A Randomized Study of Methotrexate plus Narrowband UVB versus Narrowband UVB Monotherapy in Chronic Plaque Type Psoriasis in a Rural Population.

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Abstract

Background: Psoriasis is a chronic, recurrent, inflammatory papulosquamous disease affecting skin and/or joints. The combination of Methotrexate plus narrowband-UVB phototherapy in psoriasis reduces the cumulative toxicities and UVB-exposures.

Aim: To compare the efficacy of Methotrexate (MTx) plus Narrowband UVB (NB-UVB) versus Narrowband UVB monotherapy in chronic plaque type psoriasis.

Methods: Total 30 patients with more than 10% body surface area involvement where included out of which 15 patients where in combination group who received MTx 12.5 mg once a week for 8 weeks and NB-UVB sessions thrice weekly (5th week onwards). The other 15 patients received monotherapy *i.e.* NB-UVB sessions throughout (8 weeks).

Results: Out of 30 patients, 26 completed the study. In Group A (MTx plus NB-UVB) 9 out of 15 patients attained PASI 50 at the end of 8 weeks of study. Whereas none of the patients in Group B (NB-UVB monotherapy) attained PASI 50.

Conclusion: Methotrexate when combined with Narrowband UVB phototherapy reduces the cumulative toxicities of both the agents and helps to attain a satisfactory clinical response (reduction in PASI Score) in short duration of time when compared with monotherapy in treatment of chronic plaque type psoriasis.

KEY WORDS:- Chronic Plaque Type Psoriasis, Methotrexate, Narrowband UVB

Introduction:

Psoriasis is a common, chronic, inflammatory, hyper-proliferative and a multisystem disease of the skin and joints. The natural course of the disease is marked by relapses and remission and thus has a highly unpredictable course. [1,2]

The estimated global prevalence of Psoriasis is 1% - 11.8% of the general population depending on the ethnicity served [3,4] and the approximate estimate of psoriatic patients in India accounts for 2.3%. [1,5,6]

The chronic plaque type psoriasis variety is the most common form characterized by coin-sized to palm sized well-defined erythematous squamous plaques, distributed bilaterally. Both topical and systemic therapies are used in chronic plaque type psoriasis, but when larger body surface area is involved systemic drugs are the main line of management. [7]

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Monotherapy with systemic agents may be suboptimal or produce side effects due to cumulative toxicity. In such cases combination, rotational or sequential treatment strategies may be utilized for better results and to reduce the side effects in the long run. [8,9]

Various individual & combination systemic therapies are available in developing countries like retinoids, cyclosporine and biologics. Methotrexate (MTx) is the mainstay of treatment in psoriasis. A viable combination for the treatment of psoriasis in resource limited settings is a combination of Methotrexate and Narrowband UVB (NB-UVB). The combination is capable of attaining remission in significantly less time and a lower cumulative dose of NB-UVB energy is required. [8,9,10] Few studies in literature have evaluated the efficacy of combined Methotrexate and NB-UVB.[8]

The aim of our study is to evaluate the efficacy of methotrexate and NB-UVB combination in the treatment of chronic plaque type psoriasis in the Central Indian population.

Materials & methods:

This study was carried on patients with chronic plaque type psoriasis attending OPD of Department of Dermatology, Venereology and Leprosy at Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha over a period of 2 years. The ethical clearance was taken from institutional ethics committee for the present study work. It was a single blinded, randomized control trial with a sample size being of 30 patients, divided in two groups of 15 patients each after written, informed and signed consent was taken.

The Inclusion Criteria for this study were age of 18 years above and upto 70 years, more than 10% of total body involvement, no topical treatment in the last 4 weeks and no systemic treatment in the last three month, prior to the onset of the study. [11,12,13,14]

The Exclusion Criteria being Pregnancy, lactating mother, positive history of photosensitivity. Abnormal complete blood count, renal & liver function test and abnormal serum electrolytes and excluding other types of psoriasis and patient of any other concomitant systemic or skin diseases like diabetes mellitus, hypertension, asthma, tuberculosis, malignancy (internal or cutaneous), collagen vascular disease, etc. [11,14,15]

PASI analysis of patients in both the Groups:

PASI (Psoriasis Area Severity Index) Score for the selected patients were taken at the beginning of study, at end of 4 weeks and at the end of 8 weeks during the study period. The efficacy of the treatment regimen was analysed by how many patients attained PASI 50 (i.e. 50% reduction in disease) at the end of the study i.e. 8 weeks. In literature attainment of PASI 50 is considered a satisfactory and a meaningful response. [16]

Group A, patients were evaluated and the patient was started on MTx monotherapy with a fixed dose of 12.5 mg once a week, for the first four weeks and after 4 weeks, NB-UVB was added in combination. The NB-UVB treatment session where given thrice weekly and this combination was continued for the next four weeks. [13,18,19] Routine investigations were repeated after 7 days, after 15 days and at 8 weeks of treatment.[11,12] In **Group B** the patients where started on NB-UVB thrice weekly upto 8 weeks of the study. [8,9]

Narrowband UVB Protocol by Minimal Erythema Dose [MED] for both Groups (A and B) was to obtain MED in all patients. Start at 50% of MED and increase by 10% of MED on the last erythema response. Treatment frequency of 3 times a week. Not to increase of MED if erythema persisted for more than 24 hours. [13,17,20]

Statistical Analysis

Statistical analysis was done by using descriptive and inferential statistics using chi-square test and student's paired '*t*' test. In present study, the statistical software used in the analysis was SPSS 17.0 and Graph-Pad Prism 5.0 version. All the results were tested at 5% level of significance.

DISCUSSION:

The Table 1 shows the baseline characteristics of the study population. Both the groups are compatible in terms of sex of patient, age (in years), total duration of illness (in years), age of onset of disease and mean PASI score before starting the treatment, with no significant difference in both the groups.

In this study the narrowband UVB sessions were given thrice weekly. According to literature the thrice weekly doses are equally efficacious as 5 times weekly dose with good clinical response and the cumulative dose of energy required is lesser as compared to five times weekly doses. [13,18,19]

The patients in Group A received a fixed dose of methotrexate i.e. 12.5 mg once a week throughout the study period. Studies done by **Eva Due *et al*** and **Khaled *et al*** suggested that the median weekly dose requirement of 12.5 mg was sufficient.[20,21] In this study, the mean of total cumulative dose of MTx was 91.66 ± 22.46. A total cumulative dose of 112mg (range 75-165 mg) was observed in a study done by **Paul *et al.*** [23]; 114 ± 24.7 mg (15mg / week) in a study **by Asawanonda *et al*** [9]and 200 ± 81.05 mg in a study by **Mahajan *et al.*** [8]

The, Table 2 depicts the mean of number of treatment sessions and mean cumulative energy required in both the groups. In the combination group similar findings were comparable to a study done by **Mahajan *et al*** where mean number of treatment sessions and energy required was 16.46 ± 5.95 and 8.86 ± 5.40 J/cm^2 respectively.[8] In same group the mean energy required in a study by **Asawanonda *et al*** depicted was 26.92 ± 15.54 J/cm^2.[9] The group receiving monotherapy of NB-UVB the mean number of sessions required where comparable to studies done by **Mahajan *et al*** and **Asawanonda *et al*** (29.12 ± 11.95 and 59.25 ± 16.71 J/cm^2, respectively) .[8,9]

The Table 3 and Graph 1 shows, the mean PASI score of Group A and Group B at regular intervals (i.e. at beginning, by end of 4 weeks and at the end of 8 weeks).

The mean of PASI score at all the intervals in Group A showed a significant difference. Until the 4th week, none of the patients achieved a PASI 50 but with the combination of NB-UVB there was a significant improvement in the PASI score and 60% of patients attained PASI 50. In Group B also there was significant difference in PASI score at the predetermined time intervals. Though NB-UVB monotherapy was effective, none of the patients achieved a PASI 50 in Group B and required more number of sessions, more energy and longer duration to achieve PASI 50. Thus, we believe that NB-UVB treatment sessions in adjunct to MTx have a synergistic effect in the rapid clearance of the disease in a shorter span of time.

In this study, the side effects were observed on cutaneous and investigational findings (ultrasound and hematological). In combination group one patient after 2 weeks of methotrexate, had burning and stinging sensation of the psoriatic plaques with no involvement of the mucous membrane (as by **Julie *et al***). [24] The other patient had grade I fatty liver and deranged hepatic functions at the end of the study (as by **Priya *et al***).[25] In monotherapy group one patient had appearance of new lesions while on phototherapy sessions and was withdrawn from the study as the patient had photo-aggravated psoriasis (as by **Caitriona *et al*).** [26]

There were 2 drop outs during the course of study (n=28/30). In Group A, one patient was lost to follow up by the 5th week of study while in Group B, one patient was lost to follow up by 4th week. This was probably due to inability of patients to attend the dermatology clinics thrice weekly, to receive NB-UVB phototherapy sessions. Poor compliance and economic difficulties in the rural setting making it difficult to attend the sessions regularly was believed to be the reason for the same.

Correlation between disease severity (based on PASI score) and response to treatment

The patients of both groups were again redistributed according to PASI score into two subgroups I & II (Table 4 and Table 5), respectively. This was done to analyze the response to treatment according to disease severity as found in a study by **Mahajan et al.** [8]

In Table 6, intention to treat analysis of both the groups at end of the study are compared on the basis of attainment of PASI 50, total mean cumulative sessions and total cumulative energy requirement. These observations demonstrated that combination therapy is more efficacious than monotherapy if larger body surface area is involved.

In this study in accordance to various studies quoted concludes the fact that combination therapy is significantly more efficacious for Chronic Plaque type Psoriasis when compared to monotherapy alone. Though, monotherapy with Methotrexate and NB-UVB are individually effective. However the benefits of combination therapy are the ability to reduce dosages of individual agents, reduce side effects & toxicities and at the same time achieve additive or synergistic effect for better efficacy. Of the available combinations, the combination of methotrexate and NB-UVB seems efficacious and economical in the resource limited rural setting. (14,15,16)

CONCLUSION:

Thus the combination therapy is very effective, well tolerated with minimal side effects; better compliance is seen and is cost effective. But more studies are required as there is paucity of literature using the same combination.

OBSERVATION AND RESULTS:

Table 1: Baseline characteristics of the study population

Baseline characteristics	Group A (n=15)	Group B (n=15)	Total (n=30)	p-value
Males	11	9	20	
Females	4	6	10	
Mean Age(Yrs)	45.13±14.72	42.40±11.01	43.76±12.85	0.56,NS, p>0.05
Total duration of illness(yrs)	9.39±7.87	8.81±6.45	9.10±7.08	0.70, NS, p>0.05
Age of onset(yrs)	34.93±16.03	33.60±12	34.26±13.93	0.79,NS, p>0.05
Mean PASI (pre-treatment)	18.41±2.33	16.82±2.28	17.61±2.41	0.069,NS, p>0.05

Table 2 : Comparative Descriptive Statistical Data of Mean Narrowband UVB (Sessions and mJ/cm^2) in Both the Groups

	Group A	Group B	P value

Mean NB-UVB sessions	8.93 ± 3.36	19.73 ± 4.89	0.000, S, p<0.05
Mean of cumulative energy (mJ/cm^2)	3083.33 ± 1302.18	6695.33 ± 2006.02	0.000, S,p<0.05

Table 3 : Comparative Descriptive Statistical Data of Mean PASI Score (before treatment, at 4 weeks and at end of 8 weeks) in Both the Groups

Duration of PASI (Mean)	Group A	Group B
Pre t/t	18.41 ± 2.33	16.82 ± 2.28
At the end of 4 wks	13.37 ± 4.56	14.14 ± 2.21
At the end of 8 wks	4.98 ± 3.58	7.64 ± 3.23
P value at the end of 8 weeks	0.041, S, p<0.05	

Table 4: Comparison of subgroup I (PASI < 15) in both groups

	Group A	Group B	p-value
No of patients	2	8	0.05, NS, p>0.05
No of patients who attained PASI 50	2/2	0/8	0.48, NS, p>0.05
NBUVB cumulative Dose (mJ/cm2)(Mean)	3920	7093.75	0.001, S, p<0.05
No. of NBUVB sittings required(Mean)	11.00	20.62	0.02, S, p<0.05
TCD-MTx	100 mg	0.00 mg	0.001, S, p<0.05

Table 5: Comparison of subgroup II (PASI > 15) in both groups

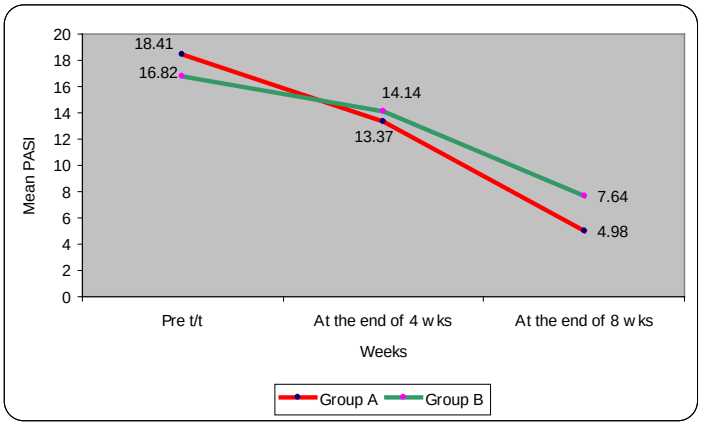
	Group A	Group B	p-value
No of patients	13	7	0.05, NS,p>0.05
No of patients who attained PASI 50	7/13	0/7	0.006,S,p<0.05
NBUVB cumulative Dose (mJ/cm2) (Mean)	2954.6	4675.7	0.0012,S,p<0.05
No of NBUVB sittings required (Mean)	7.8	14.2	0.03,S,p<0.05
Mean of TCD-MTx	90.38 mg	0 mg	0.001,S,p<0.05

Table 6: Intention - to - treat analysis

Intention-to-treat	Group A (n=15)	Group B (n=15)	p-value
Attainment of PASI 50	9/15 (60%)	0/15 (0.00%)	0.0003, S, p<0.05

Total NBUVB sessions (mean ± SD)	8.93 ± 3.36	19.73 ± 4.89	0.000, S, p<0.05
Total NBUVB energy required mJ/cm² (mean ± SD)	3083.33 ± 1302.18	6695.33 ± 2006.02	0.000, S, p<0.05

Graph 1: Comparison of PASI in Group (A and B) at end of 8 weeks



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