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**Phototherapy using NB-UVB and PUVA is beneficial in steroid dependent
antihistamine refractory chronic urticaria: A randomized prospective observer blinded
comparative study**

Running title: Phototherapy in chronic refractory urticaria

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Abstract

Background: Literature on efficacy of phototherapy in steroid dependent antihistamine refractory chronic urticaria (CRU) is limited.

Objective: To assess and compare the efficacy of psoralen and ultra-violet A (PUVA) and narrow band ultra-violet B (NB-UVB) in steroid dependent CRU.

Methods: In this randomized prospective observer blinded comparative study, 50 patients of steroid dependent CRU (6 months of spontaneous urticaria with no response from 3 consecutive months of antihistamines and steroid dependence) were administered either PUVA (group A) or NB-UVB (group B) for 90 days, with a post treatment follow-up of 90 days. The treatment efficacy was assessed using average urticaria activity score⁷ (aUAS7) and outcome scoring scale (OSS) every fortnightly.

Results: The mean values of aUAS7 progressively decreased from 4.9 ± 0.8 and 5.0 ± 0.7 at baseline to 1.9 ± 0.7 and 1.4 ± 0.7 in groups A and B respectively by 90th day. This further decreased to 1.5 ± 0.8 and 1.4 ± 1.0 at 180th day in both groups. The values of OSS progressively increased from baseline (1.6 ± 0.5 in group A and 1.3 ± 0.5 in group B) to 3.9 ± 0.3 and 4.0 ± 0.3 in groups A and B respectively by 90th day and 3.9 ± 0.5 and 4.0 ± 0.6 by 180th day. NB-UVB fared statistically better than PUVA at different time points. Adverse events encountered were minimal and did not warrant treatment discontinuation.

Conclusion: Phototherapy, especially NB-UVB is an effective, safe and affordable therapeutic modality for steroid dependent CRU and should be tried prior to 3rd line treatment options like omalizumab, cyclosporine and other immunosuppressants.

What is already known?

- Studies on use of phototherapy in chronic urticaria are limited by smaller sample size, retrospective nature and lack of characterization of disease severity.

What does this study add?

- Randomized observer blinded comparative study demonstrating that phototherapy is effective in treatment of steroid dependent antihistamine refractory chronic urticaria.
- The efficacy of phototherapy is maintained beyond completion of phototherapy.
- Both NB-UVB and PUVA significantly convert positive ASST and APST to negative post treatment and PUVA also significantly reduces serum IgE levels.

Key words: Chronic refractory urticaria; Narrow band ultra-violet B; Phototherapy; Psoralen and ultra-violet A; Urticaria activity score.

Introduction

Chronic urticaria (CU) is defined as occurrence of weals daily or almost daily, with or without angioedema, for duration of 6 weeks or more.^{1, 2} According to recent European Academy of Allergy and Clinical Immunology (EAACI) guidelines¹, second-generation H1 antihistamines (AH1) are the first line treatment options for CU. Second line treatment option is increasing the dose of an AH1 by a maximum of 4 folds. CU has a prevalence of 0.5-1% and almost 5-50% patients do not respond adequately to AH1.³⁻⁵ Third line treatment option for such patients is addition of omalizumab, montelukast or cyclosporine. These agents have systemic adverse effects and are expensive for patients from developing countries, who

usually lack insurance coverage. Therefore, a safer, effective and affordable treatment modality is needed for patients of CU who have failed second line therapy.

Phototherapy has been found to be effective in treatment of mastocytosis⁶, dermographism⁷ and CU.⁸⁻¹³ The exact mechanism of action of phototherapy in urticaria is unknown. Reducing skin mast cell reactivity, degranulation and release of histamine and other pro-inflammatory mediators is one possible explanation.¹⁴ Other plausible mechanisms include apoptosis of dermal mast cells¹⁵, immunomodulatory action and production of anti-inflammatory cytokine interleukin-10.¹⁶

In a randomized controlled trial, Engin et al¹¹ found combination of narrow band ultra-violet B (NB-UVB) and AH1 to be better than AH1 alone for CU. In an open label study, Aydoğan et al¹² observed NB-UVB to be beneficial in patients not responding to AH1. Olafsson et al⁸ and Hannuksela et al⁹ reported positive results for Ultra-violet A (UVA) and broad-band UVB respectively. Khafagy et al¹³ found NB-UVB and psoralen plus UVA (PUVA) to be equally effective in 24 patients.

However, these studies have several limitations. Many of them include physical urticaria, sample size is relatively small and the ones with larger numbers are either retrospective¹⁰ or include patients that do not have AH1 refractory CU.¹¹ Hence, we conducted this prospective, randomized, observer blinded study involving 50 patients to assess and compare the efficacy of NB-UVB and PUVA in CU patients not responding to 4 fold increased AH1 doses (chronic refractory urticaria, CRU) and dependent on recurrent intake of oral steroids for relief. We also assessed the effect of phototherapy on serum IgE levels, autologous serum skin test (ASST) and autologous plasma skin test (APST) of such patients.

Methods

Study design

This was a randomized, prospective, observer blinded comparative study conducted in a tertiary care center. All consecutive CU patients with active disease, attending the urticaria clinic of our institute from June 2013 to June 2014 were screened (n=526). A sample size of 50 patients was arbitrarily selected and consenting patients who fulfilled the inclusion and exclusion criteria, were recruited (excluded physical urticaria n=100, CU not fulfilling other inclusion criteria n=298, declined to participate n=78). The institute ethics committee approved the study and all recruited patients signed an informed written consent. The overall study design is depicted in Figure 1.

Inclusion criteria

1. Patients of CU with active disease (having hives associated with itching daily or almost daily, with or without angioedema) for 6 months or more
and
2. Refractory disease, defined for present study as failure to respond to 4 folds increased doses of 2nd generation AH1 given for at least 3 continuous months and requiring repeated courses of oral corticosteroids (chronic refractory urticaria, CRU).

Exclusion criteria

Physical urticaria, urticarial vasculitis, acute urticaria, angioedema without weals, photosensitive disorders, intake of photosensitizing medications, claustrophobia, pregnancy and lactation, underlying hepatic and renal disease, cataract and history of anaphylaxis.

Previous treatments

Apart from AH1 and steroids, patients had received leukotriene receptor antagonists (n=44) and methotrexate (n=1) for their CU with minimum relief. For the present study, a washout period of 1 month was advocated during which all treatments except AH1 were stopped. AH1 were allowed at maximum licensed doses during washout period. At the time of inclusion to the study and starting of phototherapy, all patients were uniformly started on oral levocetirizine 10 mg/day, which was continued through out the treatment period (90 days), and was further reduced to 5 mg during the follow-up (91-180 days).

Randomization

Patients were randomized into two groups A and B using computer generated random number tables; wherein, 25 random single and double-digit numbers from 1-50 were selected before recruitment, and patients coming on these numbers were randomized in a particular group. Random number generation, recruitment and randomization, were all done by the same investigator (DP).

Patients in group A received 0.6 mg/kg of 8-methoxypsoralen followed by UVA 2 hours later (PUVA) and patients in group B were treated with NB-UVB. Treatment was administered using whole body phototherapy cabinets (*Surya 440ANB, V-care/Cardiocare, UVA lamps- Philips TL-10R, NB-UVB lamps- Philips TL-01 100W*). Phototherapy doses were initiated and incremented based on Fitzpatrick skin types (III-V in our study), as per standard guidelines, thrice weekly for a period of 90 days¹⁷.

Baseline evaluation

Complete hemogram, renal and liver function tests, thyroid function tests, thyroid autoantibodies, serum IgE levels and ophthalmological evaluation to rule out pre-existing cataract were done. Serum IgE levels above 100 IU/ml were considered abnormal (as per standardized chemi-luminescence immune assay done at our institute). ASST and APST were performed at baseline using standard guidelines¹⁸ and were considered positive if average diameter of weal induced by serum and plasma was greater than 2 mm in comparison to diameter of weal induced by normal saline.

Treatment assessment and follow-up

The total study period for each patient was 180 days, divided equally between treatment and follow-up (90 days each). Investigators blinded to random allocation (A and VK) assessed the disease severity and treatment efficacy. Urticaria activity score (UAS)¹⁹ and outcome scoring scale (OSS)¹⁰ were used to measure disease activity, symptomatic improvement, frequency and extent of the disease (**Table 1**). Average UAS7 (aUAS7) over 7 days (UAS7/7, range 0-6) was calculated at baseline before starting phototherapy. Patients were instructed to write down number of weals and severity of itching in their daily urticaria diary. Every fortnightly, aUAS7 for previous 7 days and OSS (range 1-5) were assessed. After completion of phototherapy (90 days), serum IgE levels, ASST and APST were measured again. Subsequently, patients were further followed up every fortnightly for 3 more months using aUAS7 and OSS to evaluate for maintenance of treatment efficacy and relapse. The follow-up of all patients was completed by December 2014. At the end of study period, patients were asked to subjectively grade phototherapy as a treatment option for their CU on scale of 0-10, with 0 being worst and 10 being the best (defined as patient satisfaction score).

Study end-points

Primary end-point

Change in aUAS7 from baseline to 90th day (at end of treatment) within group A and B and comparison between groups A and B.

Secondary end-points

1. Change in OSS from baseline to 90th day within group A and B.
2. Change in aUAS7 and OSS from baseline to 180th day (end of follow-up) within group A and B
3. Grading of clinical improvement using patient satisfaction score at 180th day for group A and B,
4. Change in ASST, APST and IgE levels from baseline to 90th day within group A and B,
5. Comparison for the above mentioned parameters between group A and B.

Relapse

Relapse was defined as return of aUAS7 to baseline value.

Statistical analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS for Windows). Normality of the Quantitative data was assessed using Kolmogorov Smirnov test and their descriptive data was presented by Mean $\pm$ SD. The effect of treatment within a group was assessed using Student's t-test (paired). Comparison between two groups was done using Student's t-tests or Mann Whitney U test. Qualitative or categorical data was analyzed using Chi-square test or Fisher's exact test whichever was applicable. Repeated Measure ANOVA with Bonferroni corrections was also applied to see the trend of parameter values

and to adjust for multiple comparisons. All statistics were performed at a significance level of $p = 0.05$.

Results:

Patients (Table 2)

The mean age of patients in-group A was 33.7 ± 8.1 years (range 20-50 years) and that in-group B was 35.5 ± 11.7 years (range 19-65 years). There were 15 females and 10 males in each group. The mean total duration of illness in-group A and B was 34.6 ± 17.4 and 42.2 ± 29.6 months respectively (range 1-5 years).

Baseline evaluation (Table 2)

The baseline mean aUAS7 in group A and B was 4.9 ± 0.8 and 5.0 ± 0.7 respectively. The mean baseline OSS was 1.6 ± 0.5 in group A and 1.3 ± 0.5 in group B. Overall, 42 patients were ASST positive (group A-20 and group B-22) and 43 were APST positive (group A-20 and group B-23), with mean diameters of weals induced by serum and plasma being 10.4 ± 3.1 and 11.2 ± 3.4 mm respectively in group A and 9.9 ± 2.1 and 11.0 ± 2.6 mm respectively in group B. Total serum IgE >100 IU/ml was noted in 39 patients (group A-20 and group B-19) with a mean serum IgE level of 721.2 ± 735.7 IU/ml in group A and 403.0 ± 305.9 IU/ml in group B. Both groups were well matched and there was no significant difference between the two groups regarding demographic parameters, baseline disease severity and investigations.

Response to phototherapy

Primary end-point

Change in aUAS7 from baseline to 90th day within and between groups

The mean values of aUAS7 progressively decreased from 4.9 ± 0.8 and 5.0 ± 0.7 to 1.9 ± 0.7 and 1.4 ± 0.7 in groups A and B respectively by 90th day (61.4% and 70.9% reduction from baseline; Table 3, $p < 0.0001$, repeated measure ANOVA, 95% confidence interval (CI)=2.4-3.7 and 2.9-4.2 for group A and B respectively). Statistically significant decline in aUAS7 was observed as early as 15th day of starting phototherapy in both groups.

Reduction was statistically more significant in group B ($p = 0.022$, Mann Whitney, 95% CI=0.1 to 0.8).

Secondary end points

Change in aUA7S from baseline to 180th day

aUAS7 further decreased to 1.5 ± 0.8 and 1.4 ± 1.0 at 180th day in both groups (69.3% and 72.5% reduction from baseline; Table 3, $p < 0.0001$, repeated measure ANOVA, 95% CI=2.7-4.1 and 2.7-4.5 for group A and B respectively).

Change in OSS

The values of OSS progressively increased from baseline (1.6 ± 0.5 in group A and 1.3 ± 0.5 in group B) to 3.9 ± 0.3 and 4.0 ± 0.3 in groups A and B respectively by 90th day (Table 3, $p < 0.0001$, repeated measure ANOVA, 95% CI=-2.7 to -2.0 and -2.9 to -1.9 in group A and B respectively) and 3.9 ± 0.5 and 4.0 ± 0.6 by 180th day (Table 3, $p < 0.0001$, repeated measure ANOVA, 95% CI=-2.9 to -1.9 and -3.2 to -2.1 in group A and B respectively).

Comparison between groups

Change in aUAS7

The reduction in aUAS7 was more significant in group B on 45th, 75th and 90th day during treatment and on 30th day during follow-up, in comparison to group A (**Figure 2a, p=0.005, 0.033, 0.022 and 0.001, Mann Whitney; 95% CI for difference=0.2-1.0, 0.03-0.6, 0.1-0.8 and 0.3-1.2 respectively**).

Change in OSS

On comparing the two groups, the increase in OSS was more significant in group B on 15th, 30th and 45th day during treatment and on 30th day during follow up (**Figure 2b, p=0.018, 0.002, 0.001 and 0.037, Mann Whitney; 95% CI for difference=-0.6 to -0.1, -0.7 to -0.2, -0.8 to -0.2 and -0.02 to -0.5 respectively**).

Patient satisfaction score and treatment

Average patient satisfaction score was 7.6 in group A and 7.9 in group B (Table 3).

Effect on ASST and APST

From baseline to 90th day, a significant reduction in diameters of weals produced by serum and plasma was observed in both groups (6.7 ± 2.7 and 7.1 ± 2.6 mm for serum and plasma respectively in group A and 7.8 ± 3.5 and 7.6 ± 3.3 mm in group B, Figure 3a, $p < 0.0001$ in group A, $p = 0.023$ and < 0.0001 for serum and plasma in group B). Eighteen patients (9 in each group) were ASST positive and a similar number of patients were APST positive (group A-10 and group B-8; Figure 3b) at end of treatment. The trend for number of patients with positive ASST/APST to turn negative post phototherapy was significant in both the groups ($p < 0.003$, McNemar test).

Effect on total serum IgE levels

At the end of treatment, 38 patients (baseline- 39) demonstrated total serum IgE levels >100 IU/ml (Figure 3b, Table 3). When compared with baseline values (721.2 ± 735.7 IU/ml in group A and 403.0 ± 305.9 IU/ml in group B), a statistically significant reduction in serum IgE levels at 90th day was seen in only group A (441.7 ± 407.3 IU/ml and 330.6 ± 251.1 IU/ml in group A and B respectively; Table 3, $p=0.002$).

Adverse effects

Six patients (24%) in group A complained of nausea compared to none in group B ($p=0.022$). Xerosis and tanning was seen in 14(56%) and 13(52%) patients in each group respectively. Melasma was observed in 5 patients (2-group A and 3-group B).

Treatment response, relapse and residual disease activity

At the end of treatment (90th day), 1 patient was clear of urticaria, 46 (92%) had marked improvement and 3 had moderate improvement. At the end of follow-up (180th day), 4 patients achieved clearance. Forty-two patients (84%) had marked improvement with 27 complaining of mild residual pruritus in absence of weals (aUAS7 over 7 days = 1), 15 (9-group A, 6-group B) having minimal residual weals which appeared occasionally, were lesser in number compared to baseline and spontaneously improved in a short time. Two had moderate and 1 had minimal improvement (Table 3). Relapse was seen in only 1 patient (group B).

Associated findings

Fourteen patients were found positive for circulating anti-microsomal thyroid autoantibodies, with clinical hypothyroid disease in 10 patients. A personal history of atopy was observed in 16 patients (A-7, B-9) with family history of atopy in 6 patients (3 patients in both groups).

Discussion

A proportion of CU patients have persistent weals despite taking maximum licensed doses of AH1, which significantly affects their quality of life and results in repeated intake of systemic corticosteroids for relief.²⁰ Various immunosuppressants/immunomodulators have been tried in this subset of patients, with variable outcome.²¹ Phototherapy is not recommended as a treatment option for such patients in any of the standard urticaria treatment guidelines.

Midelfart K *et al*²² first reported improvement in CU following PUVA therapy in a patient who had co-existing vitiligo and CU. Few subsequent studies reported beneficial effect of different phototherapeutic modalities in the treatment of CU.⁸⁻¹³ Most of these studies are limited by small sample size and lack of definition of the baseline refractoriness of disease. Engin *et al*¹¹ compared antihistamines plus NB-UVB with antihistamines alone in a randomized controlled trial and observed that combination group had significantly more improvement in UAS as compared to antihistamine alone group, although both had statistically significant improvement. Also, improvement in combination group was maintained during follow-up, whereas that in antihistamine alone group was not maintained and patients quickly relapsed during follow-up period. Both NB-UVB and PUVA were found to be significantly effective in our study, though; NB-UVB fared statistically better than PUVA at multiple points during treatment and follow-up. As NB-UVB has already been proven to be effective in randomized controlled study by Engin *et al*¹¹, we can conclude that

PUVA is also effective. Clinically, minimum important difference (MID) for UAS7 has been defined between 9.5-10.5.²³ The difference in *a*UAS7 between baseline and 90th day as observed by us was 3.0 and 3.6 in PUVA and NB-UVB groups respectively, amounting to UAS7 of 21 and 25.2. Therefore, although statistically NB-UVB fared better at certain time-points; clinically, with regard to MID, both NB-UVB and PUVA fared almost equally well. This was also appreciated by almost similar patient satisfaction scores.

We observed clinical improvement as early as day 15 in both groups (about 7 sessions of phototherapy) and improvement achieved during treatment period was also maintained during the follow up period. Patients requiring repeated steroid intake responded effectively to a single daily dose of levocetirizine 10 mg, which could further be reduced to 5 mg during follow up period. In our experience, patients continued to be in clinical remission with none or minimal dosages of AH1 for as long as 1 year after release from the study (unpublished data). Aydogan et al¹² studied 22 CU patients (19 with skin type II) using OSS and noticed clearance in 45%, marked improvement in 22% and moderate improvement in 31% patients; whereas Berroeta et al¹⁰ in a retrospective review, noted 40% clearance, 15% marked improvement and 45% moderate improvement at the end of treatment using NB-UVB (most patients with phototypes I to III). Khafagy et al¹³ compared NB-UVB and PUVA in 24 patients and found both to be equally efficacious with 58.3% patients improving in NB-UVB group and 50% in PUVA group. In contrast, we observed complete clearance in only 4% and marked improvement in 92% in our cohort. This was due to persistent mild pruritus in 54% of patients who were otherwise free of active weals, but were scored having *a*UAS7 of 1 or OSS of 4 and hence classified as having marked improvement rather than complete clearance. This persisting pruritus could be due to underlying hypothyroidism (20%), atopy (32%) or phototherapy induced xerosis (>50%) instead of persistent disease activity and

responded effectively to application of emollients. Treatment of hypothyroidism might have also influenced the results of our study, which was not accounted for in the study design.

Omalizumab has been found to be beneficial for CU patients not responding to AH1²⁴. Baseline UAS7 values in the group receiving 300 mg omalizumab per month were 29.5 ± 6.9 , which are comparable to baseline aUAS7 in our NB-UVB group (5.0 ± 0.7 , which approximates 7 of 34.7). At 12 weeks of treatment, reduction in UAS7 was 21.7 ± 12.8 in omalizumab 300 mg group, which is comparable to a reduction of 3.5 ± 0.2 in aUAS7 seen in NB-UVB group in our study (amounting to UAS7 of 24.6). Moreover, patients receiving more than licensed doses of AH1 (more than 5 mg levocetirizine) were excluded from the omalizumab study²⁴; whereas, we included patients who were refractory to even 4 fold increased dosages of AH1. Cruz et al²⁵ reported a modest increase in geohelminth infections in allergic patients receiving omalizumab. This may be of concern for use of omalizumab in tropical countries where geohelminthic infestations are common. In contrast to omalizumab, phototherapy is a time-tested therapeutic modality. Thus phototherapy appears to be a safer and equally effective alternative for patients having refractory urticaria.

More than 80% of study cohort had positive ASST/APST at baseline, of which a significant number became negative post treatment (64%, $p < 0.05$), which reflects inhibition of serum histamine releasing factors brought about by NB-UVB and PUVA. To the best of our knowledge, effect of phototherapy on ASST/APST has not been studied previously; the results observed by us are encouraging and further studies are required to study this aspect more extensively. Huilan Z et al²⁶ reported IgE sensitization to be higher in CU patients and with 39 patients having levels more than normal, same held true for our study. There are no

previous studies documenting the effect of phototherapy on IgE levels in CU, although similar studies have been performed in atopic dermatitis²⁷ and psoriasis²⁸ with variable results. We noted a significant reduction in serum IgE levels post treatment in only PUVA treated group; however, the number of patients with raised serum IgE levels did not alter significantly post treatment in any of the groups. The exact mechanism by which PUVA brings about this change in IgE levels needs to be explored further.

Circulating thyroid autoantibodies and clinical hypothyroid disease were noted in 28% and 20% of study cohort respectively and was significantly higher in comparison to that reported previously.²⁹ Autoimmunity and clinical hypothyroidism might have led to treatment refractory, severe disease in our patients. Co-expression of allergic disease in CU patients is known.³⁰ A personal history of atopy was observed in 32% patients of our cohort, which could be explained on basis of similar nature of both diseases with a predominant Th2 pathway.

There were no dropouts indicating efficacy, tolerability and patient acceptance of the treatment provided. Common adverse effects included tanning and xerosis, which improved considerably with liberal application of emollients and sunscreens beyond phototherapy hours. Nausea and gastrointestinal adverse effects were reported only in PUVA group (24%). Mean patient satisfaction scores of 7.6 and 7.9 for PUVA and NB-UVB respectively prove patient acceptability, safety and efficacy of this treatment option for CRU.

Limitations

The limitation of the current study is shorter duration of follow-up. Longer follow-up period is required to ascertain maintained efficacy and relapse rate. Though subjective improvement perceived by the patient was assessed using patient satisfaction score, a specific quality of life measurement score for urticaria would be better. Random sample-size estimation and absence of pre-specified values of outcome measures are other limitations.

One of the perceived limitations of the current study is a lack of placebo group. However, withholding a potentially effective treatment in patients of severe refractory urticaria could not be ethically justified. Lack of placebo group did not allow us to definitely exclude the possibility of spontaneous remission. But, all our patients had prolonged and severe disease (mean disease duration > 34 months, mean continuous treatment duration > 25 months, corticosteroid dependence and baseline aUAS7 >4.9) that exceeded the time window normally associated with spontaneous remission. Hence, we can attribute significant improvement observed in our study to phototherapy.

Conclusion

Both PUVA and NB-UVB work effectively in CRU. Overall, NB-UVB is easy to administer and is devoid of gastrointestinal side effects. We propose that phototherapy is a safe, effective and affordable treatment option for patients having steroid dependent antihistamine refractory CU. It, therefore, should be employed before omalizumab, cyclosporine and other immunosuppressants and should also be included in standard urticaria treatment guidelines.

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Figure legends

Figure 1: Study design.

Figure 2: (a) Trend of Urticaria Activity Score in PUVA and NB-UVB groups. (b) Trend of Outcome scoring scale in PUVA and NB-UVB groups.

Figure 3: (a) Comparison of pre and post phototherapy diameters of histamine, normal saline, serum and plasma (in mm) in group A and B. (b) Comparison of number of patients with positive ASST, APST and raised IgE levels (>100 IU/ml), pre and post phototherapy in group A and group B.

Table 1. Urticaria activity score (UAS) and outcome scoring scale (OSS).

Urticaria activity score (UAS)*		
SCORE	WEALS	PRURITUS
0	None	None
1	Mild (<20 weals / 24 hours)	Mild (present but not troublesome)
2	Moderate (20-50 weals / 24 hours)	Moderate (troublesome but does not interfere with sleep)
3	Severe (>50 weals / 24 hours)	Severe (sufficiently troublesome to interfere with normal daily activity and sleep)
Outcome scoring scale (OSS)		
1	No improvement	
2	Minimal improvement (symptomatic improvement $\pm$, no change in frequency and extent of the disease)	
3	Moderate improvement (symptomatic improvement +, less frequent and less extensive disease)	
4	Marked improvement (occasional episodes, less extensive disease, symptomatic improvement ++, reduced antihistamine use)	
5	Clearance (with or without antihistamines)	

*Average UAS7 (aUAS7) i.e. UAS7 summed-up over a week divided by 7 was used (range 0-6)

Table 2. Clinical and demographic profile of both groups at baseline

	PUVA (group A, n=25) *	NB – UVB (group B, n=25) *
Age (mean $\pm$ SD, years)	33.7 $\pm$ 8.1	35.5 $\pm$ 11.7
Male : female ratio	2:3	2:3
Fitzpatrick's skin type		
III	17	10
IV	7	11
V	1	4
Total duration of illness (mean $\pm$ SD, months)	34.6 $\pm$ 17.4	42.2 $\pm$ 29.6
Total duration of treatment pre-phototherapy (mean $\pm$ SD, months)	26.4 $\pm$ 12.5	37.0 $\pm$ 25.7
Baseline mean aUAS7 (0-6)	4.9 $\pm$ 0.8	5.0 $\pm$ 0.7
Baseline mean OSS (1-5)	1.6 $\pm$ 0.5	1.3 $\pm$ 0.5
Mean IgE levels (IU/ml)	721.2 $\pm$ 735.7	403.0 $\pm$ 305.9
Number of patients with raised IgE levels	20	19
Number of patients with positive ASST	20	22
Number of patients with positive APST	20	23

* no statistically significant difference

APST – autologous plasma skin test; **ASST** – autologous serum skin test; **IgE** – immunoglobulin IgE; **NBUVB** - narrow band ultra-violet B; **OSS** – outcome scoring scale; **PUVA**: psoralen and ultra-violet A; **SD** – standard deviation; **UAS** – urticaria activity score.

Table 3. Treatment response in groups A and B.

	Group A (PUVA)	Group B (NB-UVB)
Baseline mean aUAS7	4.9 ± 0.8	5.0 ± 0.7
Baseline mean OSS	1.6 ± 0.5	1.3 ± 0.5
Primary end-point		
Mean aUAS7 at end of treatment (90 th day)	1.9 ± 0.7	1.4 ± 0.7, (p<0.05 inter-group)
Secondary end-points		
<i>At end of treatment (90th day)</i>		
Mean OSS	3.9 ± 0.3	4.0 ± 0.3
Clearance	0	1 (4%)
Marked improvement	23 (92%)	23 (92%)
Moderate improvement	2 (8%)	1 (4%)
Minimal improvement	0	0
Mean IgE levels (IU/ ml)	441.7 ± 407.3	330.6 ± 251.1
Reduction in IgE levels	279.6 ± 395.7 (p .002)	72.5 ± 211.7
Number of patients with raised IgE levels (>100 IU/ml)	19	19
Number of patients with positive ASST	9	9
Number of patients with positive APST	10	8
<i>At completion of follow up (180th day)</i>		
Mean aUAS7	1.5 ± 0.8	1.4 ± 1.0
Mean OSS	3.9 ± 0.5	4.0 ± 0.6
Clearance	1 (4%)	3 (12%)
Marked improvement	22 (88%)	20 (80%)
Moderate improvement	1 (4%)	1 (4%)

Minimal improvement	1 (4%)	0
Relapse	0	1 (4%)
Patient satisfaction score	7.6	7.9

.NBUVB - narrow band ultra-violet B; **PUVA**- psoralen and ultra-violet A; **UAS** – urticaria activity score; **OSS** – outcome scoring scale; **APST** – autologous plasma skin test; **ASST** – autologous serum skin test, **IgE** – immunoglobulin IgE,

Figure 1. Study design

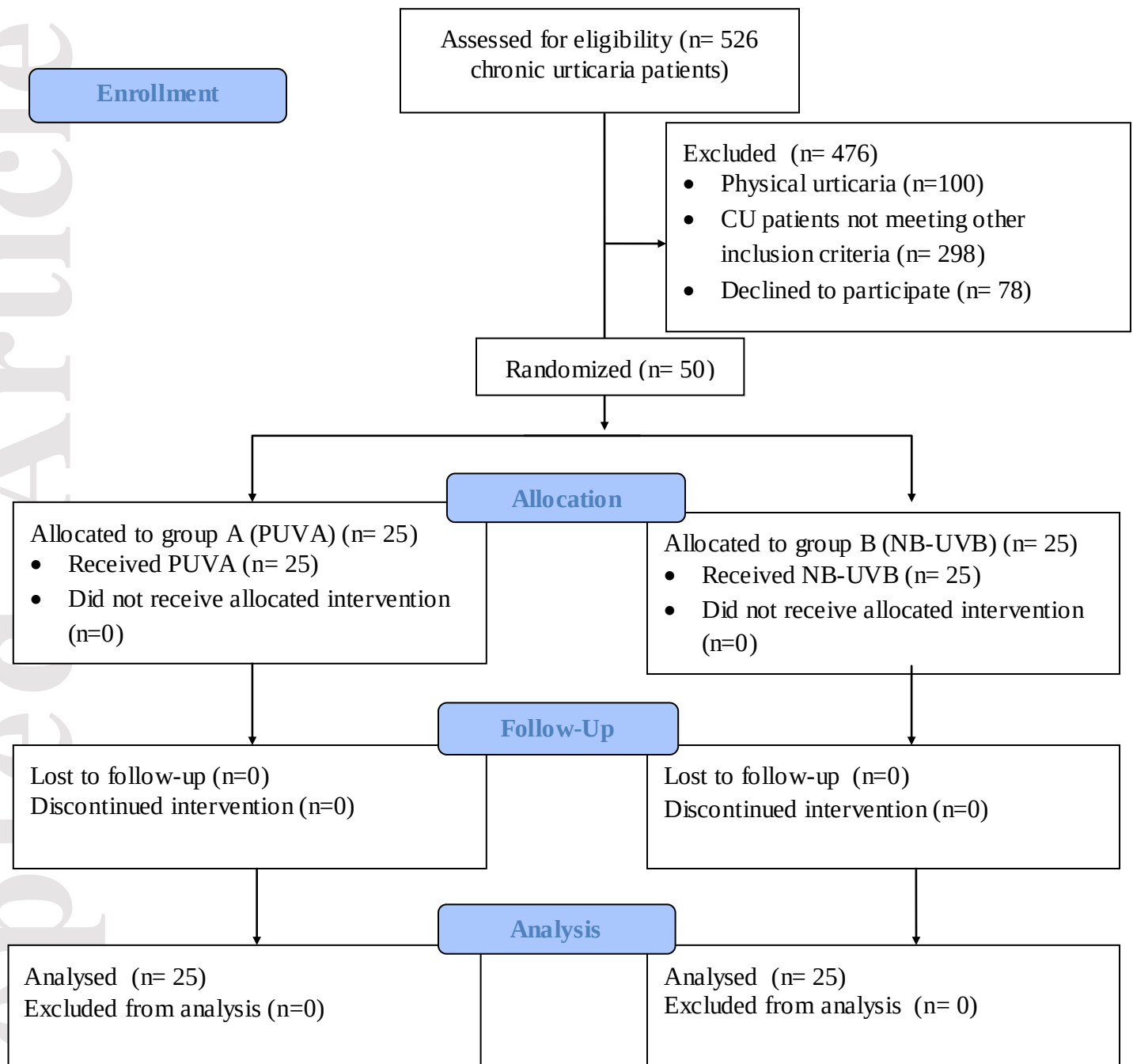
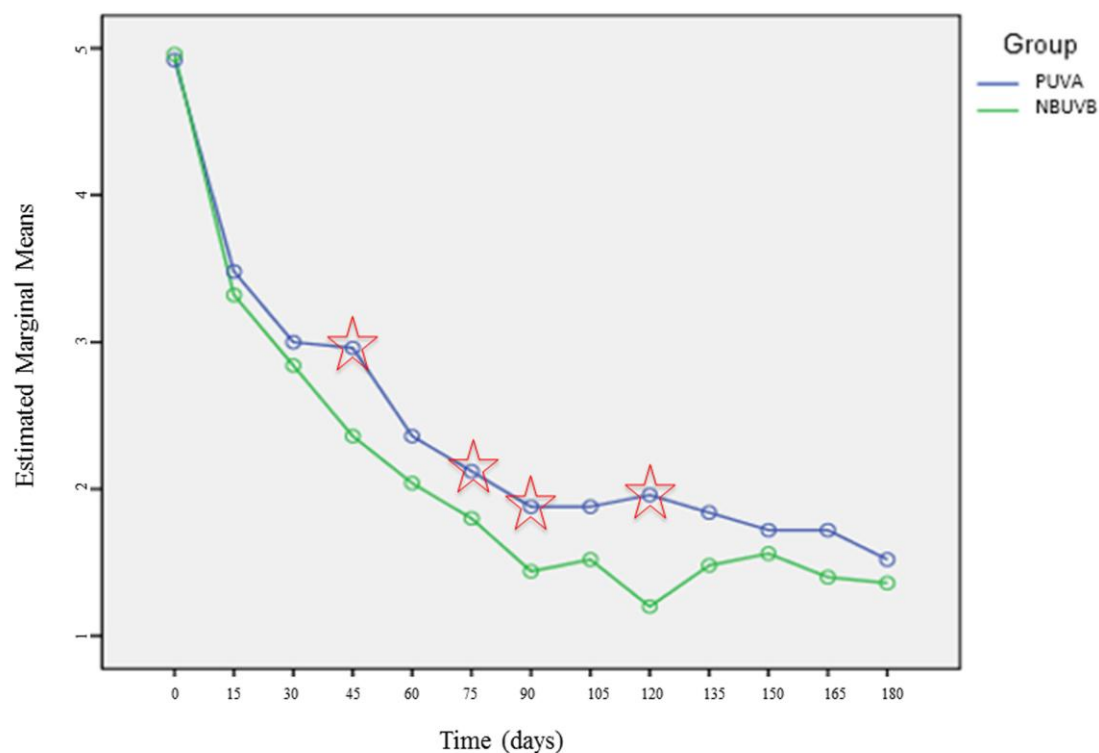
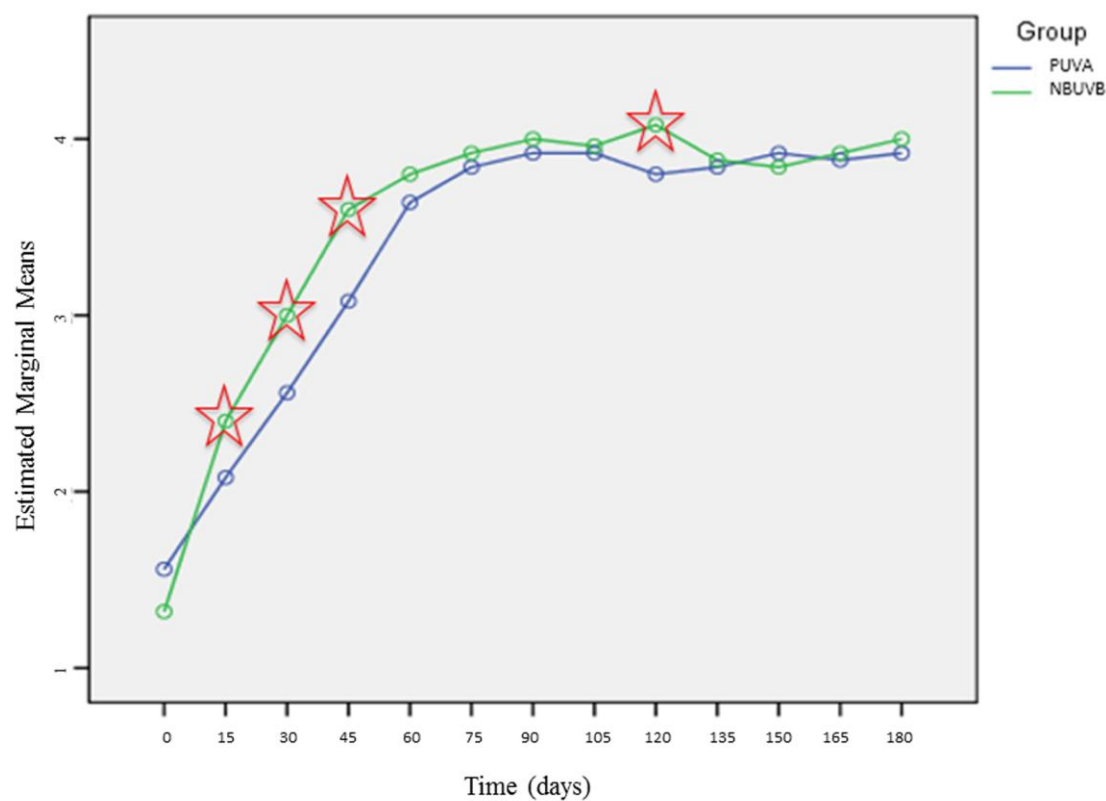


Figure 2a. Trend of Urticaria Activity Score in PUVA and NB-UVB group.



* Statistically significant reduction in urticaria activity score was seen in NB-UVB group at these time points ($p < 0.05$), including primary end-point (90th day) (graphs plotted after repeated measure ANOVA application with Bonferroni corrections)

Figure 2b. Trend of **Outcome scoring scale** in PUVA and NB-UVB group.



* The rise in outcome scoring scale was statistically significant in NB-UVB group at these time points ($p < 0.05$, graphs plotted after repeated measure ANOVA application with Bonferroni corrections)

Figure 3a. Comparison of pre and post phototherapy diameters of histamine, normal saline, serum and plasma (in mm) in group A and B.

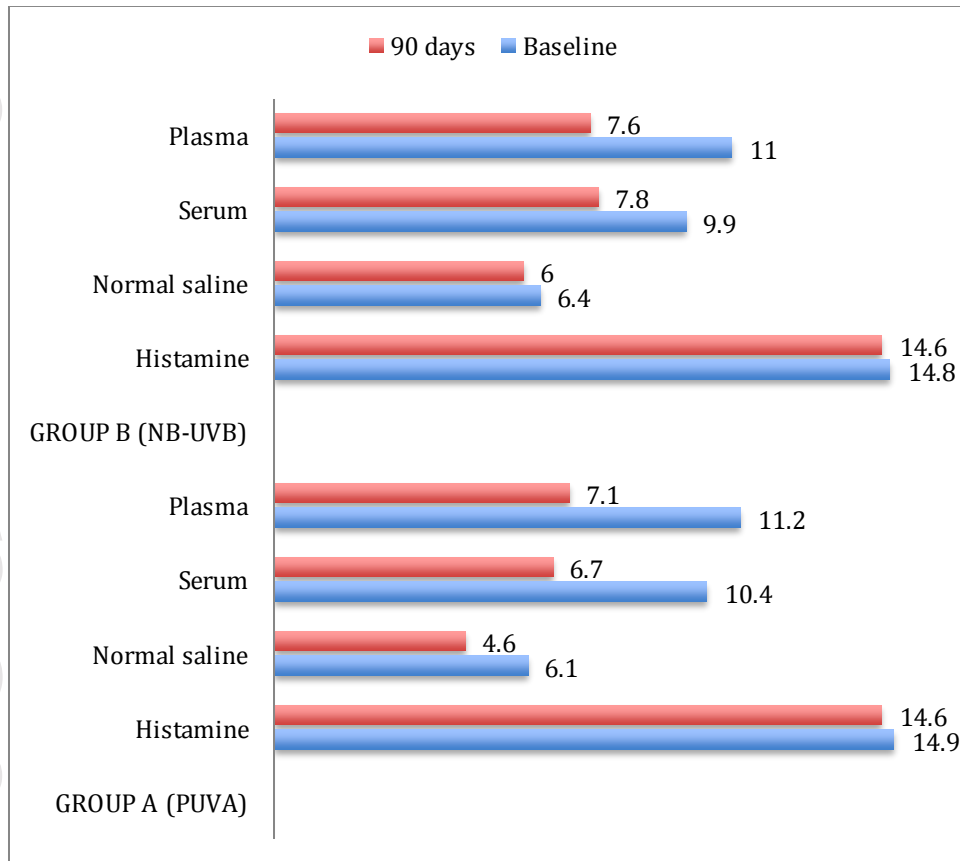
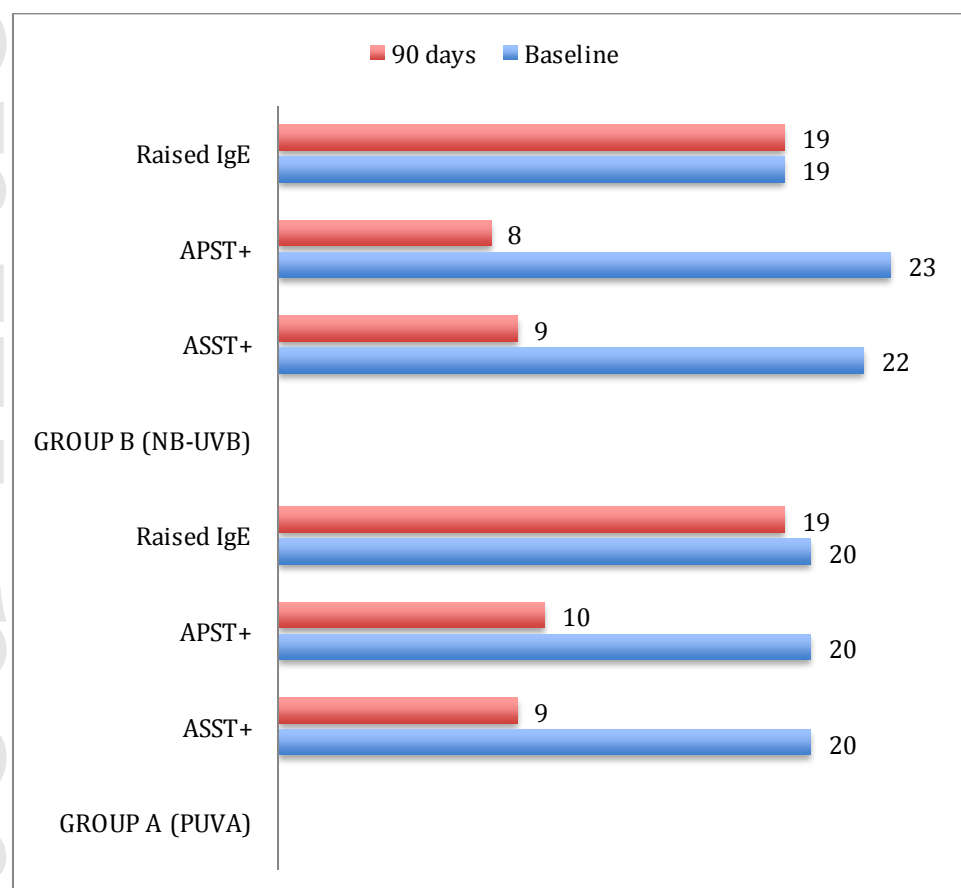


Figure 3b. Comparison of number of patients with positive ASST, APST and raised IgE levels (>100 IU/ml), pre and post phototherapy in group A and group B.



APST – autologous plasma skin test; **ASST** – autologous serum skin test, **IgE** – immunoglobulin IgE.