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ORIGINAL ARTICLE

Comparative study of systemic psoralen and ultraviolet A and narrowband ultraviolet B in treatment of chronic urticaria

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None declared.

SUMMARY

Background
Previous success rates of psoralen and ultraviolet A (PUVA) and narrowband UVB (NB-UVB) in the treatment of chronic urticaria are reported in few studies with no previous reports on the comparable efficacy of both modalities in the disease.

Aim
We aimed to compare the efficacy of PUVA versus NB-UVB in the treatment of chronic urticaria.

Methods
Twenty-four patients with chronic urticaria were included and divided into two groups: 12 patients subjected to PUVA and 12 subjected to NB-UVB. They were compared according to the urticaria Total Severity Score (TSS) before and after treatment, cumulative dose, and side effects.

Results
There was a statistically significant decrease in urticaria TSS in both the NB-UVB- and PUVA-treated groups after than before treatment ($P < 0.05$), with no significant difference between both groups regarding the percentage of improved patients and the mean decrease of urticaria TSS ($P > 0.05$). Gastrointestinal upset was reported at a significantly higher percentage in the PUVA-treated group than in the NB-UVB-treated group.

Conclusion
Both NB-UVB and PUVA show comparable efficacy in the treatment of chronic urticaria with minimal reversible side effects.

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Chronic urticaria is defined as the occurrence of cutaneous wheals with or without angioedema lasting more than 6 weeks with individual lesions lasting less than 24 h (1). Urticaria affects persons of all races and both sexes; however, it is more common in females (2).

The mast cell (MC) is the principal effector cell of urticaria. All MCs express high-affinity IgE receptors (FcεRIs). When IgE forms a complex with FcεRI on the MC to which an allergen binds, degranulation occurs (3). Theories of pathogenesis of chronic urticaria include the autoimmune theory, theories involving histamine-releasing factors, and the cellular defect theory. Hypotheses of less evidence include abnormalities in the coagulation system and chronic infection (4). When no specific external cause for chronic urticaria is identified, the disease is labeled 'chronic idiopathic urticaria'. However, up to 30–50% of idiopathic cases may be autoimmune or related to MC and basophil abnormalities (5).

Treatment of chronic urticaria is often disappointing. Basically, all treatment regimes should include the removal of any identifiable cause, avoidance of aggravating factors, advice, explanation, information and reassurance (6). Three main lines of therapy exist for treatment of chronic urticaria. First-line therapy includes patient education and general non-drug measures, followed by a trial of H1 receptor antihistamines if symptoms persist (7). Second-line therapy is considered if urticarial symptoms are not controlled by antihistamines alone. Several classes of drugs may be useful in second-line therapy including antidepressants, corticosteroids, levothyroxine, and leukotriene receptor antagonists (8). Third-line therapy for patients who do not respond to first- and second-line treatments involves the use of immunomodulatory agents, as cyclosporine, tacrolimus, methotrexate, mycophenolate mofetil, and intravenous immunoglobulins (9).

The use of psoralen and ultraviolet A (PUVA) (10, 11) and narrowband UVB (NB-UVB) (12, 13) in treatment of chronic urticaria was assessed in only few studies. Considering the paucity of studies on the use of phototherapy and photochemotherapy in chronic urticaria, with absence of previous reports on the comparative efficacy of PUVA and NB-UVB in the disease, we aimed in this work to compare the clinical efficacy of PUVA photochemotherapy and NB-UVB phototherapy in the treatment of chronic urticaria.

PATIENTS AND METHODS

After screening 47 patients with chronic ordinary urticaria, 14 were excluded as they did not fulfill the inclusion criteria, and from the remaining 33 patients, 24 (the desirable sample size) were randomly included. The patients included fulfilled the following criteria: suitable for phototherapy, not on any systemic immunosuppressive drugs or systemic steroids within 1 month or topical steroid within 2 weeks prior to the study, or recent phototherapy for any cause. Patients with physical, vasculitic, and neutrophilic urticaria were excluded. All patients had not responded to antihistamines or elimination diet. Each patient was subjected to: full history taking, general and dermatological examination, and disease severity assessment using the urticaria total severity score (TSS) (14) before and after treatment. According to this score, six separate parameters of disease activity and severity, number of wheals (none, ≤ 10, 11–50, > 50), size of wheals (none, < 1 cm, 1–3 cm, > 3 cm), intensity of pruritus (none, mild, moderate, severe), duration of persistence (none, < 1 h, 1–12 h, > 12 h), frequency of appearance (none, < once or once/week, 2–3 times a week, daily/almost daily), and frequency of antihistamine use (none, < once or once/week, 2–3 times a week, daily/almost daily), were recorded on a 0–3 scale, with a sum of 0–18 TSS.

Patients in this study were randomly assigned into one of two groups: NB-UVB-treated group and PUVA-treated group. The first group included 12 patients subjected to NB-UVB. The second group included another 12 patients subjected to photochemotherapy (PUVA). All patients gave informed consent to participate in this work. The study was approved by the research ethics committee, Ain Shams University.

NB-UVB-treated group

The patients in this group were treated by NB-UVB, three sessions/week for a maximum of 20 sessions. The machine used was UV-100 L Waldman lighting (Villingen-Schwenningen, Germany) equipped with UVB lamps (TL01 lamp) which have physical irradiance values of 7–10 mW/ cm^2 and biologically effective (erythematous) irradiance of 0.4–0.6 mW/cm^2. The starting dose was determined according to the patient's skin type where skin types I and II received 0.3 J/cm^2, skin types III and IV received 0.5 J/cm^2, and skin types V and VI received 0.8 J/cm^2. Dose increments of 20% were applied every session if there was no erythema, 10% if there was minimal erythema, while no increments were applied in the presence of intense erythema and/or edema and/or blisters (15); instead, we skipped a session and returned to the previous dose.

Table 1. Characteristics of the narrowband UVB- and PUVA-treated chronic urticaria groups

	NB-UVB-treated group Number = 12	PUVA-treated group Number = 12
Gender		
Males	3	4
Females	9	8
Age (years)		
Range	14–58	21–43
Mean ± SD	35.33 ± 13.90	30.25 ± 7.92
Skin type		
III	3	3
IV	9	9
Disease duration (months)		
Range	3–36	6–84
Mean ± SD	16.83 ± 14.53	34.50 ± 28.36
Mean urticaria TSS		
Before treatment	15.75 ± 1.76	15.08 ± 1.56
After treatment	11.00 ± 5.89	11.50 ± 4.45

NB-UVB, narrowband ultraviolet B; PUVA, psoralen + ultraviolet A; TSS, Total Severity Score.

Photochemotherapy (PUVA)-treated group

The patients in this group were treated by PUVA three sessions/week for a maximum of 20 sessions. Waldman lighting 7001 (Herbert Waldman Gmbh &Co), equipped with UVA lamps, was used. The machine has physical irradiance values of 11–13 mW/cm^2.

Patients treated with PUVA received methoxsalen (8-methoxypsoralen tablets 10 mg each), at a dose of 0.6 mg/kg taken 2 h before each session. UVA starting doses were determined according to the patient's skin type. Fitzpatrik's skin type I received an initial dose of 0.5 J/cm^2, skin type II received 1.0 J/cm^2, skin type III received 1.5 J/cm^2, skin type IV received 2 J/cm^2, skin type V received 2.5 J/cm^2, and skin type VI received 3 J/cm^2 (15). The patients had a routine increase in the UVA dose of 0.5 J/cm^2, 1 J/cm^2, and 1.5 J/cm^2 for skin types I and II, III and IV, and V and VI, respectively (16). Increments were applied if there was no or minimum erythema. In the presence of intense erythema, edema, or blisters, no increments were applied; instead, we skipped a session and returned to the previous dose. For subsequent treatments, if the patient skipped sessions between treatments and the time had been from 4 to 7 days, we kept the same dose; from 1 to 2 weeks, we decreased the dose by 25%; from 2–3 weeks, we decreased the dose by 50%; and from 3 to 4 weeks, we started over from the beginning (15).

Statistical analysis

The data were coded, entered, and processed using the SPSS Software version 15.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was used to test the association variables for categorical data. Paired *t*-test was performed to assess the statistical difference of total urticaria severity score before and after treatment. Student's *t*-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. The Fisher's exact test was used when applicable. *P* value ≤ 0.05 was considered statistically significant. Sample size estimation: as estimation of standard deviation of mean number of sessions to improvement = 7 (from previous studies) (11, 12); with 5% significance level, 80% power, difference to be detected 5.5, and smallest interest of 0.78, the required sample size was found to be 24.

RESULTS

The characteristics of the NB-UVB- and PUVA-treated chronic urticaria groups are shown in Table 1. There was no statistically significant difference between the two groups as regards the mean age, gender, skin types, disease duration, or urticaria TSS before and after treatment ($P > 0.05$).

There was a significantly lower urticaria TSS in the NB-UVB-treated group and in the PUVA-treated group after treatment with a mean of 11.00 ± 5.89 and 11.50 ± 4.45, respectively, in comparison to the scores before treatment which were 15.75 ± 1.76 and 15.08 ± 1.56, respectively ($P < 0.05$) (Table 2). The mean decrease in the urticaria TSS was 9.00 ± 5.56 in the NB-UVB-treated group and 8.25 ± 5.28 in the PUVA-treated

Table 2. Comparison between the urticaria Total Severity Score before and after treatment in the narrowband UVB- and PUVA-treated chronic urticaria groups

	Urticaria Total Severity Score before treatment		Urticaria Total Severity Score after treatment				
	Mean	± SD	Mean	± SD	*t*	*P*	Sig.
Narrowband UVB-treated group	15.75	± 1.76	11.00	± 5.89	4.24	0.001	S
PUVA-treated group	15.08	± 1.56	11.50	± 4.45	3.25	0.008	S

Paired *t*-test.
S, significant.

Table 3. Comparison between patients with chronic urticaria receiving narrowband UVB and those receiving PUVA as regards improvement and side effects

		Groups						
		NB-UVB-treated group		PUVA treated group				
		N	%	*N*	%	χ^2	*P*	Sig.
Improvement	No	5	41.7%	6	50.0	0.17	0.68	NS
	Yes	7	58.3%	6	50.0			
Side effects	None	9	75.0%	4	33.3			
	Erythema only	3	25.0%	2	16.7		> 0.99	NS
	Both erythema and GIT upset	0	0%	1	8.3		0.36	NS
	GIT upset only	0	0%	5	41.7		0.03	S

Chi-square test.
GIT, gastrointestinal tract; NS, nonsignificant; S, significant.

group with no statistically significant difference in between ($P > 0.05$). The percentages of improved patients showed no statistically significant difference between the NB-UVB-treated group and the PUVA-treated group (58.3% and 50.0%), respectively (Table 3).

The only side effects reported in this work were either erythema alone (25.0% in the NB-UVB-treated group and 16.7% in the PUVA-treated group), gastrointestinal upset alone (in 41.7% in the PUVA-treated group only), or both erythema and gastrointestinal upset (8.3% in the PUVA-treated group only). The PUVA-treated group showed a significantly higher percentage of gastrointestinal upset in comparison to the NB-UVB-treated group (Table 3).

In the PUVA-treated group, the mean cumulative dose was 76.75 ± 14.36 J/cm^2. On the other hand, in the NB-UVB-treated group, the mean cumulative dose was 37.83 ± 5.50 J/cm^2.

DISCUSSION

Urticaria affects 15–20% of the population at some point in their lives, but urticaria persists daily for more than 6 weeks in only approximately 1% of the population (17).

The significant improvement of chronic urticaria in our NB-UVB-treated group agrees with the previous study performed on NB-UVB treatment in chronic urticaria by Engin *et al.* (12) who found a significant reduction in the Urticaria Activity Score (UAS) in patients treated with 20 sessions of NB-UVB in comparison with patients treated with levocetirizine, with improvement starting from the 10th session. This start of improvement was comparable to that of our study (9th session). Likewise, the side effects were generally tolerable and reversible in the form of well-demarcated erythema in 25% of patients in our work and erythema and pruritus in Engin *et al.*'s study (12) in 9% of patients. The percentage of

improved patients in the NB-UVB-treated group in our study was 58.3%.

However, the mean cumulative NB-UVB dose was higher in our study (37.83 J/cm^2), compared with that in Engin *et al.*'s study (12) (15.090 mJ/cm^2). This could be attributed to the lower starting dose (200 mJ/cm^2) due to the presence of a higher percent of lighter skin types in the study of Engin *et al.* (12).

In Engin *et al.*'s work (12), the improvement in UAS was maintained 3 months after phototherapy had been stopped, in contrast to a significant increase in the disease activity in the levocetirizine only group. This long-term improvement with the NB-UVB group was suggested by the authors to be related to a long lasting immunoregulatory effect of NB-UVB or to a psychological effect (12).

In a retrospective review made by Berroeta *et al.* (18), they considered NB-UVB as a useful second-line therapy for chronic urticaria. In another study, NB-UVB treatment led to a good response with clearance in 45% of patients, marked improvement in 22%, and moderate improvement in 31%, according to an outcome scoring scale (comparable to our improvement rates). Side effects were mild and observed in two patients. Forty percent of patients remained clear at follow-up for 6 months to 1 year; other patients had a few recurrent lesions that did not necessitate retreatment (13).

With regard to PUVA therapy, the significant improvement of chronic urticaria in our PUVA-treated group agrees with the previous study performed by Olafsson *et al.* (11), who compared the efficacy of PUVA and UVA plus placebo in treatment of chronic urticaria. They found that both groups showed a significant improvement as regards the number of days with wheals and itching. In both groups, a significant decrease in antihistamine intake was noted after treatment had been terminated. In their patients treated for a maximum of 2 months (two sessions/week), the mean cumulative dose of PUVA was 88 J/cm^2 and this was comparable to our study in which the mean cumulative PUVA dose was 76.75 J/cm2. Midelfart *et al.* (10), in a case report found that PUVA treatment with a total dose of 300 J/cm^2 resulted in resolution of the patient's urticaria in all irradiated areas. Conversely, PUVA therapy was ranked as neutral or ineffective using a questionnaire evaluated by Canadian dermatologists and allergists (19).

Little is known about changes induced by UV in skin MC, even though UV treatment is well appreciated as beneficial in pruritic diseases and in cutaneous mastocytosis (20). MC histamine release is subjected to modulation by UV light and human MCs are proposed to be targets of UV light (21). UV light displays a dual effect on MC by triggering slight but significant histamine release from resting MC, but suppressing this same release up to 90% when cells are appropriately stimulated (22). NB-UVB can suppress the systemic immune responses (23, 24) and probably induces apoptosis of dermal MCs (25), with some controversial results regarding MC depletion (26). It decreases the production of proinflammatory cytokines, while UVB phototherapy induces the production of the anti-inflammatory cytokine interleukin-10 (27). UVB is proposed to primarily affect the T cells in lesional skin (27), which could be the mechanism of action in autoimmune urticaria.

In this first comparative study on the effect of NB-UVB and PUVA in treating chronic urticaria, both lines of treatment were comparably effective with no significant difference in between regarding the mean urticaria TSS before and after treatment or as regards the percentages of patients showing improvement (58.3% and 50.0%, respectively).

Erythema was the only side effect reported in the NB-UVB-treated group and no other side effects were reported as was previously reported by Engin *et al.* (12). On the other hand, the PUVA-treated group showed a significantly higher percentage of gastrointestinal upset mainly due to the oral psoralen intake.

In conclusion, this study shows a comparable efficacy of both NB-UVB and PUVA in the treatment of chronic urticaria with minimal reversible side effects. Consequently, they could be considered a second line of treatment in chronic urticaria. In view of the higher percentage of gastrointestinal upset with PUVA, NB-UVB might be preferred as the first choice phototherapeutic modality in the treatment of chronic urticaria.

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