COMPARATIVE EVALUATION OF NARROW BAND UVB VERSUS ORAL 8-METHOXYPsorALEN UVA IN CHRONIC PLAQUE PSORIASIS

Rachita Talwar¹, Ranjeeta Sapam², Arpana Rijal³

¹Specialist, Department of Dermatology, NMC Speciality Hospital.

²Associate Professor, Department of Dermatology, JNIMS, Imphal.

³Professor, Department of Dermatology, BPKIHS, Nepal.

ABSTRACT

BACKGROUND

Psoriasis is a chronic, disfiguring, inflammatory and proliferative condition of the skin.

The aim of this study was to study the effect of narrowband UVB (NB-UVB) and psoralen ultraviolet A (PUVA) in the treatment of chronic plaque psoriasis, and to compare the therapeutic efficacy of both.

MATERIALS AND METHODS

This was a randomised, intraindividually controlled paired comparison study. Each side of the patient's upper extremity was treated independently, with NB-UVB and PUVA. PUVA was given in a dose of 70% of MPD (minimal phototoxic dose) or depending upon the skin type and NB-UVB were given in a dose of 70% of MED (minimal erythema dose). An increment of 20% was made at each session till minimally perceptible erythema occurred. The assessment was done by calculating the MPASI_{UL} score at each visit up to 75% improvement.

RESULTS

Thirty patients were enrolled out of which 3 defaulted. The number of patients achieving 75% improvement in the MPASI_{UL} were 23 on the PUVA side and 22 on the NB-UVB side, the number of treatments required was 15.43 on PUVA side 16.09 on the NB-UVB side and the time taken was 34.26 and 36.86 days for PUVA and NB-UVB sides respectively. The adverse effects were less with NB-UVB.

CONCLUSION

There was no significant difference between the two modalities in the number of patients achieving the number of treatments required and the time taken for 75% improvement in MPASI_{UL} score. However, NB-UVB might be superior to systemic PUVA with better tolerance and low profile of side effects in the treatment of psoriasis.

KEYWORDS

NBUVB, PUVA, Psoriasis, Randomisation, Trial.

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BACKGROUND

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role.¹

Photochemotherapy using psoralen has been a time tested treatment for psoriasis. A significant advance in the phototherapy has been the introduction of narrowband UVB (NB-UVB) therapy using Phillips model TL 01 lights having spectrum of 310-315 nm with a peak at 311 nm. NB UVB has been found to be as effective as PUVA² without distinct disadvantages of the latter and considered superior to broad band UVB³ and bath PUVA.^{4,5} Various studies^{2,6} have been carried out in the western countries comparing the efficacy of NB-UVB and PUVA phototherapy with contradictory results. The present study is undertaken to compare the therapeutic efficacy of narrow band (TL01) UVB phototherapy (NB-UVB)

with oral 8-methoxypsoralen photochemotherapy (PUVA) in patients with chronic plaque psoriasis.

MATERIALS AND METHODS

All clinically diagnosed cases of chronic plaque psoriasis with involvement of >20% of body surface area (using rule of nine) and bilaterally symmetrical involvement in the upper limbs attending the Dermatology Out Patient Department of BPKIHS, Nepal from April 2006 to April 2007 were included in the study. Exclusion criteria included age less than 14 years or >70 years, pregnant and lactating mothers, renal, hepatic or cardiovascular disease, who had taken any antipsoriatic treatment within the last 4 weeks, received any form of UV therapy within the preceding 6 months, any radiation therapy or previous failure/intolerance to phototherapy, or on any photosensitive drugs and with cataract or skin cancer. Prior informed and written consent was taken from all patients. A detailed history and complete clinical examination was done. A wash off period of 4 weeks was given to patients on any kind of treatments. No concomitant therapy was allowed except for emollients and antihistamines.

Baseline investigations of routine blood counts, liver function tests and renal function tests were performed and repeated at 3 weekly intervals.

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Corresponding Author:

Ranjeeta Sapam,
Moirangkhom, Sougaijam Leirak,
Imphal.

E-mail: ranssapam@gmail.com

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The present study was designed to do half side comparison in the same patient between the two modalities. Upper extremity was chosen as the site considering the ease with which one side of the upper limb could be shielded and also to reduce the inconvenience caused to the patient.

In the present study, assessment was done by calculating the psoriasis area severity index (PASI) score⁷ for only the upper limbs, separately for each side at baseline. Therefore, the PASI score was modified for the upper limbs (MPASI_{UL}). Ralloc software was used for randomisation of the allocation of side.

Determination of MED and MPD⁸ – Prior to the study, first the minimal erythema dose (MED) of NB-UVB was determined in each patient using test doses 100, 140, 200, 280, 390, 550, 770, 1100 mJ/cm² with the help of a photo testing template. The first 6 doses were used for skin type I and II and the last 6 for types III through VI. MED was defined as the smallest dose of radiation required to achieve just detectable erythema, read after 24 hours. Subsequently, the minimal phototoxic dose (MPD) of PUVA was determined in each patient using test doses 0.5, 1, 1.5, 2.0, 3.0, 5.0, 7.0, 9 J/cm². The first 6 doses were used for skin type I and II and the last 6 for types III through VI. MPD was defined as the smallest dose of radiation required to achieve just detectable erythema and was read after 72 hours.

Phototherapy

On the first treatment day, patient received NB-UVB irradiation on one side of the extremity. Such NB-UVB sessions were planned 3 times weekly every alternate day.² During the irradiation, the rest of the body was covered by tightly woven cloth to prevent the transmission of UV light. On the second day, the patient was given oral 8-methoxypsoralen capsules in a dose of 0.6 mg/kg body weight.⁹ Two hours later, the other side of the patient's extremity and the remaining part of body was exposed to UVA while the body area previously treated with NB-UVB was shielded from receiving additional UVA radiation. These PUVA sessions were given 3 times weekly⁹ alternating with the NB-UVB sessions.

The initial irradiation dose given for NB-UVB was 70% of MED and for PUVA it was 70% of MPD.⁸ Patients with a negative MED were treated with a standard starting dose⁹ of 280 mJ/cm² (70% of MED for skin type IV, V) for NB-UVB. Patients with a negative MPD were treated with skin type based initial UVA dose of 1.5 J/cm² for skin type III, 2 J/cm² for skin type IV and 2.5 J/cm² for skin type V.^{10,11} Subsequent dose increments were aimed at eliciting or maintaining a slight erythema. The irradiation dose was increased by 20% of the previous dose if there was an absence of erythematous response. If there was Grade 1 erythema, same dose as previous visit, thereafter reduce the increments and if Grade 2 erythema, next exposure is postponed until erythema resolves; and then repeat the previous dose: subsequently, reduce increments. The half side treatment was performed until there was ≥75% improvement in the MPASI_{UL} score or for a maximum period of 30 sessions whichever was earlier.

Light therapy was administered using "Derma India, Chennai Lightning" cubicles. During phototherapy, all patients wore UV protective goggles and the genitalia were shielded.

All the patients were examined by the dermatologist not aware of the treatment allocation. The assessment was done at each visit up to 75% improvement in the MPASI_{UL} or up to 30 sessions whichever was earlier.

According to the Response the Patients were Classified as those Having

- **Marked Improvement:** ≥75% improvement in MPASI_{UL} score from the baseline within a maximum of 30 sessions.
- **Partial Improvement:** 1%-74% improvement in MPASI_{UL} score from the baseline within a maximum of 30 sessions.
- **Static Disease:** No improvement in MPASI_{UL} scores.
- **Disease Worsening:** Increase in MPASI_{UL} score.

Any adverse effect during the treatment period was recorded. Clinical photographs were taken. Outcome measures included improvement in the MPASI_{UL} scores, number of exposures for the improvement, cumulative UV dose for the improvement and any adverse effect within that period.

Statistical Analysis

Data were entered in Microsoft Excel 2000 and converted into SPSS version 10.0 for statistical analysis. For categorical and continuous data, simple percentage, mean and standard deviation were calculated. To find out the significant difference among the groups Chi Square was calculated for categorical data and Independent t test was calculated for numerical data. Significance was defined as p<0.05.

RESULTS

Of the 30 patients, 27 completed the study. Out of 27 patients, there were 16 (59.3%) males and 11 (40.7%) females and male to female ratio was 1.45:1. The age of the patients ranged from 14-70 years with the mean age of 35.7 ±14.82 years. The body surface area (BSA) involvement varied among patients. Five (18.5%) patients had up to 25% BSA involvement, 6 (22.2%) had 26-50% involvement, 10 (37.03%) had 51-75% involvement and 6 (22.2%) had 76-100% involvement.

MPASI_{UL} Scores

The baseline psoriasis area and severity index (MPASI_{UL}) ranged from 18 to 72 with the mean being 44.04 ±15.46 for both the groups. The final MPASI_{UL} for PUVA side was 13.00 ± 9.12 (range, 4-48) and for NB-UVB side was 13.67 ± 10.10 (range, 4-48). There was no statistical difference in these parameters between the two sides (p>0.05).

There was a statistically significant improvement in MPASI_{UL} score with both the modalities, PUVA and NB-UVB.

Outcome of Treatment

The outcome is depicted in table no 1. There was no statistically significant difference in these parameters of response between the two sides (p>0.05).

	PUVA side (n=27)	NB-UVB side (n=27)	p value
No. of patients with marked improvement ($\downarrow$ MPASI _{UL} $\geq$ 75%)	23 (85.18%)	22 (81.48%)	0.718
No. of patients with partial response ($\downarrow$ MPASI _{UL} 1%-74%)	3 (11.11%)	4 (14.81%)	0.500
No. of patients with disease worsening	1 (3.7%)	1 (3.7%)	0.754
No. of treatments for marked improvement (Mean $\pm$ SD) Range	15.43 $\pm$ 2.46 12-21	16.09 $\pm$ 2.29 12-22	0.36
Time taken for marked improvement in days (Mean $\pm$ SD) Range	34.26 $\pm$ 5.67 26-47	36.86 $\pm$ 5.43 27-51	0.123
Total UV dose required for marked improvement in J/cm ² (Mean $\pm$ SD) Range (J/cm ²)	127.39 $\pm$ 36.97 75.87-210.87	33.47 $\pm$ 16.81 11-75.3	0

Table 1. Outcome of Treatment

Cumulative number of patients who achieved marked improvement is depicted in table no 2.

Number of Sessions	PUVA side (n=27)	NB-UVB side (n=27)	p value
12	2 (7.40%)	1 (3.70%)	0.5
14	10 (37.03%)	5 (18.51%)	0.22
16	16 (59.25%)	14 (51.85%)	0.58
18	21 (77.77%)	19 (70.37%)	0.53
20	22 (81.48%)	21 (77.77%)	0.73
22	23 (85.18%)	22 (81.48%)	0.5

Table 2. Cumulative Number of Patients who Achieved Marked ($\geq$ 75%) Improvement

Changes in MPASI_{UL} Score on treatment

After 2 sessions the mean MPASI_{UL} in the PUVA side was 43.33 $\pm$ 15.26 and in the NB-UVB side was 43.89 $\pm$ 15.52. After 4 sessions it was 39.52 $\pm$ 15.05 in PUVA side and 41.81 $\pm$ 14.86 in NB-UVB side. At the end of 16 sessions, mean MPASI_{UL} was 18.71 $\pm$ 11.76 in PUVA side and 18.32 $\pm$ 12.56 in NB-UVB side. There was no statistically significant difference in the mean MPASI_{UL} between the two sides till the end of 16 sessions (Fig. 1).

Figure 1. Changes in MPASI_{UL} on Treatment

Adverse Effects

Eight (29.6%) patients in PUVA side and 7 (25.9%) patients in NB-UVB side experienced side effects. Two (7.4%) patients in each group developed polymorphic light eruption (PMLE). Exacerbation of pruritus was experienced by 6 (22.2%) patients on PUVA side and 5 (18.5%) patients on NB-UVB side,

which was managed with antihistamines and emollients. Six (22.2%) patients who experienced pruritus on PUVA side also had nausea due to intake of oral Methoxypsoralen tablet; it was managed with oral antiemetics half an hour before methoxypsoralen dose.

DISCUSSION

Although different modalities of treatment can induce remission in a high percentage of psoriatic patients, in the absence of a cure, both safe and effective therapy to maintain patients in prolonged remission is not found.

Different studies^{2,6} have compared the efficacy of PUVA and NB-UVB with conflicting reports as to which is superior.

Since the present study was a within-patient side-to-side comparison study, one half of the upper extremity served as a control for the other half. Similar kind of side-to-side comparison studies have been done by van Weelden et al¹² and Tanew et al² and in the past for the comparison of PUVA and NB-UVB and by Dawe et al⁴ for comparing bath PUVA and NB-UVB. This kind of a study design is advantageous as it obviates the enrolment of controls.

The regimen used in the present study for both PUVA and NB-UVB was the thrice weekly regimen. Thrice weekly frequency chosen for PUVA was in accordance to the American PUVA protocol. For NB-UVB three times weekly appeared to be the optimal regimen for efficacy in that two NB-UVB sessions took 50% longer to clear psoriasis compared to three times weekly, 88 vs. 58 days respectively.¹³ Regimens similar to ours were used by Tanew et al² and Tahir et al¹⁴ while van Weelden et al,¹² Gordon et al⁶ and Yones et al⁸ used the twice weekly regimens. A very different twice weekly frequency for PUVA and thrice weekly frequency for NB-UVB was used by Dawe et al⁴ and Markham et al¹⁵ in their studies. However, the kind of regimens used did not have any effect on the outcome of the study.

A 75% reduction in PASI score called PASI 75 is the current benchmark of primary end point for most clinical trials.¹³ In the present study, there was no statistically significant difference in the number of patients who achieved reduction in MPASI $\geq$ 75% with both modalities (85.18% on PUVA side and 81.48% on NB-UVB side; p value 0.718). This is in agreement with the previous studies done by Tanew et al² who also found statistically similar clearance rates of 43% for PUVA and 33% for NB-UVB, and Markham et al¹⁵ who found very high clearance rates of 100% for both PUVA and NB-UVB. Such high clearance rates can be explained on the basis that the patients in Markham's study were treated until they were completely clear. However, Dawe et al⁴ found significantly higher clearance rates with NB-UVB as compared to PUVA

(54% vs. 75%, $p = 0.03$). In contrast, in Gordon et al's⁶ study, clearance of psoriasis was achieved in a significantly greater proportion of patients treated with PUVA (84%) than with NB-UVB (63%, $p=0.001$). Similar results were found by Tahir et al¹⁴ who found the clearance rates of PUVA to be 85% as compared to 60% for NB-UVB ($p = 0.04$) and by Yones et al⁸ who found the clearance rates of PUVA and NB-UVB to be 84% and 65% respectively.

The number of treatments required to achieve 75% improvement with both modalities was analysed in the present study and it was found that there was no significant difference ($p=0.36$). Similar results were obtained by Tanew et al² who found that for >75% reduction of PASI score using PUVA and NB-UVB, equal numbers of exposures i.e. 15 exposures are required. This differed from study by Markham et al¹⁵, who reported significantly fewer treatments with PUVA for marked improvement as compared to NB-UVB (19 vs 25.5, $p=0.03$), although there was no significant difference in the number of days to clear. This may be due to twice weekly PUVA exposure as compared to thrice weekly regimen for NB-UVB in their study. Similarly other studies^{4,6,8,14} done by various authors have shown the median number of treatments to clearance, to be significantly lower for PUVA as compared to NB-UVB. The number of treatments to clear as reported by Gordon et al⁶ was 16.7 for PUVA vs. 25.3 for NB-UVB ($p<0.0001$), Dawe et al⁴ reported it to be 19 for PUVA and 24.5 for NB-UVB ($p=0.01$), Tahir et al¹⁴ found it to be as 17 for PUVA and 25.5 for NB-UVB ($p<0.001$) and Yones et al⁸ similarly found it to be 17 for PUVA and 28.5 for NB-UVB ($p<.001$).

There was no statistically significant difference in the present study between the time taken to achieve 75% improvement in both sides ($p=0.123$). Tanew et al's² study also concluded that statistically similar treatment duration of 38 days is required for $\geq 75\%$ reduction of PASI scores using PUVA and NB-UVB. Markham et al¹⁵ similarly found no significant difference in the number of days to clear with both modalities ($p=0.46$). In contrast, Dawe et al⁴ found that NB-UVB achieved clearance in a median of 11 days ($p=.001$) more quickly than PUVA.

The mean cumulative PUVA dose for 75% improvement was 127.39 ± 36.97 J/cm² and the mean NB-UVB dose was 33.47 ± 16.81 J/cm² in this study. Yones et al⁸ reported that mean PUVA dose for >75% improvement was 126 J/cm² and mean NB-UVB dose was 41.3 J/cm².

Since only the upper extremity was chosen as the area of evaluation in the present study, the anatomical area wise comparison of effectiveness of the two modalities could not be analysed as shown by van Weelden et al¹², who concluded that PUVA was more effective in clearing extremities and NB-UVB was more effective in clearing trunk. His findings indicated that PUVA may be better for clearing lesions that are more recalcitrant to therapy, such as those found on the extremities. None of the patients in the present study came for followup after the 75% clearance, so the mean remission period with PUVA and NB-UVB could not be compared. Gordon et al⁶ had reported three times more remission period for PUVA as compared with NB-UVB (12% of those treated with NB-UVB were clear of psoriasis 6 months after finishing treatment compared with 35% for PUVA, $p = 0.002$). Similarly Yones et al⁸ reported that 6 months after cessation of therapy, 68% of PUVA treated patients were still in remission vs. 35% of NB-UVB treated patients ($p=.02$). However, in Markham et al's¹⁵

study, an average remission period of 288.5 days for NB-UVB and 231 days for PUVA group, was observed during the followup of 1 year, which was not found to be statistically significant.

In the present study, 1 (3.7%) patient had a flare up of disease in the form of grade 2 erythema and an increased scaling which was observed equally in both sides. The reason could be photoexacerbation due to improper photoprotection. Markham et al¹⁵ had reported that a similar percentage of patients in each group (PUVA, 80%; NB-UVB, 75%) developed grade 1 erythema showing that the regimens were equally erythemogenic; however, grade 2 erythema occurred only in PUVA group. Gordon et al⁶ observed an increased percentage of erythematous episodes with NB-UVB as compared to PUVA (73% vs. 35%) while in contrast Yones et al⁸ observed a significantly increased frequency of erythema with PUVA than NB-UVB (49% vs. 22%, $p=.004$).

Exacerbation of pruritus (PUVA 22.2%, NB-UVB 18.5%) and PMLE (PUVA 7.4%, NB-UVB 7.4%) was observed equally with both modalities while nausea in 22.2% of patients was observed solely due to methoxypsoralen ingestion. This was comparable to observations made by Markham et al¹⁵ who also concluded that pruritus and polymorphic light eruption occurred equally in both groups, but only patients in the PUVA group developed nausea.

Three patients (10%) were lost to followup which could be due to economic constraints, family and social obligations. This may be a handicap in widespread use of NB-UVB and PUVA as treatment modality.

CONCLUSIONS

It is therefore concluded from the present study that NB-UVB and PUVA are equally effective in treatment of severe chronic plaque psoriasis in patients of Nepali and Indian origin.

Considering the good therapeutic efficacy, no drug related side effects, the low profile of acute and possibly also longterm side effects and the safe use in children and pregnancy, the present study considers narrowband UVB as first-line treatment for moderate-to-severe plaque psoriasis. PUVA on the other hand remains the mainstay of treatment for severe recalcitrant psoriasis.

The optimum treatment protocol for narrowband UVB and, in particular, the average duration of remission is yet to be determined in larger patient cohorts. In addition, prospective followup studies are required to assess the longterm risks in humans associated with therapeutic exposures to narrow band UVB radiation.

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