses for uremic itch. It was found that gabapentin blocks neuronal calcium influx, thus inhibiting ectopic discharge activity from injured nerves leading to interruption the series of events that perhaps lead to the pruritus sensation in uremic patients (Naini *et al.*, 2007).

Gabapentin is eliminated primarily through the kidney. Moreover, it can be removed by hemodialysis. This drug has a significantly longer half-life in patients on hemodialysis than in those with normal renal function and, thus, these patients need lower doses and less frequent intervals of gabapentin than patients with normal renal function. The recommended dose for patients on hemodialysis is 200-300 mg after each hemodialysis session (Rose and Kam, 2002).

This study aimed to assess the efficacy of NB-UVB alone vs NB-UVB and gabapentin as a treatment of HAP.

MATERIALS AND METHODS

This study was conducted on 48 patients with HAP. The patients were recruited during the period from September 2011 to February 2013. The patients were referred to the out-patient clinic of Dermatology Department from Nephrology Unit of General Medicine Department for management of their pruritus. All patients were complaining of pruritus which lasts 6 weeks or More and started after initiation of hemodialysis sessions for chronic renal failure. An informed consent was provided by all participants before inclusion and the study was approved by the local medical ethical committee.

Inclusion criteria were:

- Patients' age above 18 years
- Pruritus was not responding to treatment with ordinary regimens as antihistamines, moisturizers and topical anti-pruritics
- Patients have no dermatologic disorder that can cause pruritus
- Patients with no other systemic disorders which can cause pruritus as hepatic disorders, internal malignancies, myeloproliferative disorders, uncontrolled diabetes and hematologic disorders including patients with hemoglobin level less than 10 g dL^{-1}
- Non-pregnant or lactating women
- Serum levels of parathyroid hormone $>300 \text{ pg mL}^{-1}$ were excluded. Also, patients with serum calcium (albumin-corrected, $>10.2 \text{ mg dL}^{-1}$), serum phosphorous levels ($>5.5 \text{ mg dL}^{-1}$) or calcium phosphorous product concentrations $>70 \text{ mg}^2 \text{ dL}^{-2}$ were excluded because they had a significantly higher odds of having moderate-to-extreme pruritus (Wikstrom, 2007)

Any medication with presumed antipruritic effects was discontinued 2 weeks before the study.

All patients were on thrice weekly outpatient maintenance hemodialysis schedule with biocompatible membranes and received adequate dialysis dose via a polysulphone dialyser

(1.3-1.6 m² surface area (Fresenius 4008B, Fresenius Medical Care, Bad Homburg, Germany)), with Hydlina 1.4 filters, using bicarbonate dialysis fluid containing 136 mmol L⁻¹ Na, 1.5 mmol L⁻¹ Ca, 0.5 mmol L⁻¹ Mg, 110 mmol L⁻¹ Cl, 2 mmol L⁻¹ acetate and 33 mmol L⁻¹ bicarbonate. Blood flow and dialysate flow were 250-350 and 500 mL min⁻¹, respectively. During hemodialysis, patients were under regular assessment for levels of serum creatinine, blood picture, serum calcium and phosphorus, blood urea and arterial blood gas analysis.

We used an Arabic Translation of the 5-D itch scale (Elman *et al.*, 2010), to assess response to treatment. We used this scale because it is multi-dimensional and includes five dimensions (5-D) which are the degree, duration, direction, disability and distribution of pruritus in a given patient. Also its Arabic translation was easy and no difficult terms were used. Each dimension has a score range of 1(lowest response) to 5(maximum response) and the total score of the patient will be the sum of the scores of the 5 dimensions. Thus the final total score for every patient ranges from 25 (most severe pruritus) to 5 (no pruritus). All patients were asked to answer the 5-D itch scale questionnaire before treatment (baseline), at the end of 6 weeks study period and after 6 months from the end of treatment period. The patient was considered as responder if there is reduction of the 5-D itch score by 50% or more from his baseline or if the minimum score of 5 was recorded (corresponding to no pruritus). Recurrence was considered if there is return of score to/or above the baseline values.

Phototherapy was delivered to the whole skin surface 3 times a week for 6 weeks in a UV irradiation machine (Waldmann 7001K, Waldmann Medizinische Technik, Villingen-Schwenningen, Germany) supplied with 20 100-W fluorescent lamps (TL01, Philips Co, Eindhoven, The Netherlands). According to Ada *et al.* (2005), the starting dose was 400 mJ cm⁻² for skin phototype III and 500 mJ cm⁻² for skin phototype IV. There was no patients with skin phototype I, V or VI. Doses were increased by 100 mJ cm⁻² at every session, until a maximum daily dose of 1500 mJ cm⁻² had been achieved. Oral gabapentin 300 mg was administrated immediately after each hemodialysis session for 6 weeks.

Statistical analysis: Recruited data were subjected first to test for normal distribution (KS test). Student t test were used for parametrically distributed variants. Mann-Whitney test and Wilcoxon -matched pairs signed rank test were used for non-parametric variants. Chi square and Fisher's exact test were used for categorical variants. Analysis was done using MedCalc Statistical Software version 12.7.2 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2013).

RESULTS

Among a total of 48 cases that were enrolled, 43 cases completed the study including 22 cases of the control group and 21 cases of the study group. All patients were Egyptians, including 29 males and 14 females. The mean age of the patients was 42.52±12.36 years. No statistically significant difference were found between both groups in terms of age, sex, the mean duration of HAP or mean 5D-itch score before treatment (p>0.05, Table 1). NB-UVB was generally tolerable but intolerance to gabapentin therapy was recorded in the form of marked sedation in 4 patients and urticarial eruption in one patient. Mild and transient dizziness and nausea were recorded in three patients that continued the study.

Statistically significant difference was recorded between the 5-D score before and after each treatment modality in each group separately (Wilcoxon test, p<0.0001). However, no statistically

Table 1: Patients characterization before treatment

Parameters	Control (22)	Study (21)	Test	p-value
Age in years (Mean±SD)	41.51± 11.21	43.22±13.32	0.456*	0.6506
Sex				
Male	15	14	0.0482**	0.8262
Female	7	77		
Duration of HAP (weeks) (Mean±SD)	10.54±3.57	11.82±3.92	1.120*	0.2690
Baseline 5-D score				
Median(range)	18(12-24)	19.5(12-25)	0.523***	0.6007

*Student t test, ** Chi-square test, ***Mann-whitney test

Table 2: Median, range of 5-D itch score and distribution of response to treatment after 6 weeks

Parameters	Control (22)	Study (21)
Baseline 5-D score median (range)	18 (12-24)	19 (12-25)
Score after 6 weeks median (range)	6 (5-13)	6 (5-15)
Responders (%)	14 (63.64)	16 (76.19)
Non-responders (%)	8 (36.36)	5 (23.81)

Table 3: Statistical significance of 5 D-itch score results after treatment

Parameters	Test	p-value
Baseline score vs. score after treatment (control group)	Z = 4.1069*	<0.0001
Baseline score vs. score after treatment (study group)	Z = 4.0145*	= 0.0001
Score after treatment in control vs. study group	Z = 0.125**	0.99
Response rate in control vs. study group	$\chi^2 = 0.318$ ***	0.5728

*Wilcoxon-matched pairs signed rank test, **Mann-Whitney test, ***Chi-square test

Table 4: Relapse among responders after 6 months-follow up in both groups

Parameters	Control (14)	Study (16)	p-value
Relapse	8 (57.14%)	2 (12.5%)	0.0187*
Non-relapse	6 (42.86%)	14 (87.5%)	

*Fisher's exact test

significant difference was recorded between both groups in terms of the 5-D itch score or the distribution of responders and non-responders after treatment (Mann-whitney test, $p > 0.05$). This is demonstrated in Table 2 and 3.

After 6 months follow up, 8 responders in the control group (57.14%) and 2 responders in the study group (12.5%) developed recurrence of pruritus and this was statistically significant ($p < 0.05$, Table 4).

DISCUSSION

Pruritus is a common symptom in chronic hemodialysis patients with significant impact on quality of life (Zucker *et al.*, 2003). Despite improvements in dialysis technology, the incidence of HAP remains high and may reach 20-30% of cases (Pauli-Magnus *et al.*, 2000a; Pisoni *et al.*, 2006). The exact pathophysiology of HAP is not clear, a factor that limits the effectiveness of treatments. Most patients are treated with topical emollients, though the majority requires the addition of

systemic therapy (Patel *et al.*, 2007). Some of the most frequently used drugs are oral antihistamines (including hydroxyzine, cetirizine, loratadine, desloratadine), gabapentin, ondansetron, thalidomide, naltrexone/nalbufine, UV light and topical tacrolimus (Russo *et al.*, 1986; Vila *et al.*, 2008; Murphy *et al.*, 2003; Silva *et al.*, 1994; Wikstrom *et al.*, 2005; Gilchrest *et al.*, 1977; Pauli-Magnus *et al.*, 2000b). Unfortunately, the results of different studies are not uniform and many methodological inconsistencies are found, so that the best treatment options of HAP still uncertain (Manenti *et al.*, 2009).

In our study, almost 63.6% of patients of the control group and 76% in the study group were responders to treatments. The 5-D itch score for each treatment modality after 6 weeks treatment- in each group separately-was significantly lower than the baseline score (Table 3). This means that each treatment modality-whether NB-UVB alone or NB-UVB and gabapentin-was per se an effective line of treatment of HAP. Actually this finding is not a new one but it can add a further support for previous reports about successful treatment of HAP with phototherapy (Szepietowski *et al.*, 2002; Ada *et al.*, 2005). Review of literature revealed that phototherapy was tested in many studies as a treatment of HAP. In the study of (Ada *et al.*, 2005), the efficacy of NB-UVB-as a treatment of HAP-was evaluated in 20 Turkish patients using a maximum daily dose of 1500 mJ cm⁻² for 6 weeks. Ten cases only completed the treatment period while 6 of the remaining 10 cases-who did not complete the study- reported a satisfied response to NB-UVB. Among the 10 cases that completed the study, total of eight patients (80%) were responders and they recorded a 70.8% decrease in the VAS score. In comparison with our study, we included a larger number of Egyptian cases and we assessed the response via 5-D itch scale not by the VAS. We also assessed response to two modes of therapy not one.

In another study by Seckin *et al.* (2007), 60% of uraemic patients were responders to NB-UVB (9 out of 15). Among the responders, four of six patients who returned for follow up (66.7%) had recurrence. The authors concluded that remission after a single course of NB-UVB therapy is not prolonged and maintenance NB-UVB therapy appears to be a reasonable approach to prevent relapse. The response to NB-UVB alone obtained by Seckin *et al.* (2007) was close to that of our study, but the relapse rate they recorded was higher. This apparent difference could be explained by the fact that they had used NB-UVB in a lower dosage (200 mJ cm⁻² for skin types III-IV) and also a smaller number of cases were included compared to our study.

On the other hand, Ko *et al.* (2011) conducted a single-blind, randomized, controlled trial for 11 patients with refractory uraemic pruritus using NB-UVB in a dose started from 210 mJ cm² and was increased by 10% each setting. The assessment was done using VAS and the control group (10 patients) received time-matched exposures to long wave UVA. They reported that NB-UVB phototherapy does not show a significant effect in reducing pruritus intensity compared with a control group. Actually, the differences in the methods used for assessment of pruritus (VAS versus 5-D itch score), the variable dosage of NB-UVB and the smaller sample size could explain their variable results compared to our results in terms of response to NB-UVB for treatment of HAP.

Although the addition of gabapentin to NB-UVB increased the response rate from almost 63.6% in the control group to 76% in the study group, the difference was not statistically significant. It seems that -for the first look- there is no significant extra-benefit was gained by the addition of gabapentin to NB-UVB therapy (Table 3). This also appears to contradict Gunal *et al.* (2004), who reported high efficacy of gabapentin alone in treatment of HAP. The authors then suggested that neuropathy is the main cause of pruritus in HAP. Gunal *et al.* (2004) based their conclusion by

recording highly significant decline in the mean baseline VAS in 25 Turkish patients of HAP treated by gabapentin versus placebo, but actually no cut-off values of VAS was used to delineate between the responders and non-responders was applied in their study. Moreover, no follow up assessment of recurrence of itching -which is a major concern in HAP- was done. In our study, however, the addition of gabapentin to NB-UVB therapy in such patients succeeded to reduce significantly the rate of recurrence of pruritus among the responders in the follow-up period from around 57-12.5%. As high relapse rate represents a real problem in HAP (Seckin *et al.*, 2007), we can conclude that addition of gabapentin to NB-UVB can improve the overall benefits from treatment of HAP by NB-UVB through overcoming this major problem. Review of literatures revealed no satisfactory explanation of the high rate of recurrence of HAP after NB-UVB alone. However, from our results we suggest that neuropathy may be the main cause of recurrence of itching in HAP. Treatment of HAP by NB-UVB alone will target mainly the immunologic component of HAP with high rate of recurrence after treatment, while the addition of gabapentin to NB-UVB will help to control this neuropathic component and this is responsible for the significant reduction of the rate of recurrence of HAP in patients treated by such combination.

This study was limited by many obstacles. The most important was the number of cases that would give more powerful results if it increased and the absence of placebo in the control group that would allow the application of a blinding process.

In conclusion, the addition of gabapentin to NB-UVB in treatment of patients with HAP has no significant additional effect regarding the response rate, but it have a significant beneficial effect regarding reduction in rate of recurrence of pruritus which is a major problem in such cases. We also found that NB-UVB whether alone or combined with gabapentin were generally safe and well-tolerated moods of treatment of HAP.

CONCLUSION

Response to gabapentin and NB-UVB was not significantly superior to NB-UVB alone in treatment of HAP. However, this mode of therapy significantly reduces the rate of recurrence of pruritus.

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