Controversial Results of Phototherapy in The Treatment of Psoriasis

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Abstract

Background: Phototherapy remains an essential option for patients with moderate to severe psoriasis or when topical measures alone are insufficient. Photochemotherapy with PUVA and later NBUVB are becoming more popular and more trusted. Yet, there is a great controversy of which modality is more beneficial and less risky.

Objective: to compare PUVA and NBUVB as regard their therapeutic effect and side effects in psoriasis.

Subjects and methods: Seventeen patients with chronic plaque psoriasis were included in a twice weekly regimen. Each patient received NBUVB on the right side of the body with starting dose 0.3 J/cm2 and low incremental regimen depending on erythema response. Immediately after exposure to NBUVB, the patient ingested a dose of 0.6 mg/kg of 8- methoxypsoralen. Two hours later, the left side of the patient was exposed to UVA with starting dose depending on patient’s skin type and incremental regimen based on erythema response.

Clinical evaluation was performed at every session until complete clearance or at most 30 sessions using the PASI score.

Results: The NBUVB side responded as equal as the PUVA side (comparison of PASI score on both sides showed no significant difference). In five patients, improvement of the lesions was excellent, good in three patients, mild in four while no improvement was observed in five patients on either side. Twelve patients developed local complications (erythema, itching and/or pigmentation) on the PUVA side compared to 11 patients on the NBUVB side with no significant difference between both sides. There was a higher cumulative dose on the PUVA side in contrast to that on the NBUVB side (approximately 3 folds). There was a significant difference as regard the dosimetry for the benefit of NBUVB and some unwanted effects of psoralen.
**Conclusion:** We concluded that the therapeutic effect of NBUVB phototherapy is as effective as PUVA on a twice-weekly treatment schedule in chronic plaque psoriasis. However, NBUVB is more convenient for the patient and less time consuming, because no exogenous photosensitizer is used. This prevents the potential drawbacks of psoralens and the need for eye and skin protection after sessions. Moreover, the therapeutic effect of NBUVB is achieved with a lower cumulative dose which means a lower risk for incidence of complications with special reference to skin malignancy.

**Introduction**

Photochemotherapy with Psoralen-UVA (PUVA) has been mastering the field of phototherapy of extensive plaque psoriasis for years\[1\]. The efficacy of PUVA has not been surpassed by another form of phototherapy. It still plays a significant role especially in extensive resistant cases and with precautions and limitation of total dose; it gives excellent response\[2\].

It acts through immuno-modulatory and anti-proliferative actions. In addition, it acts for the generation of reactive oxygen species which damage DNA, cell membranes & cytoplasmic constituents\[3\].

However, it is associated with certain dangers especially gastrointestinal irritating effect of oral psoralens, photoaging and affection of lens and retina which requires protection from other sources of UVA for 18 to 24 hours after session\[4\]. More important are the reports of cutaneous and genital tumors after prolonged PUVA therapy\[5,6\]. This is because psoralens on UVA exposure results in the formation of cyclobutane photoconjugation products with pyrimidine base of native DNA. Further mechanism is the downregulation of immune and inflammatory cell functions through the decrease of the number of inflammatory cells and Langerhans cells in the affected area\[7,8\].

The addition of UVB to the photochemotherapy of psoriasis revealed that PUVA is more effective than the conventional broad band UVB\[9\]. The breakthrough in this issue came in the late eighties of the last century\[10\] when narrow band UVB (NBUVB) phototherapy with a wave length of 311+2 nm was introduced as an appealing tool for the treatment of psoriasis.

It acts mainly through local effects, including the induction of anti-inflammatory or immunosuppressive soluble mediators as IL4 and IL10, suppression of -INF inducers ;IL-12, IL-18 and IL-23 and decrease in local immunoreactivity\[11,12\]. It also modulates the expression of cell surface molecules and induces apoptosis in pathologically relevant cells\[13,14\].

It was claimed that it rarely induces erythema or Koebner effect and has a good therapeutic effect\[15\]. Nevertheless, NBUVB confers a modest increase in non melanoma skin cancer risk which could be explained by its local immunosuppressive effect, albeit much less than that observed with PUVA. Therefore, it remains a relatively low-risk treatment for psoriasis. \[16,17,18\].

There has been a great enthusiasm for NBUVB as an alternative therapy to replace PUVA. It was suggested that both modalities has an equal therapeutic effect\[19,20\]. If confirmed, this will be of considerable importance, as NBUVB therapy is likely to be safer on the long run than PUVA \[21\].
**Aim Of The Work**

The aim of this study is to compare the therapeutic effects, side effects, and cumulative dose of NBUVB with PUVA in Egyptian patients with chronic plaque psoriasis.

**Patients And Methods**

Seventeen patients (7 males and 10 females) with plaque psoriasis affecting more than 20% of their total body surface area were included in a randomized, paired (within-patient) comparative study. They were treated in the Phototherapy Unit in Dermatology Outpatient Clinic at Zagazig University Hospital. The age of the patients ranged between 22-67 years. Eight patients were of skin type III and 9 patients were of skin type IV. The duration of psoriasis ranged between 6 months and 20 years. Five patients had previous PUVA therapy. Family history was found in 3 patients and 7 patients showed exacerbations (4 by stress and 3 by infections). (Table1).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>22 – 67 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Males : 7 patients (41.1%)</td>
</tr>
<tr>
<td></td>
<td>Females: 10 patients (58.8%)</td>
</tr>
<tr>
<td>Family history</td>
<td>3 patients (17.6%)</td>
</tr>
<tr>
<td>Previous phototherapy</td>
<td>5 patients (PUVA) (29.4%)</td>
</tr>
<tr>
<td>Duration (range)</td>
<td>0.5 – 20 years, 12 ±3.21</td>
</tr>
<tr>
<td>Precipitating factors</td>
<td>Stress: 4 patients (23.5%)</td>
</tr>
<tr>
<td></td>
<td>Infection : 3 patients (17.6%)</td>
</tr>
<tr>
<td>Skin type</td>
<td>Type III: 8 patients (47%)</td>
</tr>
<tr>
<td></td>
<td>Type IV: 9 patients (52.9%)</td>
</tr>
</tbody>
</table>

Table (1): Demographic data of the patients.

Exclusion criteria were; age less than 18 years, cataract or aphakia, pre-existing light aggravated disease, history of previous or existing cutaneous or internal malignancy, pregnancy or lactation and any type of UV therapy within the preceding 6 months. Patients were instructed not to use any topical treatment apart from emollients for one month prior to the study. Full history, general examination, and dermatological examination were carried on before starting treatment.

Diagnosis of cases was done on clinical ground confirmed by histopathology and evaluation of the severity of psoriasis was done using the PASI score (Psoriasis Area and Severity Index[22]). The score ranges from 0 to 72.

Since we dealt with each half body side as a separate entity, we had to calculate the PASI score for each side as a whole body so the calculated score was divided by two.
**Investigations:**
For every patient; complete blood picture, liver and kidney function tests and ophthalmological assessment were done before starting treatment.

**Irradiation cubicles:**
For NBUVB a Cosmedico Steinkirching 56 Germany cabinet fitted by 10 philips 100 W (TL-01) lamps emitting radiations between 310-315 nm was used in this study.
For PUVA a Dixwell whole-body cubicle housing 40 UVA lamps (Phillips 75185 PUVA 802/100 W) emitting radiation between 315-400 nm with peak at 365 nm was used.

**Treatment Protocol**

The patients were treated twice weekly. Each half-patient (sagittal plane) was treated independently. The right half of each patient was treated by NBUVB phototherapy. Based on previous works\[23\]; we started with a standard starting dose (0.3 J/cm²) and stepwise increase (20% increase of the previous dose) depending upon the patient’s erythema response. If mild erythema occurred, we decreased to the previous dose without further increase. In case of moderate or severe erythema, we stopped sessions until erythema faded and then started with 50% of the previous dose without further increase.

The left half of the patients was treated by PUVA photochemotherapy depending on the patient skin photo-type regimen\[3\]. The starting dose of PUVA was 1.5 J/cm² for patients with skin types III, and 2 J/cm² for patients with skin type IV. The dose was increased by 0.5 J/cm² every second session until erythema (mild) occurred, then fixed.

At first, the patient received the NBUVB irradiation on the right half of the body covering the left half by a protective half body leather cover to prevent transmission of radiation to the PUVA half-side. Immediately after NBUVB exposure, the patient ingested 8-methoxypsoralen tablets at a dose of 0.6 mg/kg body weight. Two hours later, the left half of the body was exposed to UVA with the right side shielded. Patients wore protective goggle in the machine and thereafter wore sunglasses during the rest of the day. The male genitalia were shielded during exposure to both treatments.

Patients were evaluated after every session for erythema, scaling, infiltration and side effects. Final evaluation was performed after complete remission or after a total 30 sessions for each half independently.

Improvement was considered as excellent (75-100 %), good (50 -75%) and poor (<50%) according to decrease in PASI score, while fixed or increased PASI score after treatment was considered as no response.

**Results**

**Pretreatment:**
Before starting treatment, there was no significant difference between the PASI score on the right side (NBUVB side) of the patients and the left side (PUVA side) (P>0.05), (table 2).
**Table (2): Base line PASI score.**

**Post treatment:**

At the end of treatment, comparing the NBUVB side to the PUVA side there was no significant difference in the PASI score ($P>0.05$), (table 3), while the cumulative doses of NBUVB and PUVA showed a high significant difference ($P<0.001$), (table 4).

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**Table (3): PASI score on each side at the end of treatment.**

**Table (4): Cumulative doses of both NBUVB and PUVA at the end of treatment.**
depending on the difference of PASI score between pre and post treatment using the median statistical test (table 5, and figures 1-6 showing more or less similar response on both sides).

<table>
<thead>
<tr>
<th>Response</th>
<th>NBUVB SIDE</th>
<th></th>
<th>PBVA SIDE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
<td>Median (pre treatment)</td>
<td>Median (post treatment)</td>
</tr>
<tr>
<td>Excellent</td>
<td>6</td>
<td>35.3</td>
<td>12.8</td>
<td>0.85</td>
</tr>
<tr>
<td>Good</td>
<td>2</td>
<td>11.8</td>
<td>12.7</td>
<td>5.15</td>
</tr>
<tr>
<td>mild</td>
<td>4</td>
<td>23.5</td>
<td>13.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Poor or no response</td>
<td>5</td>
<td>29.4</td>
<td>14.2</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>100</td>
<td>13.5</td>
<td>8.43</td>
</tr>
</tbody>
</table>

Table (5): The response to treatment on each side.

<table>
<thead>
<tr>
<th></th>
<th>Pre treatment median (PASI)</th>
<th>Post treatment median (PASI)</th>
<th>K.W</th>
<th>K.W value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB UVB</td>
<td>13.5</td>
<td>8.43</td>
<td>14.4 (p&lt;0.05)</td>
<td>0.02</td>
<td>0.92</td>
</tr>
<tr>
<td>side</td>
<td></td>
<td></td>
<td></td>
<td>non significant</td>
<td></td>
</tr>
<tr>
<td>PUVA</td>
<td>13</td>
<td>8.5</td>
<td>14.2 (p&lt;0.05)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (6): Analysis of the response on each side.
Fig 1: Before treatment

Fig 2: Excellent response after treatment

Fig 3: Before treatment

Fig 4: Good response after treatment

Fig 5: Before treatment

Fig 6: Poor response after treatment
The results are analyzed using the non parametric statistical test Kruskal Wallis (K.W). On the NBUVB side, the K.W was 14.4 with a significance difference (P<0.05) between pre and post treatment PASI score. On the PUVA side, the K.W was 14.2 with a significance difference between pre and post treatment PASI score (P<0.05). Comparing the median of NBUVB side response to that of PUVA side response, there was no significance difference (P= 0.92), (table 6).

**Complications:**

Erythema, itching and pigmentation were the local side effects of treatment, whereas nausea and headache were the side effects of psoralen.

1-Systemic complications:

Systemic complications (nausea and headache) affected 5 patients; 4 patients (23.5%) complained from episodes of headache after treatment and one patient (5.8%) complained from nausea after taking the psoralen tablets. These complications disappeared with appropriate symptomatic treatment.

2-Local complications (table 7):

Twelve patients (70.5%) developed local complications (erythema, itching and/or pigmentation) on the NBUVB side in contrast to 11 patients (64.7%) on the PUVA side. Using the McNemar’s exact test for paired proportions (Mc) there was no significant difference (Mc.value =1.0)

<table>
<thead>
<tr>
<th>Complications</th>
<th>NBUVB SIDES</th>
<th>PUVA SIDES</th>
<th>Mc value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Percent</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Total complications</td>
<td>12</td>
<td>70.5</td>
<td>11</td>
</tr>
<tr>
<td>Erythema (total)</td>
<td>11</td>
<td>58.8</td>
<td>8</td>
</tr>
<tr>
<td>Grade I</td>
<td>8</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>Grade II</td>
<td>3</td>
<td>17.6</td>
<td>2</td>
</tr>
<tr>
<td>Itching</td>
<td>7</td>
<td>41.1</td>
<td>7</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>3</td>
<td>17.6</td>
<td>2</td>
</tr>
</tbody>
</table>

Table (7): Local complications on each side.

**Erythema:** Erythema was reported on the NBUVB treated side in 11 patients in contrast to 8 patients on the PUVA side. NBUVB side was affected by grade 1 (asymptomatic-not well demarcated) erythema episodes (8 of 17, 47%) in contrast to (6 of 17, 35.3%) on the PUVA side. Grade II (well
demarcated-not painful) erythema affected (3 of 17, 17.6%) on the NBUVB side in contrast to (2 of 17, 11.7%) on the PUVA side. There was no significant difference between both sides (Mc value = 1.0)

**Itching:** Seven patients (47.1%) complained from recurrent episodes of itching on both sides with no significant difference (Mc value=1.0). They were managed with antihistamines and emollients and sometimes periodic stoppage of sessions for 1-2 sessions.

**Pigmentation:** Pigmentation (tanning & postinflammatory hyperpigmentation) appeared in 3 patients (17.6%) on the NBUVB side in contrast to 2 patients (11.8%) on PUVA side with no significant difference (Mc value = 1.0).

**Discussion**

Since the introduction of NBUVB to the field of phototherapy for psoriasis many studies reported that it is more effective and safer than PUVA and has a good impact on the quality of patient lives[24,25]. However, other authors recommended the superiority of PUVA[26]. On the other side, some reports revealed that both therapies have equal effects[27,28,29]. Which one is the most effective is still a matter of controversy. The reasons for these conflicting outcomes probably relate to the different treatment regimens.

To gain our own experience, this study was designed to compare NBUVB to PUVA in the management of chronic plaque psoriasis. We used NBUVB twice weekly and it is actually not the commonly used frequency by most studies which used it thrice weekly(3,4,24,35) but in two studies(26,27) it was used twice weekly. We found that this is more suitable and less disrupting to the patient professional and private lives and reducing costs as most of them were living in places at a distance from the hospital and most people work in daytime shifts so more hospital visits per week could not guarantee good patient compliance.

We found no significant difference in the therapeutic effect between both modalities These results are consistent with others[19]. However, they used the whole-body treatment regimen by either NBUVB or PUVA therapy and our study involved within-subject paired comparison. This design has several advantages over the parallel group studies : (I) increased statistical power; (II) no risks of differences that occur in groups studies; (III) it determines which treatment is most effective for each individual patients. However, it has some disadvantages; (I) it makes the study more complicated for the patients; (II) the possibility that treatment of one side might affect the other; and (III) the fact that when patients withdraw from the study, data from both body halves are lost.(IV) oral psoralens may have a cumulative effect which may influence the validity of results[24].

Extra-inconvenience for patients taking part in a paired study, is the too long time (2 hours) consumed during each session after treating the NBUVB side, waiting for the PUVA treatment. An oral liquid psoralen preparation was tried and found to be absorbed more quickly than the standard 8-MOP tablets[30], so the patients had to wait only 1 h instead of 2 after psoralen administration before treatment of the PUVA side. Unfortunately this preparation was unavailable for our patients.

Moderate itching was reported by 7 (41.1%) of our patients. It is a relatively common unexplained problem, reported in up to 25% of patients receiving phototherapy or photochemotherapy[31]. Severe itching is rare but well-recognized. The itch usually starts 4-8 weeks after onset of therapy and sometimes after treatment has been stopped. Attacks may last from 15 min. to several hours and can be provoked by scratching or pressure[32,33].
Itching is assumed to be related to prostaglandin release. It was reported that there is an increase in the skin concentration of prostaglandin E in the treated skin. This itching may affect the patients response to treatment as it leads to trauma of the skin and appearance of lesions due to Koebner phenomenon.

It was reported that psoriatic patients with previous history of phototherapy appear to be more liable to exacerbation and treatment resistance than other patients who have not been treated by photo or photochemotherapy before. However, in our study only 5 patients (29.4%) had a past history of PUVA treatment, three of them had no response and the two showed a good response.

At the end of the treatment protocol (30 sessions) only about one third of patients achieved clearance, so we had to exclude the number of days to achieve clearance and the period of remission as comparative measures, because not all patients could be evaluated by them. Accordingly, the final evaluation involved the comparison of both treatments according to the response, cumulative doses and adverse reactions. The response of our patients to treatment differed from previous reports of complete clearance on both the PUVA and NB UVB sides. However, their treatment protocol was based on the continuation of treatment until complete clearance is achieved on each side no matter how much sessions are taken.

The response of patients ranged from excellent (75% or more decrease in PASI score) to no response (fixed or increased PASI score). Patients showed no detectable difference in response to both treatments. These results are consistent with some authors whereas others found NB UVB more effective than PUVA, but all of them used bath-PUVA as a PUVA treatment regimen and the frequency of NB UVB in these studies were thrice weekly. On the other side, in a different report PUVA was more effective than NB UVB in treatment of psoriasis. The aforementioned study involved the whole-body treatment regimen by either NB UVB or PUVA therapy in thrice weekly sessions. In addition, the cumulative dose of PUVA was higher with the potential risk of radiation hazards.

Erythema, pigmentation, itching, nausea and headache were the side effects of treatment. Although our NB UVB regimen resulted in more mild, asymptomatic erythema episodes than PUVA, there was no detectable difference in the frequency of the more severe grades of erythema. Pigmentation and itching showed no significant difference between NB UVB and PUVA. These results are consistent with previous studies although in some cases, PUVA was more erythemogenic than NB UVB. This may be due to the fact that PUVA was used thrice weekly.

Pigmentation had not much been reported as a complication of treatment in previous studies. This may be because pigmentation is a common complication in dark skinned UVR treated patients and their patients were of skin type I and II. A trial of a combination therapy of NB UVB plus cream PUVA resulted in a significantly higher efficacy compared with either monotherapy alone and the cumulative UV doses were significantly lower in the combination therapy.

In our study, the main significant difference between NB UVB and PUVA was in the cumulative dose, as the cumulative dose of PUVA was much higher (three folds) than that of NB UVB. This high difference had been reported in all other studies which compared NB UVB and PUVA in treatment of psoriasis despite difference in the frequency of both therapies and the number of sessions needed to induce remission. Therefore, the PUVA side is considered to be at a higher risk of radiation hazards particularly cutaneous malignancy. In addition, NB UVB saves the patients the need for skin and eye protection throughout the day of treatment.

So from our results and those of previous studies we can roughly define certain factors influencing
the outcome of therapy:

Skin type: PUVA is more effective on skin types I-II while for darker skin types NBUVB is preferred and PUVA better reserved for those who do not respond to NBUVB[3,24].

Severity of psoriasis: NBUVB is observed to be mainly effective in mild and moderate forms of psoriasis while PUVA could be considered the mainstay for recalcitrant and severe forms of psoriasis[4,24].

Starting dose and rate of increment: higher individual UVA doses allow patients to clear before PUVA induced melanization and hyperkeratosis occur leading to lower total cumulative dose. This applies for darker skin types because in fair skin high doses provoke severe erythema and itch with no considerable pigmentation [32-36,39].

Previous exposure to UV rays: cases treated previously with PUVA are more resistant to more PUVA[24,36].

Type of psoralen: oral psoralen liquid is found to be more convenient than tablets, less time demanding and with less GIT irritating effect[24]. Topical psoralens whether cream-psoralen or bath may save the patients systemic side effects but local irritation could be an obstacle[29,35].

Frequency per week: fewer sessions/week means less disruption to the patient life, more compliance to treatment, and reduced costs[40]. Fewer but larger individual doses of UVA has less risk of carcinogenesis than multiple lower doses for the same cumulative UVA dose[41].

Occurrence of side effects: tanning and pigmentation decrease the penetration of UV rays and hence the therapeutic effect especially with PUVA. Pruritus and acute phototoxic reactions are not only distressing but also induce Koebner’s phenomenon and prolong the time for complete remission[41,42,43].

Total cumulative dose: higher total cumulative dose means higher opportunity to develop radiation related risks and higher chance to be resistant to further treatment with phototherapy if needed in the future[2,3,24,36,43,44].

**Conclusion**

Phototherapy with NBUVB on a twice-weekly treatment schedule is as effective as a twice-weekly PUVA photochemotherapy schedule in treatment of chronic plaque psoriasis.

However, NBUVB could be more convenient for the patient and less time consuming, because no exogenous photosensitizer is used before treatment, so, there is no need for eye or skin protection after sessions and no side effects of psoralens.

Moreover, the therapeutic effect of NBUVB is achieved with a lower cumulative dose than PUVA which saves the patient the hazardous effects of irradiation. So, NBUVB could be used in pregnancy, lactation and is a useful and well-tolerated treatment for children with severe or intractable cases, but concerns remain regarding its long term side effects.
References


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