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Original Research Article

Comparison of Effects of Injection Methotrexate with Injection Methotrexate and Injection Triamcinolone Acetonide in the Management of Palmoplantar Psoriasis- An Open, Randomized Comparative Study

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ABSTRACT

Introduction- Chronic PalmoPlantar Psoriasis (PPPs) is an idiopathic condition located on palms and soles. As complete clearance is difficult, Pain reduction and functional improvement may be the more important therapeutic goal.
Aims and objectives - To compare the effects of injection Methotrexate (MTX) and Inj TATA Acetonide (TA) in Palmoplantar Psoriasis with injection Methotrexate and relapse after stopping the therapy.
Materials and methods- Clinically PPPs Patients (16 -65 years) with involvement of more than 25% of palm and/or sole was included in the study and divided in two groups. Group A consisted of patients getting MTX 15mg single weekly dose for 6 weeks, Group B patients got MTX 15mg single weekly dose for 6 weeks and Injection TA40mg deep IM injection, 2 injections each in 3 weeks interval. Disease improvement documented and assessed by Modified PASI scoring system and Target area Scoring.
Results – Both the modalities of treatments were effective. In MTX Group, reduction of Mean Modified PASI was 45.58% at 4 weeks and in combined group it was 66.3%. In MTX only group PASI75 (Mean Modified PASI) was achieved in 13.6% patients after 6 weeks whereas 31.8% patients in combined group achieved PASI75 (Mean Modified PASI). After 6 weeks of therapy, 64.68% reduction occurred in MTX only group but in combined group the reduction was 83.8%. The MTX- TA group showed significant early improvement in Target Area Score. There were no differences of relapse pattern and rate in MTX and TA injection group. Patients' satisfaction after treatment was recorded in a graded scale. Only 9.1% patients opined excellent about the response of therapy in MTX group whereas 40.9% excellent in combined group. The differences of Dermatology Quality of Life Index at beginning and end of the study were significant.
Conclusion –Combination of MTX with inj TA is more effective therapy for early reduction of severity of PPPs. It changes the Quality of life dramatically. Patients satisfaction with this combination therapy is higher than Methotrexate only therapy. Chances of relapse are same in both groups, and rebound exacerbation of disease was not an apprehension in combination therapy.
Key words- *Palmoplantar Psoriasis, Methotrexate, Inj Triamcinolone, Modified PASI, Target Area Score, DLQI*

INTRODUCTION

Chronic Palmoplantar Psoriasis (PPPs) is an idiopathic condition located on palms and soles and characterized by erythema, scaling and fissuring. Although PPPs appears to be a distinct entity in terms of epidemiology and pathophysiology, it might be associated with other forms of

psoriasis. [1] Palmar or plantar psoriasis lesions occur in 17.6% of psoriasis patients. Typical psoriatic lesions elsewhere in the body in patients of PPPs were present in only 30.3% patients. In a recent study in south India 2.4% of total outpatient patients had psoriasis and about 58% psoriasis patients were suffering from PPPs [2] although previous studies mentioned prevalence of PPPs is next to chronic Plaque Psoriasis and significantly high. [3,4]

PPPs may affect people of all ages. Once established, it might last for decades and can cause impaired dexterity or mobility, as well as discomforting pruritus and pain. [1]

Morphologic patterns of PPPs, ranging from predominantly pustular lesions to thick, hyperkeratotic plaques, with a spectrum of overlap of these two polar entities. [5]

In Hyperkeratotic Hand Eczema, the eruption present as hyperkeratotic, fissure prone, erythematous areas of the middle or proximal palm. The volar surface of fingers may also be involved. Planter lesions occur in about 10% of patients. Its most important differential diagnosis is psoriasis, and some of the patients of chronic hyperkeratotic hand dermatitis will ultimately prove to be psoriasis. [6] However, there can be tremendous clinical overlap between the two conditions. Many a times, the histopathological findings are also similar [7] and overlapping each other. [8]

As complete clearance is difficult, Pain reduction and functional improvement may be the more important therapeutic goal. Management usually involves topical therapy, that includes tar, salicylic acid and corticosteroids, either alone or in combination. Systemic therapy includes Acetretin, Methotrexate, Cyclosporine, Biologicals, and different combinations. [9] Oral retinoids have been the drug of choice except in women of childbearing age though not effective frequently. [10] MTX has been used in the treatment of psoriasis as monotherapy or in combination with other drugs. It may be more effective than Acitretin. [11]

Very few clinical studies address treatment, and there is a lack of data and quality-of-life assessment beyond anecdotal case reports and small studies with alefacept, [12] acitretin, [13,14] Psoralen plus Ultraviolet A [15] and *Efalizumab*. [16,17] This lack of data is in large part because these patients are seldom included in clinical trials. Although pure PPPs without involvement elsewhere affects less than 5% body surface area (BSA), a number significantly below the 10% usually required for inclusion in most systemic treatment studies, it is notoriously difficult to treat and unresponsive to traditional topical agents. [5] It is the improvement in quality of life that patients and physicians rely upon when selecting treatment.

We have planned an open-ended comparative study to analyze the effect of MTX and injection TATA Acetonide (TA) in respect of clearance of PPPs like disease and also duration of relapse-free period. For diagnostic dilemma, we included clinically PPPs look like patients in our study.

Aims and objectives

To compare the effects of injection MTX weekly for 6 weeks (Group A) with combination of weekly injection MTX for 6 injections and TA40 mg injection once in three weeks for two such(Group B) in PPPs .

To document the disease relapse in a fixed period of 6 months in different groups after stoppage the therapy

MATERIALS AND METHODS

It was an open-labeled randomized control study conducted on 46 consecutive patients of clinically PPPs attended in the dermatology outpatient department at a tertiary care centre in Eastern part of India, from May 2015 to January 2017. Clinically PPPs Patients (16-65 years) who have involvement of more than 25% of palm and/or sole was included in the study.

Patients <16 years of age, pregnant or lactating mothers, those with renal or hepatic disease, photosensitivity or cardiac disorder, malignancy, systemic therapy/ PUVA within the previous 8 weeks, topical therapy/UVB phototherapy within the past 4 weeks or taking immunosuppressive agents were also excluded.

Patients were divided in two groups. Group A consisted of patients getting MTX 15mg single weekly dose for 6 weeks, Group B patients got MTX 15mg single weekly dose for 6 weeks and Injection TA40mg deep IM injection, 2 injections each in 3 weeks interval. The random allocation sequence was computer generated and consisted of Simple randomization for each consecutive patient. Allocation concealment maintained. the sample size was calculated 21. We have included 23 patients in each group. Sample size n= [DEFF*Np(1-p)]/[($d^2/Z^2_{1-\alpha/2}$*(N-1)+p*(1-p)]. Results from OpenEpi,Version3,open source calculator]

Schedule of visit showed in Table 1.

Table -1. Schedule of Patients visit.

	0 Day	1st week	2nd week	3rd week	4th week	5th week	6th week
Visit	1st		2nd		3rd		4th
Inj.Methotrexate	√	√	√	√	√	√	√
Inj. triamcinolone	√			√			√
Record Keeping	√		√		√		√

A Detailed history were recorded, detail physical and dermatological examination including Modified PASI and Target Plaque Score were performed. Investigations include CBC, LFT, RFT, FBS, electrolytes and chest X-ray were done. All data were recorded in predesigned proforma.

Assessment method- Disease improvement documented and assessed by Modified PASI scoring system and Target area Scoring. we also assessed the Dermatological Quality of Life(DLQI)

Modified PASI score [1] was calculated by multiplying the proportion of area involved and the severity of erythema, infiltration and desquamation, ranking from 0 (normal) to 4 (severe). The proportion of involved area in %:

0% = 0; 1–20% = 1; 21–40% = 2; 41–60% = 3; 61–80% = 4; 81–100% = 5 score points.

Morphological scoring of psoriatic plaques was carried out by evaluation of three parameters, i.e. erythema, scaling and thickness, each of which will be graded on a severity scale of 0-4, where:

0 = nil,,1 = mild,2 = moderate,3 = severe,4 = very severe. The Modified PASI score ranges from 0 to 60 on a scale, can reach a maximum of 60 points [5×(4+4+4)].

For Target Plaque Scoring method, one plaques of psoriasis (most prominent and if happens largest) was selected from the palm or sole of the patient. Morphological scoring of psoriatic plaques was carried out by evaluation of three parameters, i.e. erythema, scaling and thickness, each of which was graded on a severity scale of 0-4, where:0 = nil,1 = mild, 2 = moderate, 3 = severe,4 = very severe. The sum of scores for each parameter gave the target plaque score. The range of target plaque score is 0-12 [18]

DLQI is a dermatology-specific 10-item questionnaire related to symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. [19] It measures how much a skin problem has affected the life of patient over the previous week. The instrument consists of 10 items; DLQI is calculated by summing the score of each item, resulting in a maximum of 30 and a minimum of 0. the higher the score, the more Quality of life is impaired. At a same time, a four level patients self assessment – Poor, Good, Very Good and Excellent were designed. It was asked to each patient to categories their disease improvement and grade, we recorded that also.

Data was entered in excel spreadsheet and was analyzed accordingly.

Relapses were documented only by visual impression.

Statistical methods- Medcal C was used for statistical analysis. Arithmetic mean and standard deviation were calculated for each visit in each group. Independent samples t test were calculated for comparison of data between two groups in each visit.(P value < 0.05 was defined as statistically significant).

RESULTS

All the patients attended were put into two different groups randomly. In each group 23 patients were enrolled. One patient in Group A and Group B were removed for MTX intolerance.

The Demographic Profile of patients were as follows. (Table -2)

Table 2 Demographic profile

	TOTAL PATIENT	MTX	MTX+TA
Number	44	22	22
Gender	M- 26(59.09%) F- 18(40.91%)	M- 15(68.2%) F- 7 (31.8%)	M- 11 (50%) F-11 (50%)
Age (years)	43.25± 11.1900	42.22± 10.75	44.27 ± 11.77
Duration of disease (Years)	6.7045 ± 4.8252	5.72 ± 4.96	7.90± 4.66

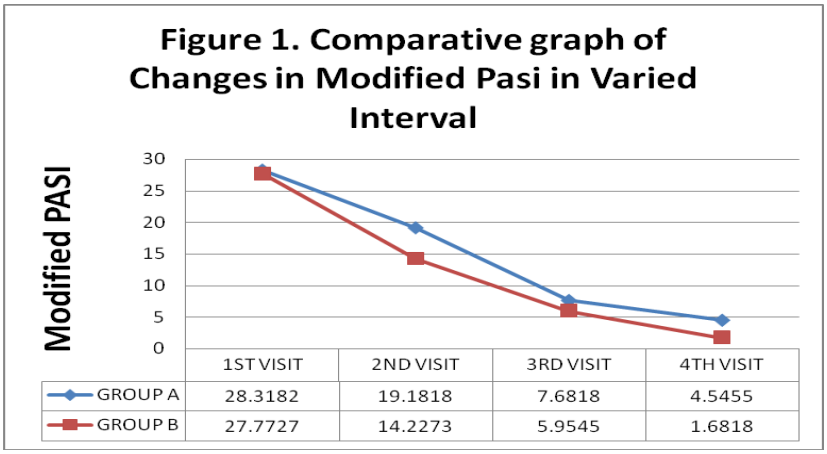
Both the modalities of treatments were effective. In MTX Group (Group A), reduction of Mean Modified PASI was 45.58% at 4 weeks and in Combined group (Group B) it was 66.3%. In MTX only group PASI 75 (Mean Modified PASI) was achieved in 13.6% patients after 6 weeks whereas 31.8% patients in combined group achieved PASI75(Mean Modified PASI – reduced 75% of the baseline). After 6 weeks of therapy, 64.68% reduction occurred in MTX only group (Group A) but in Combined group(Group B) the reduction was 83,8% .

At the beginning, there was no statistical difference in Target Area Score between Group B (Injection TA Acetonide 40 mg and Inj MTX weekly) and Group A (Inj MTX only weekly) . But as the study proceeded, the differences changed significantly and the MTX- TAgroup showed significant early improvement in Target Area Score (Table 3).

Table 3. Comparison of Target Area Score

	O week/ 1st visit	2 weeks	4 weeks	6 weeks
Group A	8.5909±1.2212	6.5000± 1.4720	3.6818±1.2105	2.5455± 1.0568
Group B	8.4091± 1.5011	5.4545 ± 2.1320	3.0000 ± 1.6903	1.4545± 1.3355
Independent samples t test	P = 0.6617	P = 0.0027	P = 0.0006	P < 0.0001

Changes in Modified PASI also followed the same pattern. At beginning of study there was no difference but at 6 weeks of treatment, there was significant reduction in Mean Modified PASI (2nd visit *p*=.0106, 3rd visit *p*=.0013, 4th visit *p*= .0001. *P*- (Significance) (Figure-1).



Adverse effects were severe in two patients, one in group A with thrombocytopenia and another in group B with raised bilirubin and hepatic enzymes. Both of them were discontinued from study (and not included in analysis also).Minor laboratory changes occurred in 13 patients, six in group A and 7 in group B, none required to stop therapy. Nausea and vomiting were another common side-effects (8 patients, 4 in each group), mainly on the day of MTX administration, though in 2 patients they continued for 2-3 days. Oral folic acid (5 mg/day) improved the symptoms in 7 of these patients, but one had severe vomiting controlled with ondansetron injections. Patients satisfaction after treatment was recorded in a graded scale. In MTX group, 4.5% patients opined poor, 45.5% -good, 40.9% very good and only 9.1% patients excellent about the response. In comparison, in combined group, 22.7% patients opined good, 36.4% very good and 40.9% excellent about the response of therapy. (Table 4).

Table-4- Patients assessment about response to therapy

Remarks	Group A	Group B
Poor	4.5%	0
Good	45.5%	22.7%
Very Good	40.9%	36.4%
Excellent	9.1%	40.9%
Total	100.0%	100.0%

We have assessed the Dermatology Quality of Life Index, according to Finlay and Khan, [27] at beginning and end of the study (Table -5). The differences are significant. Also the difference between two groups at the end of study is significant.

Table 5. Assessment of Dermatology Quality of Life Index, according to Finley and Khan

Type		Pretreatment Mean ± Sd	After Treatment Mean	Independent sample t test, between pre and post -treatment	Independent sample t test, between Gr A and Gr B, post-treatment
Symptoms And Feelings	Group A	5.45 ±0.91	1.68 ± 0.64	P < 0.0001	P = 0.0150
	Group B	5.09±1.06	1.14±0.77	P < 0.0001	
Daily Activities	Group A	4.81 ±1.00	1.40 ±0.50	P < 0.0001	P = 0.0594
	Group B	4.77±0.97	1.05±0.72	P < 0.0001	
Leisure	Group A	5.22 ±0.92	2.00 ±0.69	P < 0.0001	P < 0.0001
	Group B	5.09±0.92	1.09±0.61	P < 0.0001	
DLQI_work	Group A	4.54±1.10	1.18 ±0.50	P < 0.0001	P = 0.0206
	Group B	4.50±1.06	0.82±0.50	P < 0.0001	
Personal Relationships	Group A	2.18 +0.50	0.68 ±0.64	P < 0.0001	P = 0.1259
	Group B	2.18±0.50	0.41±0.50	P < 0.0001	
Total	Group A	22.22 ±3.43	6.95 ±1.61	P < 0.0001	P = 0.0016
	Group B	21.64±3.22	4.86±2.41	P < 0.0001	

Relapse after stopping the systemic therapy, was compared between two groups. In both groups, all patients relapsed in 12 weeks period. In MTX only group, three patients those achieved PASI75 relapsed at the end of 12 weeks, fifteen patients achieved PASI 60 relapsed between 6 to 8 weeks. There were no differences of relapse pattern and rate in MTX and TA injection group.

DISCUSSION

In the absence of any published reports about the efficacy of injection TA on PPP, we could compare our results only with the studies using methotrexate on psoriasis vulgaris. We kept MTX in both groups, as it is the mainstay of therapy. Addition of TA was only to give early relief from difficulties and given under coverage of MTX to avoid rebound increase of psoriasis.

Various treatment modalities for PPPs were tried. They are mainly for treating psoriasis vulgaris, for palmoplantar and pustular variety. But treatment targeted for clinical improvement of PPPs, so that early reduction of discomfort and improvement of quality of life was less tried.

Heydendael et al [20] compared MTX to Cyclosporine without a placebo arm. There were approximately 45 patients in each group. The primary end point of PASI (Psoriasis Area and Severity Index) 75 response at 12 weeks was 60% for MTX

and 71% for cyclosporine. Our study has similar effect in MTX group (64.21% reduction), but the combined group had 83.8% reduction in Mean Modified PASI. It is also comparable with study of Flytstrom, Stenberg, and Svensson [21] who compared MTX to cyclosporine without a placebo arm. The mean PASI change from baseline was 72% in the cyclosporine group and 58% in the MTX arm.

So far no study on using systemic TA for PPPs was done, but Intralesional TA was given for PPPs. [22] Five patients with chronic intermittent palmoplantar pustulosis were treated with intralesional injections of 3.3 to 5.0 mg/mL of TA. Prompt clearing of symptoms and lesions ensued, lasting three to six months. Despite the discomfort experienced from the injections, patients preferred this treatment modality over others. Minor side effects included hypopigmentation, cutaneous atrophy, and, in one case, exacerbation of a latent dermatophyte infection.

In another study, Sixty-four patients who received corticosteroid injections into the hands and feet were followed up for a period of up to three years. Injections offer a safe, popular, limited advance in the treatment of chronic eczema and psoriasis in these areas. The periods of remission varied from a few weeks to several months. The concurrent use of topical treatment was reduced although most patients continued to use them. No subcutaneous atrophy was observed and no serious side effects occurred. Most patients were willing to receive the injections again. [23]

Numerous clinical trials have demonstrated the efficacy of CSA in psoriasis. CSA given at 2.5 to 5 mg/kg/d for 12 to 16 weeks leads to rapid and dramatic improvement in psoriasis in up to 80% to 90% of patients. When dosed at 3 mg/kg/d, CSA leads to a PASI 75 response in 50% to 70% of patients and a PASI 90 response in 30% to 50% of patients. [24- 27]

In our study, result of MTX was at or above par to other studies. Result of combination therapy with inj MTX and TA showed result as per or better than intermittent cyclosporine therapy. Parenteral rout of MTX may be an explanation of that as intramuscular administration results in rapid and complete absorption and higher serum concentrations.[28] Various clinical experiences have suggested that SC MTX is more effective than oral MTX and may provide significant benefit even in patients in whom oral MTX proved to be inadequate. [29]

Any side-effects of intralesional TA was not appeared in our study, relapse rate after 6 weeks of follow up was same in both groups. We were very much cautious about rebound exacerbation of disease, and informed the patients to contact immediately if any slightest evidence of such lesion appears though it was not happened. There was no superficial skin infection of any sort during these periods. We have assessed the Dermatology Quality of Life Index, according to Finlay and Khan, at beginning and end of the study. The difference in DLQI from beginning to end of therapy came as significant in both groups and in between two groups. At the beginning of study the total DLQI were same in both groups, but at the end the DLQI changed more in Combination group than MTX only group and it came as significant. It also corroborate with patients self assessment where in MTX group, 4.5% patients opined poor, 45.5% -good, 40.9% very good and only 9.1% patients excellent about the response. In comparison, in combined group, 22.7% patients opined good, 36.4% very good and 40.9% excellent about the response of therapy.

Remarkably, side effects were low and insignificant with combination therapy. Ten patients (45%) with MTX group and, 8(36%) patients of combination group had raised liver enzymes, but it was not significant. No patients were discontinued, only addition of hepato-protective drugs it became normal and patients completed therapy.

There was a significant risk of aggravation or rebound of psoriasis after stopping of the combination therapy. But the relapse rates between the two groups were at per. The reason may be, all patients in combination group were given Triamcinolone under cover of MTX, that may take care of sudden rebound or relapse.

Patients' satisfaction about the therapies showed that more patients are satisfied with combination group because of early reduction of discomfort.

CONCLUSION

Our study showed combination of MTX with inj TA is more effective therapy for early reduction of severity of PPPs. It changes the Quality of life in dermatologic patients dramatically. Patients satisfaction with this combination therapy is higher than Methotrexate only therapy. Chances of relapse are same in both groups, and rebound exacerbation of disease was not an apprehension in combination therapy.

Limitation- Increase in sample size, more prolong follow up will help for further evaluation.

Conflict of Interest- None.
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